REDUCE ŞI AJUTĂ LA PREVENIREA PROBLEMELOR GINGIVALE ÎN 4 SĂPTĂMÂNI PENTRU A ÎNTRERUPE CICLUL GINGIVITEI

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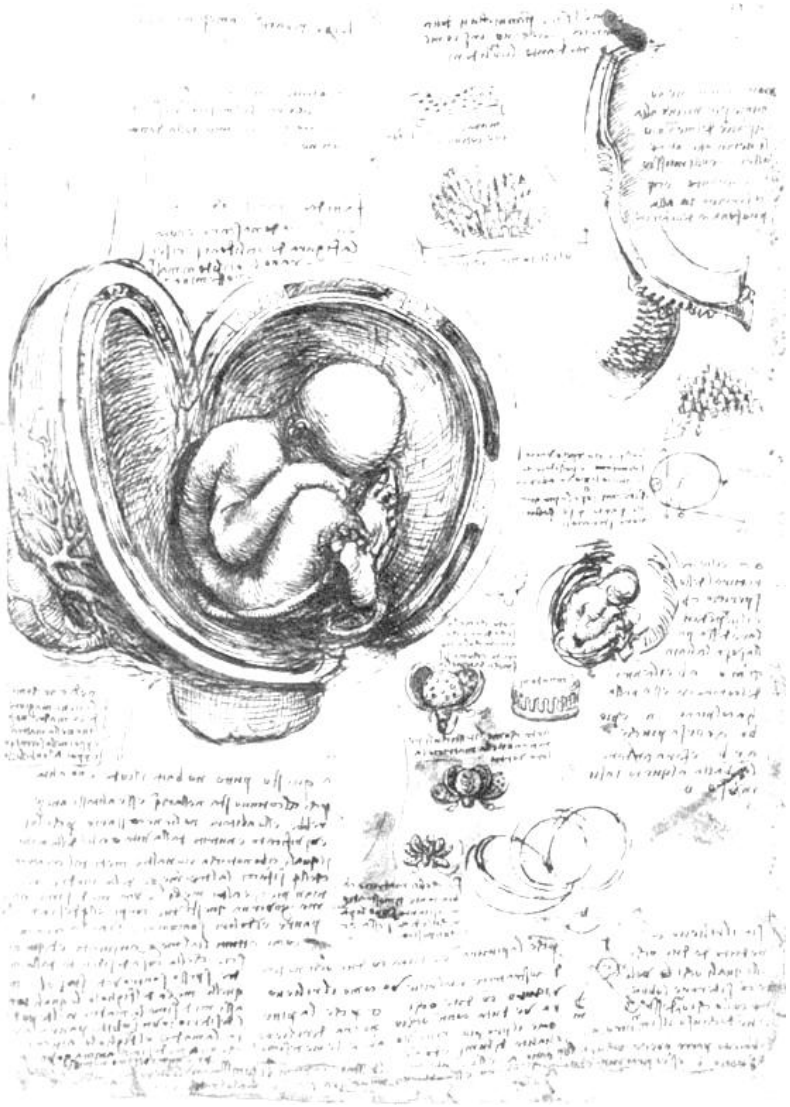

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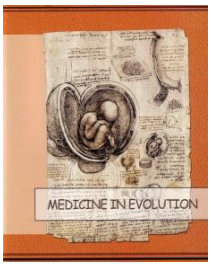
STATINS – BENEFITS AND RISKS: CONTROVERSIAL OPINIONS



ALINA DUNE[1*], DANIELA BACONI[2], DAN BALALAU[2], MIHAELA ILIE[2], DANIELA IONESCU[1], ALEXANDRA CĂLIN[1], MARIANA POPESCU[1], CARMEN POPESCU[2]

[1]HofigalExport Import SA, Bucharest, Romania
[2]"Carol Davila"University of MedicineandPharmacy, Faculty of Pharmacy,Bucharest, Romania

ABSTRACT

As inhibitors of HMG – CoA reductase, statins are subject to many medical uses, mainly in diseases associated with cardio-vascular risk. Rather easily prescribed by geriatricians, cardiologists and family physicians, statins account for a significant decrease of dangerous cardiovascular and cerebral events, morbidity and mortality.Yet, there is enough data in the literature documenting the dangerous adverse effects of the statins: miotoxicity, the effects on nervous, hepatic or immune systems, cytogenotoxicity, as well as interactions with other drugs or diet.A very disputed subject, the use of statins in the treatment of cardio-vascular diseases, is therefore as actual now as ever.

Based on the most recent literature data, the present article tries to formulate most frequent nowadays opinions in favor and againstthe use of statins the therapy of cardio-vascular and other diseases.In conclusion, utmost care and thoughfullness are necessary for the prescription of statin based treatments.

Key words: *statins, risk, benefits, disease*

Correspondence to:

Alina Dune
Address: HofigalExport Import SA, 2 Intr. Serelor, district 4, code 042124, Bucharest, Romania
Phone: +4 0724294824
E-mail address: alinadune@yahoo.com

INTRODUCTION

Being defined as a drug class which determines the lowering of the cholesterol levels, the natural and synthetic statins are recommended in the treatment of diseases associated to the impairment of biological parameters associated with cardiovascular disease (CVD).

Initially discovered in fungi [1,2], the statins action consist in the inhibition ofthe enzyme 3-hydroxy 3-methyl-glutaryl CoA reductase(HMG – CoA)reductase,which plays an important role in the cholesterol production in the liver. Having a similar structure to HMG — CoA, the statins take the place of the enzyme and reduce the rate of mevalonate formation, which represents the first molecule in the process of cholesterol production [1].

In addition, other studies emphasize the importance of statins in the increase of low density lipoproteins (LDL) uptake [3] and their inhibitory activity of the specific protein prenylation [4].

It was assumed that statins prevent the cardiovascular diseases via four mechanisms [5]: they improve the endothelial function, modulate the inflammatory responses, maintain the plaque stability and prevent the thrombus formation. The statins are recommended in the primary prevention (for the people without a history in heart diseases) but especially in secondary prevention (for persons withpreexisting CVD) [6].

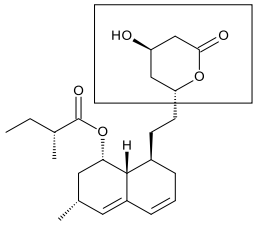
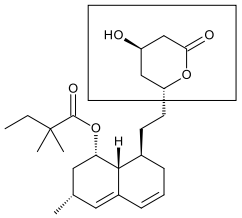
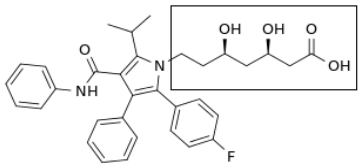
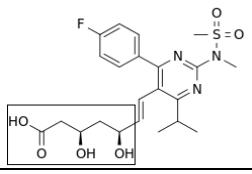
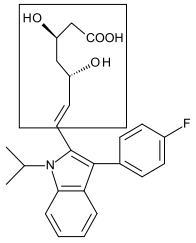
While having a rather neat effect on lowering blood cholesterol and increasing LDL uptake, statins have also well-known adverse effects, among which increase of diabetes risk, liver and muscle problems are most studied.

Being given the numerous applications of statins and their increased popularity among physicians, it is imperative to review the current state of the debate regarding the desirability of their prescription. Therefore,the paper present a review of latest favorable and unfavorable opinions concerning the use of statins in therapy.

CHEMICAL STRUCTURE AND CLASSIFICATION OF STATINS

Statins were first isolated from mushrooms in the 1970s [7], but soon they were also synthesised. Their chemical structure consists in two components, one of which, *the pharmacophore,* has the role of the inhibition of the HMG-CoA reductase enzyme in a competitive, dose-dependent, and reversible manner (table 1). The pharmacophore of statins is a dihydroxyheptanoic (hydroxyl-glutharic) acid group (sometimes in lactone form), which is very similar to the endogenous substrate of HMG-CoA reductase[8]. The moiety of the pharmacophore, according to the chemical modified ring systems and the nature of the substituents, generates the different structures of the statins. In fact, the opened ring gives the active compound responsible for the effect.

Table 1. Chemical structures of mostly used statins (pharmacophores are included in rectangle)

Name / brand name	Structure	Observation
Lovastatin Mevacor, Altocor, Altoprev		Natural,fermentation-derived. Found in oyster mushrooms and red yeast rice
Simvastatin Zocor, Lipex		Natural,fermentation-derived.Found in *Aspergillusterreus*
Atorvastatin Lipitor, Torvast		Synthetic
Rosuvastatin Crestor		Synthetic
Fluvastatin Lescol, Lescol XL		Synthetic

The nature of the group attached to the pharmacophore is also important. Depending on this and on their origin, the statins can be divided into two categories: natural ones, having a decalinic group and synthetic ones, having a heterocyclic group in the neighbourhood (table 1).

A number ofQuantitative Structure-Activity Relationships (QSAR) studies were performed in order to improve the statins activities [9].

OPINIONS IN FAVOR OF STATINS USE

Use of statins in cardio-vascular diseases

Though the statins were initially conceived for decreasing the cholesterol levels and for protection against the dangerous vascular-coronary and cerebral events, a lot of other medical applications involving them were discovered in the last decades.

As inhibitors of HMG-CoA reductase, the statins prove their efficiency in the prevention of dangerous cardiovascular events in patients having or not previously suffered of cardiovascular diseases

(Figure 1). The statins were used in the primary and in the secondary prevention as well [10-12]. They are effective in decreasing mortality due to previous cardiovascular affections.Previous cardiovascular diseases are defined as prior myocardial infarct (MI), angina, any cardiac intervention, any stroke or transient ischemic attack, peripheral arterial disease or more than three cardiovascular risk factors. By association to a LDL lowering, statins therapy reduces the recurrence rate of any type of cardiovascular event, any kind of MI, coronary death, cardiac intervention and any stroke type. The benefit of statins remained significant for all outcomes in men in the primary and secondary prevention.

Venous thrombosis or thromboembolism (VTE) is a disease in which a blood clot (thrombus) forms in a vein or in a deep vein (DVT) and causes a blockage. The clot is carried through the blood stream to the lungs provoking a life threatening pulmonary embolism (PE). The statins have a protective anticloting effect and may be effective in the prevention of VTE, DVT and PE [12, 13].

Atherosclerosis (arteriosclerotic vascular disease – ASVD) is a specific form of arteriosclerosis in which, as a result of the accumulation of calcium and fatty materials, the artery walls thicken,losing their elasticity and obstructing the blood circulation. Due to their cholesterol lowering and to the pleiotropic effects, statins are also used in the atherosclerosis treatment [14].

The atrial fibrillation, the most common kind of arrhythmia, is complicated by an increased risk of stroke and thus increased mortality. Atrial fibrillation represents a frequent complication after cardiac surgery, coronary artery bypass or valve replacement. A recent review [15] concluded that in addition to cholesterol lowering, the statins have an antiarrhythmic effect by improving endothelial nitric oxide (NO) availability and reducing inflammation, oxidative stress and neurohormonal activation.

For the patients having stable coronary diseases or acute coronary syndromes (ACS) the lowering of LDL cholesterol is an important goal. Therefore, an early statin therapy reduces the cardio-vascular events [16] mostly unstable angina, but not death, myocardial infarction or stroke [17].

Statins seem to have a modest but clinically relevant antihypertensive effect. These properties are in connection to the beneficial effect of statins inflammation, endothelial function, oxidative stress, fibrinolytic parameters, platelet function and other activities related to the atherosclerotic process [18].Figure 1presents the main directions of the statins therapy.

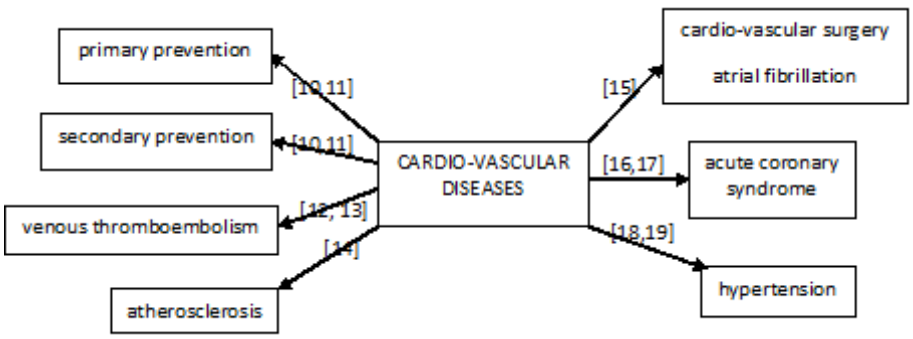


*Figure 1.**Statin therapy in cardiovascular diseases***

Other suggested uses of statins in therapy

It was appreciated that a high level of LDL cholesterol is an important cardiovascular risk factor for diabetes,

therefore The American Diabetes Association (ADA) standards of care for diabetes state"that statin therapy should be initiated in individualswitha target of LDL cholesterol of < 100 mg/dl"[20]. Yet there are other new data emphasizing that the statin therapy is associated withan increased risk for developing diabetes [21].

The hypothesis that statins may exert a protective effect in age-related macular degeneration (AMD) is based on epidemiologic, genetic and pathological evidences. They emphasized that AMD presents the same risk factors as atherosclerosis. Recent reviews did not find sufficient evidence to determine the effectiveness and safety of statins in theprevention and delay of the AMD progression [22].

Hotersal (2006) suggested that in the severe asthma population statin users achieved better asthma control compared to non users [23], while reviews concerning this topic agree that"statins do not seem to have additional benefit in asthma control"[24].

As statins might attenuate inflammation, statins therapy was thought to reduce mortality in HIV infected patients,but the impact of individuals with no comorbidity seems small or absent [25].

An ample review [26] concluded that the statins represent a fair possibility to improve adjuvant therapies in some cancer types, but large scale and well planned clinical studies are still necessary in order to prove that.

Statins may reduce cardiovascular events in kidney transplant recipients, although treatment effects are imprecise. Statin treatment has uncertain effects on overall mortality, stroke, kidney function, and toxicity outcomes in kidney transplant recipients [27].

Biological and epidemiological studies emphasized that the high level of cholesterolmight promote the apparition of Alzheimer's disease (AD); using statins (lowering cholesterol drugs) it is possible to prevent or treat AD. However, a recent review considers that there is insufficient evidence to recommend statins for the treatment of AD [28].

Figure 2 presents other suggested diseases in which statins could be effective.

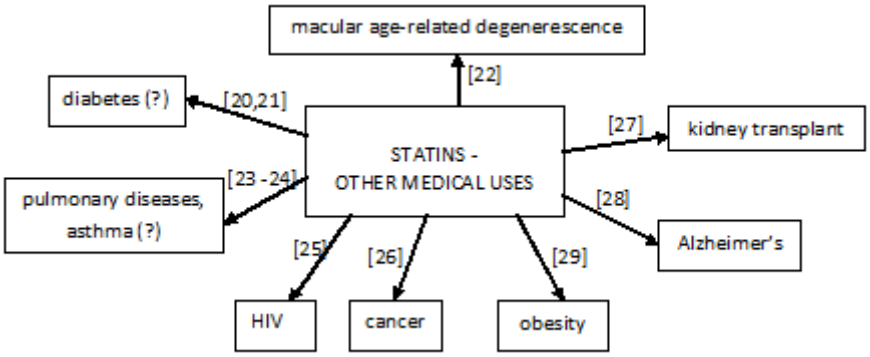


*Figure 2.**Other possible use of statins in therapy***

OPINIONS AGAINST STATINS USE

While the use of statins in prevention of cardio-vascular events is largely accepted [30], a number of adverse effects of this class of medicines is also acknowledged (Figure 3).

The common adverse unwanted side effects of statin use are muscle problemsand rising of the liver

enzymes levels [31]. It was emphasized that statins treatment impairs the mitochondria, depolarizing their membrane and inducing the cell death in Hep G2 cells [31].

Recent data [32] state the neurotoxicity of statins: as they can cross the blood-brain barrier, the statins inhibit the cholesterol biosynthesis in the brain,withconsequences on the synaptic cholesterol homeostasy. Other possible adverse effects refer to cognitive neuropathy and sexual disfunctions.

There is some data [33] emphasizing the cytotoxycity of statins on hepatocytes by following their metabolic inhibition and membrane integrity by fluorescent test.

The genotoxicity and embriotoxicity of statins arealso a problem, discussed in the literature in correlation to the impairing of DNA and cellular mutations probability [34].

The statins diminish the organism immunity having an immunosuppressive effect [35].

Other adverse effects include the chatharactogen effects of statins [36], the risk of diabetes [21, 37] or cancer incidence[38].

There are some sceptics arguing that the high level of cholesterol is not the main cause of cardiovascular diseases.They appreciate that even the idea of blocking the biosynthesis of cholesterol withstatins (HMG – CoA reductase) is a dangerous one. This is because at the same time and withthe same mechanism the statins interrupt an important number of other reactions useful to the organism. An example is the synthesis of coenzyme Q_{10}, well-known andpowerful antioxidant and a free radical scavenger compound [39].

To resolve these adverse side effects, a combined statins therapy using naturalhypolipemiant and antioxidant compounds wasproposed [39, 40].

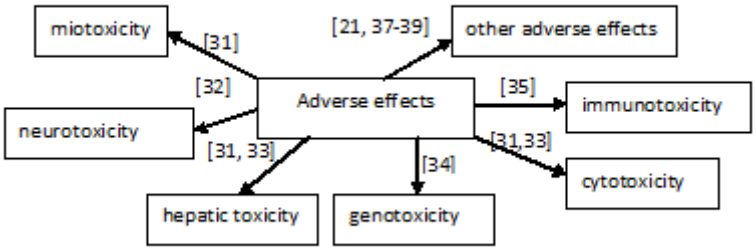


*Figure 3.**Adverse effects of statins***

CONCLUSIONS

Based on the recent data, the present review tries to formulate favorable and adverse opinions concerning the use of statins in the therapy of cardiovascular and other diseases.

The drugs are a"fashion"and now is the time of"statins fashion", when cardiologists, geriatriciens and family physicians prescribe the statins in the primary and secondary prevention of cardiovascular diseases.

The statins inhibit the HMG – CoA reductase, an enzyme having an important role in the cholesterol production. There is a correlation between cardio – suffering and a high level of cholesterol. The available statistical data prove the reducing of dangerous events, mortality and morbidity for the patients treated withstatins.

The adverse effects in the drugprospects are commonly qualified

as"rare and very rare". All of these facts enable the specialists to recommend the statins in cardio-vascular therapy. However, there is enough data in the literature documenting the dangerous adverse effects of the statins on one hand, drug or diet interactions on the other hand, the main of these being miotoxicity and the effects on nervous, hepatic but also unwanted effects on the immune systems, cytogenotoxicity, etc.

In order to be protected against an imminent and virtually dangerous cardio-vascular event, the physician has a difficult choice to make, between the statins therapy or a natural treatment, probably not so efficient in cholesterol lowering, but certainly cheaper and not so aggressive.

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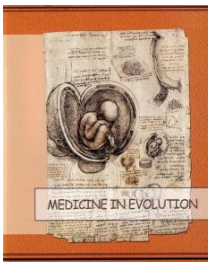
STREPTOCOCCUS GALLOLYTICUS SPONTANEOUS INFECTIVE ENDOCARDITIS ON NATIVE VALVES, IN A DIABETIC PATIENT



FLORINA CÃRUNTU[1,2*], MINODORA ANDOR[1,2], CAIUS STREIAN[1,3], MIRELA TOMESCU[1,2], IOSIF MARINCU[1, 4]

[1]"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania
[2]Department of Internal Medicine
[3]Department of Cardiovascular Surgery Clinic,
[4]Department of Infectious Diseases

ABSTRACT

The immune depressed patients are at increased risk of developing Streptococcus gallolyticus endocarditis. The infection is easily controlled by antibiotics but a valvular replacement may be needed for gross valvular dysfunction, embolization or severe heart failure. Some patients may have associated colonic or hepatic lesions needing surgical intervention that increase morbidity, mortality and costs. We describe a 55-year-old diabetic patient with spontaneous Streptococcus gallolyticus endocarditis on native valves and discuss some specific aspects regarding infective endocarditis with Streptococcus gallolyticus.

Key words: *diabetes mellitus, endocarditis, Streptococcus gallolyticus*

Correspondence to:

Dr. Mirela Tomescu
MD,PhD
Address: Cardiology Clinic, Department of Internal Medicine I,"V. Babeş"Timisoara University of Medicine and Pharmacy, Bd Revolutiei din 1989 nr 12, Timisoara, cod 300024, Romania
Phone: +4 0722979516
Fax: +4 0256220636
E-mail address: cleopatratomescu@yahoo.com

INTRODUCTION

Viridans streptococci are the most important causative agents for native valve infective endocarditis (IE) in non-drug-addicted patients [1]. Streptococcus gallolyticus, subspecies gallolyticus, formerly referred as Streptococcus bovis biotype I, is a member of group D streptococci, and is estimated to be incriminated in 24% of streptococcal endocarditis [2]. Based on genetic, physiologic and phylogenetic criteria, Schlegel et al. [3] proposed the reclassification of Streptococcus bovis biotype I as Streptococcus gallolyticus. In Southern Europe, the proportion of endocarditis which is caused by Streptococcus gallolyticus has increased duringrecent years [4]. Hoen[5] et al. documented that Streptococcus gallolyticus is responsible for an important proportion of streptococcal IE cases: 58% in France, 9.4% in other European countries and 16.7% in USA. Immune depressed patients, as well as nutritional habitssuch as frequent consumption of uncooked meat and fresh milk products, might have an impact on *S. gallolyticus* intestinal colonization and subsequent bacteremia, increasing the risk of developing *Streptococcus (S) gallolyticus* endocarditis. This infection is usually well controlled by antibiotics; however, in certain cases, valvular replacements may be needed for gross valvular dysfunction, embolization or severe heart failure. Additionally, some patients may have associated colonic or hepatic lesions that require surgical interventions, that increase morbidity and mortality.

We report a case of Streptococcus gallolyticus, subspecies gallolyticus,spontaneousinfective endocarditis on native valvs,in a diabetic patient.

CASE REPORT

A 55 –year-old men was admitted to our clinic for one month after the onset of persistent fever. He had been hospitalized in another department, where pneumonia had been suspected and ceftriaxone therapy had been administered. Under this treatment, the fever persisted, associated with fatigue, profuse sweating, decreased appetite and 8 kg weight loss. The patient was referred to a clinic for infectious diseases, where echocardiography was recommended, which set the current diagnosis.The patient was a non-drug abuser and had no previous history of rheumatic or degenerative valvular heart disease. He had no recent dental or other invasive bleeding procedures. He was known with diabetes mellitus complicated with grade III sensitive and motor polyneuropathy, non-proliferative diabetic retinopathy, requiring insulin therapy. Physical examination on admission revealed: temperature 38.8°C, mild pallor of the conjunctiva. Irregular heart rhythmus, 130 beats/minute; blood pressure 120/60 mmHg, respiratory rate 18 per minute. No pulmonary rales were heard. The jugular venous pressure was normal, no legs edema were found. The apex beat was not displaced. A 3/6 decrescendo diastolic murmur was heard along the left sternal border and cardiac apex. Abdominal examination revealed mild hepatosplenomegaly. Laboratory tests demonstrated an inflammatory syndrome (erythrocyte sedimentation rate of 88 mm after an hour, fibrinogen of 7,8g/L, white cell count of 15,500 per mL with 75% neutrophils) and a mild normochromic, normocytic anemia (hemoglobin of 10.8 g/dL). Electrocardiogram showed atrial fibrillation with a ventricular rate of

130 bpm. A chest-X ray demonstrated moderate pulmonary venous congestion. Echocardiography showed aortic valve vegetation, a moderate (grade 2) aortic regurgitation, normal diameters of the left ventricle and normal (>50%) left ventricular ejection fraction (**Figure 1**).

Blood cultures were positive for Streptococcus gallolyticus and the antibiogram showed sensibility of the infective agent to Ampicillin and Linezolid. Antibiotic therapy was started with intravenous Ampicillin 12g daily. The treatment for atrial fibrillation consisted in Digoxin and anticoagulation with Enoxaparin. The response to Ampicillin was good, as the fever ceased, the laboratory values returned to normal and the general health status of the patient improved.

Two weeks following the institution of therapy, the patient developed acute ischemia in the left leg, by embolization with a fragment of the aortic valve vegetation. Embolectomy was performed with a Fogarty arterial catheter introduced in the left popliteal artery. The echocardiographic control showed the persistence of the vegetation, but having a smaller sizeand an increase in the severity of the aortic regurgitation (grade 3). The patient was referred to Cardiovascular Surgery, where he suffered an embolic cerebrovascular accident, with syncope followed by obnubilation and complete recovery. Because of these embolic events, emergency open heart surgery was performed, revealing extensive vegetation of the right aortic cusp, with necrosis of the valve (**Figure 2**). Debridement and replacement of the aortic valve with a Sorin Carbomedics prosthesis was performed (**Figure 3**). The antibiotic therapy was continued for 4 weeks following the surgery. The post-operative evolution was marked by a toxic hepatitis following general anesthesia and severe variations of the glycaemia, requiring an attentive dosing of insulin therapy. The recovery was successful and the patient was discharged after completing the antibiotic therapy and postoperative care. Colonoscopy was performed and revealed no abnormalities. We believe that decreased immunity and diabetic neuropathy with reduced intestinal motility favored bacteremia and infective endocarditis in this patient with no previously known valvular lesion.Another possible explanation could be the diabetic microangiopathywhich leads to lesions of the colonic mucosa, followed by the bacterial entry into the blood stream.

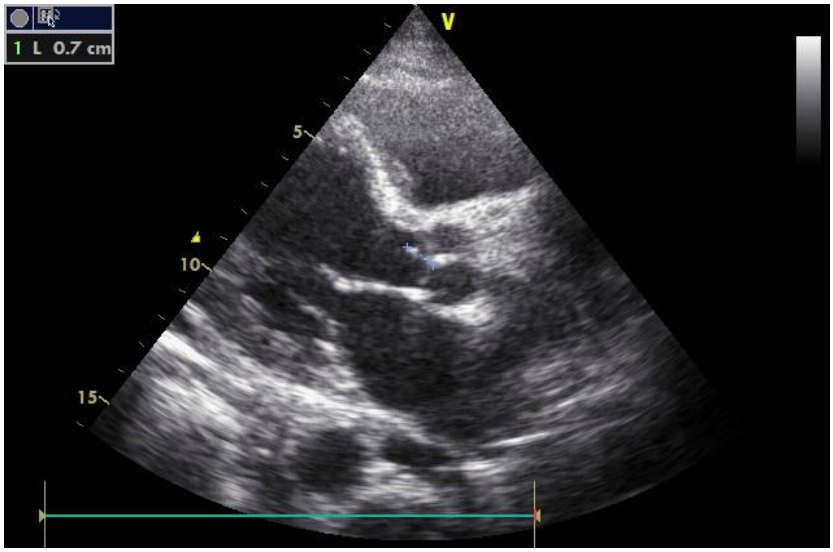


*Figure 1.**2-D echocardiography of the heart showing large vegetation on the aortic valve***

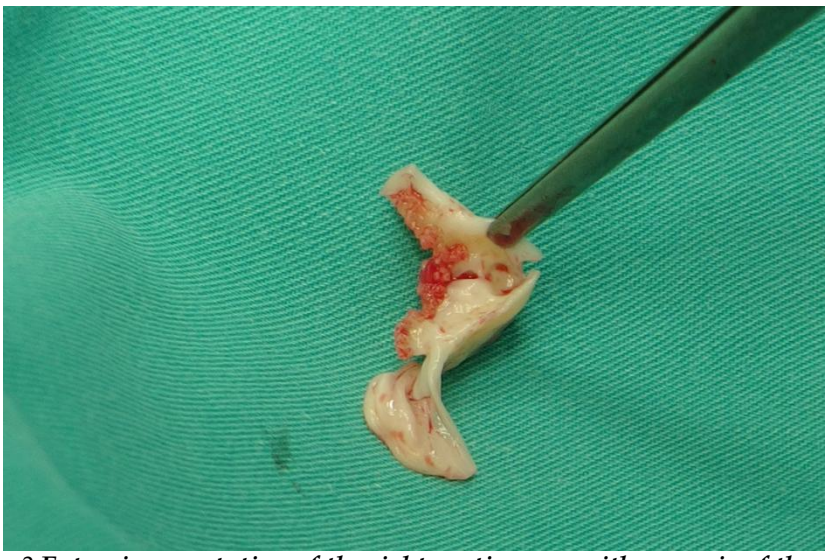


*Figure 2.**Extensive vegetation of the right aortic cusp, with necrosis of the valve***

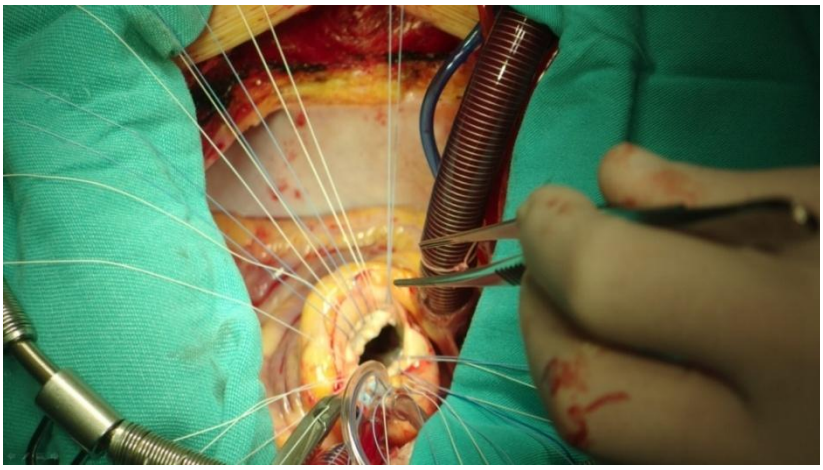


*Figure 3.**Replacement of the aortic valve with a Sorin Carbomedics prosthesis***

DISCUSSION

Streptococcus gallolyticus is a normal inhabitant of the human gastrointestinal tract. There is a demonstrated association between Streptococcus gallolyticus,IE, gastroin-testinal neoplasia [6-7] and liver disease [8, 9]. One explanation could be that the underlying colonic disease or the altered hepatic function may favor the bacterial migration [10]. The exact reason why the streptococcus suddenly becomes invasive is not known, but it is thought that intestinal or liver pathology might decrease the intestinal motility thereby and thus allowing its overgrowth. It is also possible that colonic carcinogenic metabolites and chronic inflammatory mediators change the local conditions and disrupt the capillary channels which allow the entry of bacterial into the blood stream.The subsequent bacteremia leads to seeding in- different parts of the body,–particularly in the heart valves, the bones, and the vertebral discs. A decrease in immunity, described in the elderly, in those with co-morbidities (particularly diabetes mellitus, chronic liver disease and rheumatic disorders) and in those treated with immunosuppressants, favors severe infections [11].

S gallolyticus endocarditis is different from other endocarditis because it is highly susceptible to intravenous antibiotics and is therefore considered as"benign". Even then it affects valves of patients who are not

known to have cardiac valvular abnormalities [12, 13, 14]. In our patient, a previously normal aortic valve was damaged by S gallolyticus endocarditis. The predilection of infection is the aortic valves, but the mitral as well as the tricuspid valves may also be affected, singly or in combination. The vegetations tend to be larger than those produced by other organisms and were noted in our patient. Patients with persistent bacteremia and those with documented embolism or with resistant heart failure need to have a valvular replacement. Early valvular replacement may be needed in patient with massive vegetations and recurrent embolisms. Colonoscopy is indicated in the context of S gallolyticus bacteremia or endocarditis to look for colonic neoplastic changes. If the examination is normal, a repeat colonoscopy should be scheduled in 4 to 6 months, with regular surveillance subsequently. The patient should also be evaluated for liver disease and possibly extra colonic malignancy. However, frailty and co-morbidities may preclude invasive investigations and operative management.

In conclusion, the presented case informs the physicians about the risk of spontaneous infective endocarditis in non-drug-addicted patients, withouta history of congenital or acquired valvular heart disease. Immune-depression, as well as nutritional habitssuch as frequent consumption of uncooked meat and fresh milk products, might have an impact on *S. gallolyticus* intestinal colonization and subsequent bacteremia and IE.

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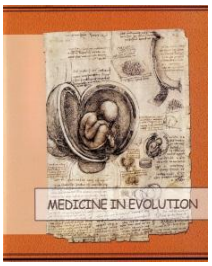
CT VALUE ON MEDIASTINAL LYMPHATIC GANGLIA OF BRONCHOPULMONARY CANCER EXTENSION ASSESSMENT



DANIELA CIPU, BRAD SILVIU

"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania, Department of Radiology and Medical Imaging

ABSTRACT

Classic radiology only reveals pathological mediastinal lymph nodes that produce a change in the mediastinal outlines and lines pleural reflection, with an inability of their splitting in regions located within the mediastinal outlines or for their hided by other masses tumoral groupd present in the mediastinum. CT scan examination is the first choice investigationin exploring mediastinal adenopathies, allowing their detection in difficult regions for classic radiologyor for those hided by other tumoral masses, in the same time dealingaccurately to reveal relations and / or infiltration of surrounding structures.

Differential diagnosis of adenopathies was made by: successive analyzing of the sections in order to detect any suspected lesions continuity with adjacent vascular structures, intravenous contrast agent administration for identifying mediastinal vascular axes, density and topographic disposal.

Mediastinal adenopathy positive diagnosis was established according to sizing criteria defined by Webb and al., apply equally to explore CT and MRI, meaning thatany node with thetransversal diameter over 10 mm is considered pathologic,except superior paratracheal groups, where limit descends to 7 mm,and the subcarinal ganglia,where the limit ascends to 11 mm.

Statistical analysis of thelocation of the 134 cases of lung cancer with detected mediastinal lymph nodes showed, in each studied case, a predominant involvement of drainage lymphatic ganglionicgroups specified to the area and morbid entity in question.

Key words: *lung cancer, mediastinal adenopathies, lymphoganglia spreading*

Correspondence to:

Dr. Daniela Cipu
Address: University of Medicine and Pharmacy"Victor Babes"Timisoara DEPARTMENT OF RADIOLOGY AND MEDICAL IMAGING of County Hospital Timisoara;Iosif Bulbuca street, nr. 10-300736 Timisoara, Romania
Phone: +4 0728106535
E-mail address: danscipu@yahoo.com

INTRODUCTION

Mediastinal adenopathies, morbid lymph-nodes entities, characterized by increasing volume and structural changes in response to any pathological process: inflammation, leukemia, tumoral or dysmetabolic, having location or mediastinal extension, in most cases suggests the possibility of a bronchopulmonary lymphatic malignancy extension, often in the early stages with discrete volume, but often complicates a scar.

Classic radiology only reveals pathological mediastinal lymph nodes that produce a change in the mediastinal outlines and lines pleural reflection, with an inability of their splitting in regions located within the mediastinal outlines or for their hided by other masses tumoral groupd present in the mediastinum. CT scan examination is the first choice investigation in exploring mediastinal adenopathies, allowing their detection in difficult regions for classic radiology or for those hided by other tumoral masses, in the same time dealing accurately to reveal relations and / or infiltration of surrounding structures.

MATERIAL AND METHODS

Were assessed to retrospective statistical analysis 134 cases of lung cancer with mediastinal lymph extension, examined by chest CT in CT Laboratory Military Hospital in Timisoara in the period: January 2004-December 2006, investigated from clinico-biological bronchoscopycal and pathological point of view for the diagnosis , staging, appropriate treatment conduct and, in some cases, for posttherapeutic evaluation.

Each case was analyzed startinh with clinical and biological, epidemiological ,histopathological and bronchoscopical data, which were combined with results of radiographic and CT examination, the radiographic protocol of records and patient assessment images obtained by scanning, in many density areas, to detect morphological damages of mediastinal lymph nodes.

1. radiographic examination

Radiographic examination was the first choice exploring in all studied cases, being made on SIEMENS SIREGRAPH CF device, in at least two incidents: anterior and lateral, being completed whenever it was necessary with oblique incidences, hard-ray radiography or even mediastinal plane CT scans.

SPREADING RADIOGRAPHIC DIAGNOSIS

Metastatic mediastinal adenopathies from lung cancer allow a TNM staging (Bonomo L):

- N1 - ipsilateral right or left tracheobronchial lymph nodes,
- N2 - subcarinal adenopathies,
- N3 - right or left tracheobronchial adenopathies, controlaterale in unresectable stage IIIB and are accompanied by typical lesions of parenchyma (MILLER WT).

2.CT examination

Computed tomographic explorations were performed as sequential chest scans using a PICKER IQ PREMIER device, assessing obtained images in multiple slides density,in order to detect morphological alterations of mediastinal lymph nodes.

According to the"American Thoracic Society"classification lymph node groups are divided into two main categories: parietal and visceral (Chiu LC).

I. PARIETAL LYMPH NODE GROUPS

Internal mammary group

It is located laterally of the sternum, behind the anterior thoracic wall, along the internal mammary vessels. Normally they are not revealed. Pathologically are affected by metastases from a breast carcinoma and less in a mediastinal lymphoma.

Diaphragmatic group

There are described the classic three groups:

• Prepericardic,located between the sternum and xiphoid appendix;

• Paracardiac, located laterally, behind the heart along the phrenic nerves;

• Retrocrural, behind the diaphragmatic insertions.

Posterior group

They are located paravertebral, normally are not highlight. Pathologically, are interested in Hodgkin disease and inflammatory and neoplastic pathology of the posterior mediastinum and rachis.

II. VISCERAL LYMPH NODES GROUPS

Right paratracheal group (D2, D4)

They include two groups of ganglia, disposed right to the midline, around the trachea, from the thorax apex to the superior level ofthe azygos vein arch. The plane of separation between the superior group (D2) and the inferior one (D4) is passing through the point where the brahio-cephalic trunk is crossing the trachea. Normally shows a number of 1-3 superior lymph nodes and about 2-4 inferior ones. Pathologically, are by far the most frequently affected in inflammatory and in the tumor pathology.

Left paratracheal group (S2, S4)

Being disposed left paratracheal,medial to the epiaortic vessels and aortic arch, forming two groups, the plan of separation between the upper group (S2) and the lower one (S4) consisting of the superior level of the arc aortic. Inferior left paratracheal gangliadiffers from the aorto-pulmonary group, by medial location to the arterial ligament. They are normally highlighted, but the number and volume less than the right ones. Pathologically, are also the most common affected lymph node groups.

Aortic-pulmonary group (5)

They are located outside the arterial ligament, occupying the fatty space between the aortic arch and left pulmonary artery, being disposed on the outline of their external edge. Normally are 2-5 in number, maximum 10, with a diameter of 4-8 mm. Pathologically are affected in lymphoma and in lung cancer metastases.

Anterior mediastinal group (6)

They are disposed retro-sternal, in front of the aorta, being described classically in three groups:

• the right, in front ofthe superior vena cava;

• transversal, in front of the left brahio-cephalic vein;

• the left, outside the epiaortic vessels.

Normally, are highlighted in the number of 1-6 nodes below 8 mm diameter. Pathologically are affected in lymphoma, sarcoidosis and bronchial cancer metastases.

Subcarinal group (7)

They are located between the tracheal bifurcation and the left atrium. Normal number is 1-3 nodes with diameter below 15 mm.pathologicallyare affected in pneumopathies, lymphoma and metastasis of bronchial cancer.

Paraoesophageal group (8)

It is formed of ganglia disposed around the oesophagus. Normally they

are not highlighted, it is difficult to distinguish from the oesophagus wall. Pathologicallyare affected in oesophageal cancer metastasis and in lung cancer with lower lobes and pleural dome location.

Pulmonary ligament group (9)

They include ganglia contained between two pleural sheets. Normally are impossible to reveal. Pathologically are affected in lung cancer metastases and in lymphoma.

Righttracheo-bronchial group (D10)

They are disposed medial from the superior lobar bronchus origin, above right pulmonary artery. Normally they are highlighted and have low volume. Pathologically, are consistently affected in the infectious pulmonary episodes.

Left tracheo-bronchial group (S10)

Normally they are difficult to reveal. Pathologically, adenopathies give compression on the carina and upper lobar bronchus in front of the common bronchus.

Intrapulmonary group (11)

They include all ganglia disposed around the bronchial branches, inferior to the main bronchi,located on the hylum.

All these mediastinal lymph-nodes received within this classification a numerical code as follows (**STUART S**):

- 1-Supraclavicular- scaleni
- 2D, 2S -right and left superior paratracheal.
- 3-Pre and retro –tracheal
- 4D, 4S- right and left inferior paratracheal.
- 5 - Aortic-pulmonary
- 6 – anterior mediastinal
- 7 – Subcarinal
- 8 – Paraoesophageal
- 9 – of the pulmonary ligament
- 10D,10S – left and right tracheobronchial
- 11D,11S – right and left intrapulmonary
- 12 – Lobar
- 13 - Segmentary
- 14 - Diaphragmatic

POSITIVE CT DIAGNOSIS CRITERIA

Mediastinal adenopathy is an identifiable CT mass located in the mediastinum, which semiological is characterised by the following: shape, outline, size, density + / - calcification, iodophilia, relationship with interstitium (**BELLIN M.F**).

I. SHAPE

In an axial computer tomography section, mediastinal lymph nodes may appear as round when the section plane is perpendicular to the greater axis of the lymph node or may be oval when the section plane is parallel to it.

II. OUTLINE

A clear, regular outline of a lymph node reveals an integrate ganglionic capsule, adenopathy with this character may have a compressive effect on adjacent structures.

A diffuse irregular outline signifies overcoming the capsule by the morbid process, revealing the existence of infiltration of adjacent structures: tumoral process, inflammatory process,mediastinal reaction to pathologic node, being impossible to distinguish the cause based on the appearance of CT scan (**GREGSON R.H**).

III. SIZES

It is taken into account the scanned transverse diameter of node,the borderline stretching the limits of visibility more than 2 cm, according to theliterature data. Thus, approximately 25-30% of nodes measuring 1-2 cm are malignant, while nodes larger than 2 cm are found to be malignant in 75% of cases (CHERRYMAN G).

According to dimensional criteria, mediastinal lymph node groups are divided into two categories (GAMSU G)Lymph node groups that normally are not showed on CT scan:

- internal mammary
- diaphragmatic
- posterior
- para-oesophageal
- of pulmonary ligament;

any visible node is likely to be pathological.

Lymph node groups identified as normal on CT scan:

- para, pre and retro-tracheal
- subcarinal,
- aortic-pulmonary,
- anterior mediastinal;

any ganglion with thetransversal diameter over 10 mm is considered pathological with the following exceptions:

- more than 7 mm for upper right and left paratracheal group;
- more than 10 -11 mm for subcarinal and right tracheo-bronchial groups.

These have vailability under the amendment that even in a normal-sized lymph node may be located a malignant process, proving the decisive role of cytological and histopathological examination for definite assertion of malignancy (**GEORGESCU Ş**).

IV. DENSITY

Normal or pathological lymph nodes are divided after densitometric structure into several categories (**GAMSU G.):**

1.-homogeneous density lymph nodes between 30 and 60 UH.

2.- central hypodense lympf nodes that may occur under the following conditions:

- normally because of the fatty central involution where the density is equal to the lax mediastinal tissue;
- in tuberculosis, because of the caseous necrosis, whendensity is slighty superiorthan the fluid one;
- in lymphoma, after radio and chemotherapy, because of the necrosis.

V. CALCIFICATIONS

CT scan examination reveals thesmall calcifications existence,whichoften are proving a benign etiology (non-specific infection or postradioteraphy, tuberculosis, in silicosis, in sarcoidosis –"eggshell'' '), but they do not exclude malignancy when the parenchymal component prevails (**GAMSU G.).**

VI. IODOPHILIA

Normally density of the ganglion increases less after administration of contrast substances,certifying a slightly iodophilia. Depending on the appearance intake lymphatic gangliamay have the following aspects **(PROCACCI C):**

- central hypodensity with hiperdensity marginal ring,normally found in tuberculosis, post radio and chemotherapy lymphoma, as well in metastases from testicular cancer or bronchial adenocarcinoma;
- important hiperdensity after administration of contrast agent, certifying the existence of inflammatory or tumoral hypervascularisation, found in: Castleman disease, angioimunoblastic lymphadenopathy; metastases from: melanoma, hipernefroma, thyroidian cancer, sarcoma, carcinoid tumor.

VII. RELATION WITH THE INTERSTITIUM

New semiotical element, based on radio-anatomical appearance of hylum lymphatic nodes in relation with the bronchi and vessels at interstitial level, detected on their examination by spiral computed tomography.

Normal hylum ganglia, located in the interstitium between the bronchi and pulmonary vessels, often difficult to distinguish from it, cause some straight or concave interstitial edges to thepulmonary parenchyma.

The interstitium containing metastatic ganglia has slightly convex edges to the pulmonary parenchyma due to the inflammatory reaction caused by carcinomatous lymphangitis **(SHIMOYAMA K).**

ediastinal lymph node extension of broncho-pulmonary cancer benefits of both computed tomography examination andthrough semiotic elements that indicate primitive tumor location, as wellby highlightingadenopathies, whose topography and features may be resectable and unresectable criteriaaccording toTNM staging **BUTHIAU D**):

Ganglionic metastatic disemination areas of the pulmonary cancer.

N1 - ipsilateral lymph nodes in the 10D and 10S

N2 - lymph nodes in 7

N3 - the 10D and 10S adenopathies revealing controlateral lung cancer in unresectable IIIB stage (**WEYNANTS P**)

CT exploringrequired scanning the patient blocked in deeply breath, using a mediastinum opening,width of 300-500 UH and center between 0-60 UH.

Mediastinal adenopathy once highlighted, it was performed thestudying in details, usingcontiguous thin sections of 3 mm, the specific CT semiologic elements: form, shape, size, density, presence or absence of calcification and iodophilia. A total of 7 patients with lung cancer were investigated by spiral CT of hylum region, made using a SIEMENS SOMATOM PLUS 4 device, with a technique in apnea after deep inspiration, with 3 mm thick sections and 3 mm / s advancement of examination table, resulting a pitch 1: 1.

Diagnosis of mediastinal lymphadenopathies benefited by acquiring the spiral data, identifying their relationship with the interstitium, new semiotic element, based on radio-anatomical aspect ofhylum gangliain relation to bronchi and vessels at interstitial level.

3. criteria, cuantifications and diagnosis classifications

Differential diagnosis of adenopathies was made by: successive analyzing of the sections in order to detect any suspected lesions continuity with adjacent vascular structures, intravenous contrast agent administration for identifying mediastinal vascular axes, density and topographic disposal.

Mediastinal adenopathy positive diagnosis was established according to sizing criteria defined by Webb and al., apply equally to explore CT and MRI, meaning thatany node with thetransversal diameter over 10 mm is considered pathologic,except superior paratracheal groups, where limit descends to 7 mm,and the subcarinal ganglia,where the limit ascends to 11 mm.

Table 1.

These are vailable, with the amendment that a ganglion of normal sizes could be location for a malignancy, stating the decisive role of cytological and histopathological examination for definite assertion of malignancy(**GEORGESCU Ş**).

The presence and location of mediastinal adenopathies was quantified according to"American Thoracic Society"classification of mediastinal lymph nodes

Table 2.

Mediastinal lymphatic node extension of lung cancer was staged according to the"American Joint Commitee on Cancer"criteria as follows: lesions of lymphnodes groups right 10 and left 10 onthe same side as the tumor is stage N1, and when are contralateral to the tumor areN3 stage, lymph node lesions in group 7 representing stage N2.

Table 3.

Table 1. Normaland pathologic dimensional criteria in mediastinal lymph node CT examination

Dimensional criterion in normal CT	Dimensionalcriterion in pathologic CT
Lymph node which normally could not be seen on CT: • Internal mammary, • diaphragmatic, • posterior, • paraoesophageal, • of the pulmonary ligament;	• **any visible ganglion is susceptible to be pathologic.**
Normal lymph nodes highlighted on CT: • para, pre and retro-tracheal, • subcarinal, • aortic-pulmonary, • anterior mediastinal;	• **any ganglion with transversal diameter over 10 mm is considered pathologic, except the following:** - over 7 mm, for superior right and left paratracheal; - over 10-11 mm, for subcarinal and right tracheobronchial groups.

Table 2. Mediastinal lympho ganglia"AMERICAN THORACIC SOCIETY"Classification

Numerical code	Lympho ganglia topography
1	Supraclavicular - scaleni
2D,2S	Right and left superior paratracheal
3	Pre and retro -tracheal
4D, 4S	Right and left inferior paratracheal
5	Aortic-pulmonary
6	Anterior mediastinal
7	Subcarinal
8	Paraoesophageal
9	Of the pulmonary ligament
10D,10S	Right and left tracheobronchial
11D,11S	Right and left intrapulmonary
12	Lobar
13	Segmentary
14	Diaphragmatic

Table 3. Mediastinal lympho ganglia staging concerning bronchopulmonary cancer, accordingthe N criterion of the TNM classification

N staging	Lympho ganglia spreading
No	-no adenopathies;
N1	-peribronchial metastatic adenopathy and/or in hylum in the homolateral gangliaor metastatic adenopathy directly intrapulmonary due to primary tumor extension (locations 10 in hylum, 11 interlobary, 12 lobary, 13 segmentary, 14 subsegmentary);
N2	-homolateral metastatic adenopathies, mediastinal and/or subcarinal (locations 1 superior mediastinal, 2 superior paratracheal, 3 prevascular and retrotracheal, 4 inferior paratracheal and azygos crossa ganglia, 5 subaortic, 6 paraaortic, 7 subcarinal, 8 paraoesophageal, 9 of triangular ligament);
N3	-heterolateral metastatic adenopathies, mediastinal and/or subcarinal (locations 1 superior mediastinal, 2 superior paratracheal, 3 prevascular and retrotracheal, 4 inferior paratracheal and azygos crossa ganglia, 5 subaortic, 6 paraaortic, 7 subcarinal, 8 paraoesophageal, 9 of triangular ligament);

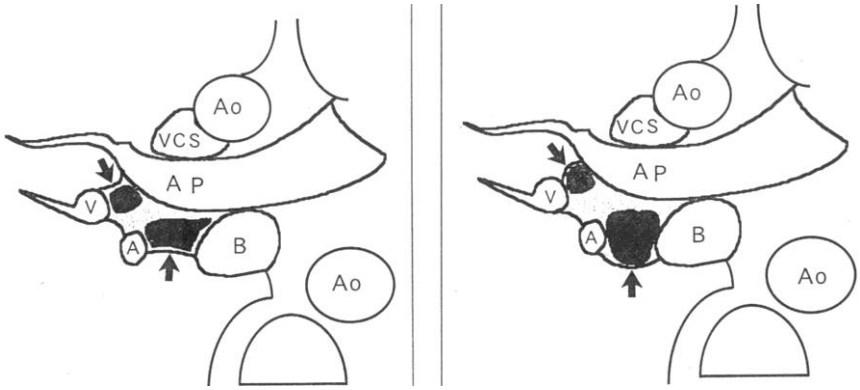


Figure a. ***A new CT diagnosis criterion***

RESULTS AND DISCUSSIONS

Diagnosis, staging and posttherapeutic imaging evaluation of the mediastinal lymphatic nodes extension of broncho-pulmonary cancer has established the presence of adenopathies in 134 of cases.

In 88 of lung cancer cases examined cases for diagnosis and staging lymph nodes were isolated, which their quantification set the N1 stage in 31 cases, N2 stage in 34 cases and N3 stage in 23 cases.

Postoperative imaging evaluation, revealed mediastinal adenopathies in 17 cases of resected lung neoplasms, which was an important argument for the association of radio-and chemotherapy.

In examinations for evaluation postradio-and chemotherapy, detection of mediastinal lymph nodes in 29 cases required continuity or a new start, respectively.

Thus, lymphatic invasion staging of the mediastinal lymph nodes in the 88 cases of lung cancer, revealed involvement, on the top, in order of frequency, the following groups: right tracheobronchial in 15%, 12% right paratracheal, right intrapulmonary 6% and the right lobar in 6% of cases, which correlate with neoplastic affecting more common in N1 and N2 stages in the right lung in this study, as well as the increased N3 stage cancer of the left, on the left appeared in groups: left paratracheals in 6%, aortic-pulmonary opening in 4%, 4% and left tracheobronchial in 4%, and left lobar in 4%, according tofewer cases of cancer left N1 andN2 stage.

The large number of subcarinal lymph nodes, which occurred in 17% of studiedcases, the stations are due to affecting this lymphoganglionic location,both in rightlung and in left, and because of 39% of cases in N2 stage.

CONCLUSION

Affecting preferences of thethe lymphatic extension of lung cancer among different groups drainage mediastinal lymph node groups, are specific to area and histological type, with the corollary true reflection of feed-back location of primitive lesions territories.

Radiographic examination reveals only pathologic mediastinal lymph nodes that produce a change in the mediastinal outlines and pleural reflection lines.

Disadvantages of classic radiological examination consist in their splitting inability to regions located within mediastinal outlines.

Also, if their masking by other tumoral masses present in

mediastinum, the adenopathies escape radiographic diagnosis.

It also provides little information on reports and / or mediastinal adenopathies infiltrating adjacent structures: vessels, lungs, pericardium, pleura, thoracic wall.

Thanks to the highlighting possibilities of all pathologic mediastinal lymphnode groups, computer tomography is firstchoice examination for diagnosis of mediastinal adenopathies.

Computed tomography has a low specificity, so that the criteria for positive diagnosis of adenopathies (density, transversal diameter, presence or absence of calcification, iodophilia etc.), although establish a clinical and morphological interrelation, are merely indicators of susceptibility to etiologic diagnosis, the confrontation with clinical issuesis mandatory and certainty is assured only using anatomopathological examination.

Through the skills of diagnosis, staging, measurement and monitoring therapeutic thoracic CT scan examination is strongly required to assess mediastinal lymphatic extension of lung cancer.

Highlighting the relationship with interstitium is a diagnostic criterion of maximum specificity for showing neoplastic hylum adenopathies by using spiral CT, which became a standard method of investigation, with comparative interferences in radioimaging field.

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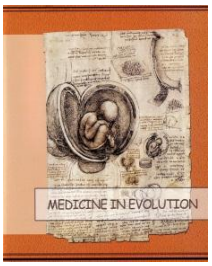
LIFE THREATENING ASYMPTOMATIC WOLFF-PARKINSON-WHITE SYNDROME



ALINA G. NEGRU[1,2], GABRIEL IVÃNICÃ[1], LAVINIA SORCA-ALBIȘORU[1], ȘERBAN NEGRU[2], LUCIAN PETRESCU[1,2], ADINA IONAC[1,2], C.T.LUCA[1,2], STEFAN I. DRÃGULESCU[1,2]

[1]Timisoara Institute of Cardiovascular Medicine
[2] Department of Cardiology,"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania

ABSTRACT

Current guidelines for diagnosis and treatmentof Wolff-Parkinson-White (WPW) syndrome promote evaluation by electrophysiological study (EPS) of symptomatic patients, patients with a history of tachycardia or patients belonging to the high risk occupational groups (athletes, drivers, pilots, persons working at heights, etc.).The presented caseis a patient aged 22 years, a Medicine University student, who was incidentally diagnosed with WPW syndrome while he was volunteering for a sample electrocardiogram (ECG) during practical training in the Cardiology Clinic. Given the patient's desire of pursuing sports, the risk assessment by EPS study was required.A left accessory pathwaywas diagnosed using the Arruda algorithm. The properties of the accessory pathway and of the normal conduction system were highlighted during the EPS: short refractory period, minimal RR intervalequal to 180 ms and the presence of associated atrial vulnerability. Standardprogrammed atrial stimulationinitiated atrial fibrillation (AF)with fast conductionthrough the accessory pathway (up to 1:1 conduction), leading to a ventricular response up to 300/min and over with degeneration into ventricular fibrillation (VF) in less than 30 seconds.The patient required five external electric conversions and concomitant rapid infusion ofamiodaroneup to 600 mg over20 minutes (4 consecutive 150 mgvials)in order to obtain and stabilize thesinus rhythm. The radiofrequency catheter ablation (RFA) of the left accessory pathway was then successfully performed. Since sudden death is sometimes the first manifestation ofthe WPW syndrome and the properties of the accessorypathway can change during time, we suggest performing the EPS and the RFA shortly after the very first diagnosis. The EPS should become mandatory in every person diagnosed with WPW syndrome in order to stratify the associated risk, to put in the balance the benefit of ablating and the decision to not ablate the accessory pathway in case of major associated procedural risks.

Key words: *Wolff-Parkinson-White syndrome, Sudden death, Accessory pathway, Atrial fibrillation, Ventricular fibrillation*

Correspondence to:

Alina G. Negru
MD
Address: University of Medicine and Pharmacy"Victor Babes", 2 E. Murgu Square, 300041 Timisoara, Romania,
Phone: +4 0746239777
E-mail address: eivanica@yahoo.com

INTRODUCTION

It is now widely recommended by the approved guidelines that the asymptomatic WPW syndrome with no history of tachycardia is a candidate to conservative treatment and pending the specific clinical manifestations that would justify theEPS or the intervention by RFAis the appropriate management of such cases. Exceptions are the situations where WPW is diagnosed in a patient belonging to a professional high-risk group (athletes, drivers, pilots, workers at heights, etc.). The syndrome is caused by the presence of one or multiple pathways, usually a myocardial fiber that constitutes itself intoan atrioventricular connection along the rings of the mitral or of the tricuspid valve.The accessory pathway acts as a conductor withdifferentelectrophysiological propertiesthen the specialized tissue found inthe normal atrioventricular pathways. The location of the accessory pathway can be deduced using the delta wave polarity on the surface electrocardiogram (ECG) and confirmed by EPS before ablation.[1]Parameters defining the degree of risk for sudden death associated to this syndrometook shapeover the years, including minimal RR interval less than 220 ms and the presence of multiple accessory pathways. The main mechanism of cardiac arrest in these patients is considered to be due to fast conductionof the AF waves through the short refractory period accessory pathwayand consecutive fast ventricular response with degeneration into VF. There were proposed three main models as mechanisms of AF. Those are: intrinsic atrial vulnerability, myocarditis plot and the atrial reentry microcircuits between the insertion endsof the multiple accessory pathways.[2]In addition to the previouspossible mechanisms stands the theory that patients with WPW syndrome and AFwould have a wide atrial conduction range and fragmented endocavitarysignals, associated with increased vulnerability to progressively increasing frequency atrial stimulation or to fast atrial stimulationwith constant frequency.[3]

Several studies have shown the importance of the accessory pathways in initiation and maintenance of AF by demonstrating the decreaseof the arrhythmia incidencein patients in which theRFA of accessory pathwaywas performed. It is important that the incidence of AF is relatively high,occurring in up to one third of the cases diagnosed with WPW syndrome.[4]

CASE REPORT

Patient O.O., 22 years old, without any cardiovascular history, asymptomatic, incidentally diagnosedwith WPW syndrome (third year studentat the University of Medicine, volunteering for a sample ECG during internal medicine practical training in the Cardiology Clinic), was addressed to the Electrophysiology Department because the patient wanted to develop athletic activity and occasional extreme sports.Note that the patient was neither under antiarrhythmic therapy nor any other type of medication.Standard12 leads ECG recorded at rest, showed regular sinus rhythm, short PR interval and clearpositive delta waves in DI, aVL, V1-V6.

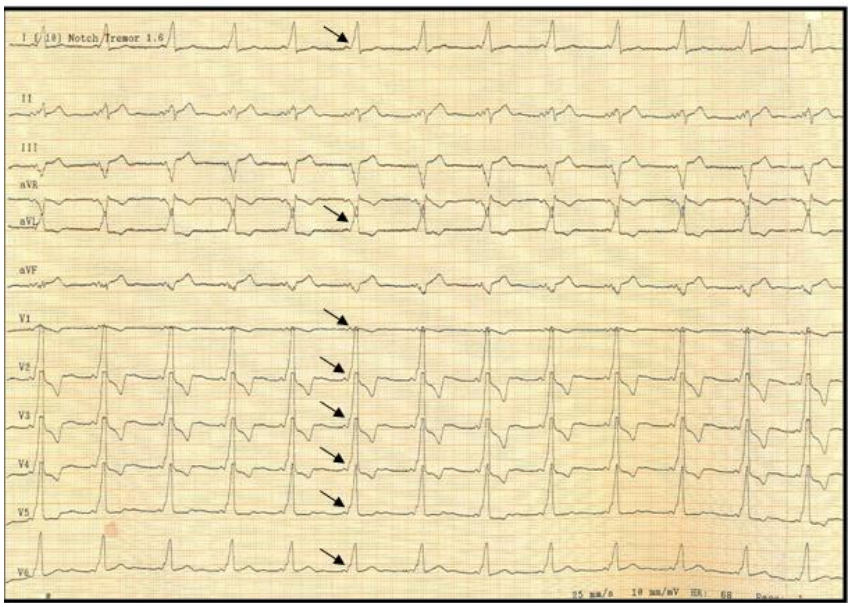


Figure 1. Standard surface12 leads ECG, short PR= 80ms, large QRS complex=140ms, positive delta wave in DI, aVL, V1-V6 suggestive for a left accessory pathway. All the standard 12 lead ECG tracings presented in this case were recorded at 25mm/s and 10 mm/mV.

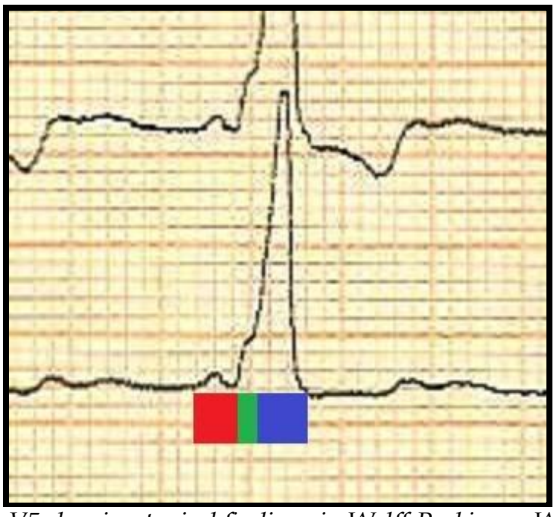


Figure 2. The QRS complex in V5 showing typical findings in Wolff-Parkinson-White syndrome. Red bar- short PR interval, green corresponding to the first part of the QRS complex, the delta wave, blue- the rest of the long QRS complex

Echocardiography was performed. The heart was normal, with normal structure and function.

Exercise testing was performed up to 175 W maximum, with a normal response of heart rate and blood pressure, without arrhythmic events, stopped for physical exhaustion. After the confirmation of normal blood tests, EPS was performed.Thepatient, in fasting conditions, with an intravenous access, was installed in the electrophysiology laboratory. Electrodes were attached in order to provide a continuous 12 leadssurface ECG during the procedure. A blood pressure cuff and a finger pulse-oximeter were also attached. Defibrillation electrodes were attached where if defibrillation would be required to be performed with minimal discomfort and no interference with the sterile field.

Indifferent electrode was placed in the thoraco-lumbar skin area for the possibility of RFA necessity. Right groin local anesthesia was achieved with 5 ml Lidocain 1%, then three femoral vein punctures were performed using the modified

Seldinger technique.The diagnostic catheters were placed by right femoral venous approach.Aquadripolar catheter with 5-5-5-mm spacingwas advanced from the right femoral vein and placed at the right ventricular apex. A steerable quadripolarcatheterwith a 2-2-2-mm electrode spacingwas placed on the His bundle, a quadruple catheter with a 5-5-5-mm electrode spacing on the lateral wall of the right atrium. For the coronary sinus we used a decapolarcatheter with a 2-8-2-8-2-8-2-8-2-mm spacing which results in five closely spaced dipoles 1 cm apart.

Basic electrophysiological data were recorded. The basic intervals were measured during sinus rhythm, at a stable heart rate:the PP interval (the interval between two consecutive P waves of sinus rhythm) 170 ms, PA interval (interval between onset of surface P wave and earliest endocavitaryatriogram) 30 ms, the AH interval (the interval between atrial electrogram recorded by thee His catheter and the beginningof the His electrogram) 100 ms, H-delta interval (interval between the onset of His electrogram and the delta wave) (-30) ms. The programmed ventricular stimulation with a 500 ms driven cycle length evidenced the earliest atriogram at the level of the mid coronary sinus, an effective retrograde refractory period of 200 ms equal to the effective refractory period of the right ventricule.

The incremental ventricular pacing showed a 1:1 retrograde conduction up to a limit pacing cycle of 300 ms.

Right atrial extrstimulus testing with a driven cycle length of 500 ms evidenced an effective anterograde refractory period of the accessory pathway under 200ms.

The incremental right atrial pacing revealed an anterograde conduction 1:1 with sudden degeneration into AF at 270 ms driven cycle lengt.

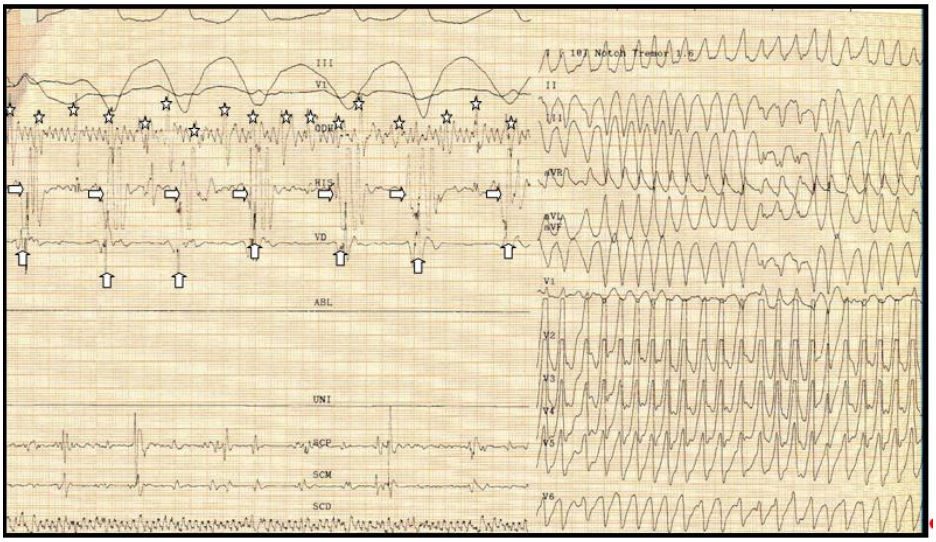


Figure 3. Atrial fibrillation declanched at programmed atrial stimulation. The first half of the tracing represent the endocavitary signal tracings and three of the surface ECG tracings, in order: derivations DI, DIII and V1 of standard ECG, ODH- the right atrium lateral wall electrogram, HIS- his bundle electrogram, VD- right ventricular electrogram recorded at the right ventricular apex, SCP- proximal coronary sinus electrogram,SCM- medium coronary sinus electrogram, SCD- distal coronary sinus, the ablation (ABL) and unipolar (UNI) channels were not connected at the time of the electrophysiological study. The star symbol on the endocavitary tracings shows the atrial fibrillation waves reccorded with maximal accuracy in ODH channel. The orizontal respectively vertical arrows on the HIS and VD tracings are coressponding to the fast ventricular waves, in response of the atrial fibrillation. The second half of the image is the standard 12 lead ECG tracing, with large, not regular QRS complexes, corresponding to the fast ventricular response of the atrial fibrillationconducted through the accessory pathway, heart rate between 170 and 300/ minute

The declanched AF had a minimal pre-excited interval RR under 200ms (~180 ms)resulted in a heart rate wich exceeded sometimes 300/min with consequent hypodiastolic cardiogenic shock.In less than a minute, the fast conducted AFthrough the accessory pathway degenerated into VF with rapid hemodynamic deterioration and loss of consciousness.

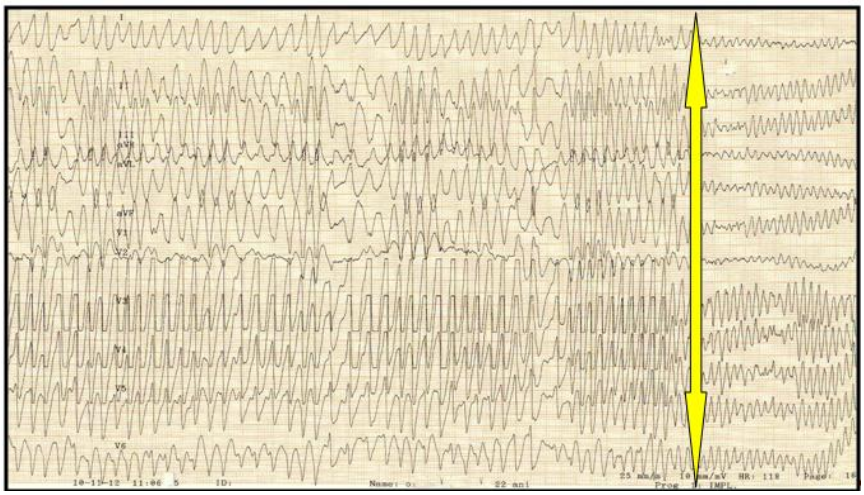


Figure 4. Fast conducted atrial fibrillation through the accessory pathway degenerated into ventricular fibrillation (transformation of the rythm marked bythe arrow)

TWe proceeded to external electrical conversionwith a brief return to sinus rhythm.

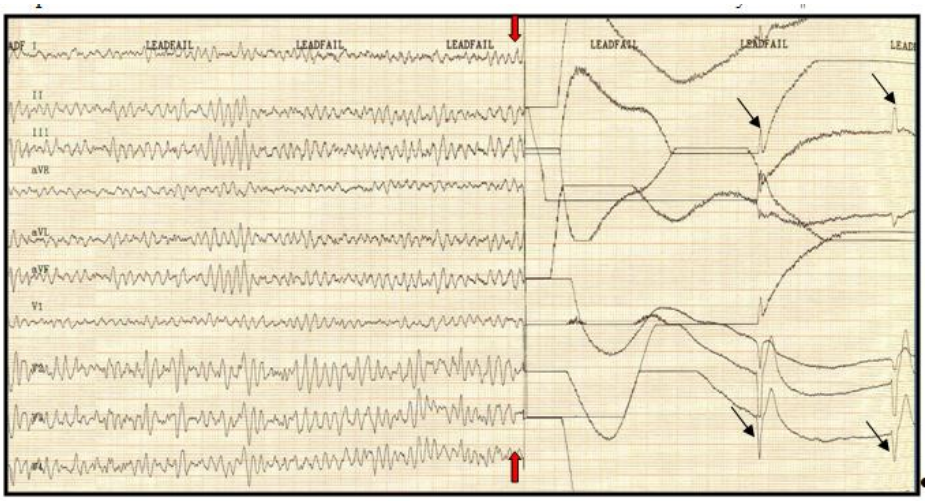


Figure 5. Standard 12 lead ECG recording showing ventricular fibrillation electrically interruptedusing a 300 W current (red arrow). The first two QRS complexes after conversion corresponding to slow junctionalrhythm (black arrows).

The AF with rapid heart rate spontaneously redeclanched with a new degeneration into VF. A new electrical conversion to sinus rhythm was necessary.

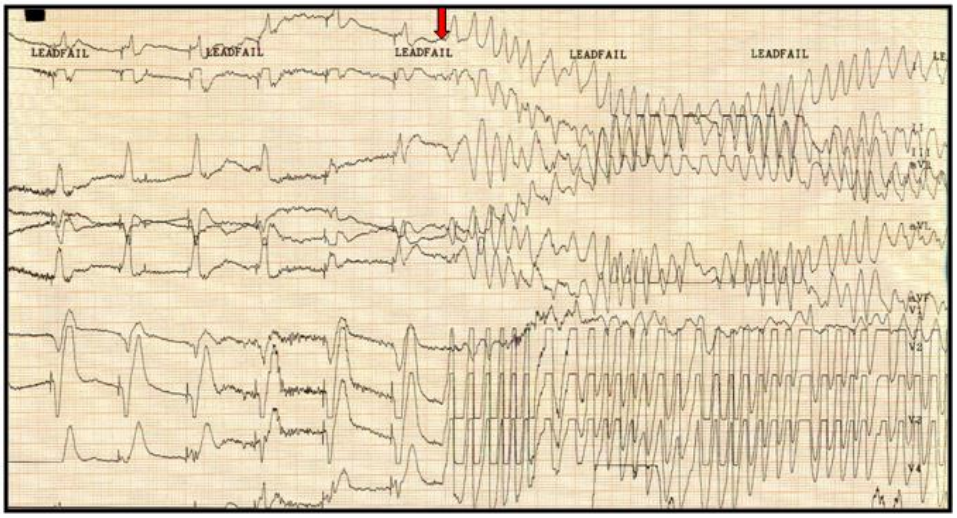


Figure 6. Standard 12 lead ECG of ventricular paced rhythm with spontaneous degeneration into atrial fibrillation conducted through the Kent bundle (arrow). The first half of the recording shows ventricular pacing rhythm in the attempt of the stabilization.

Overall,there were necessary five electric conversionsand the simultaneous injection of four 150 mg vials of amiodaroneduring 20 minutes, to stabilize to sinus rhythm post conversion.After a waiting period of several minutes during while sinus rhythm stability was carefully monitored,confirmation of full recovery of consciousness, signs of hemodynamic stability and confirmation of complete cooperation of the patient, the right femoral arterial puncture was performed to provide the retrograde arterial access of the mitral ring, the origin of the accessory pathway being confirmed as a left one by the EPS.

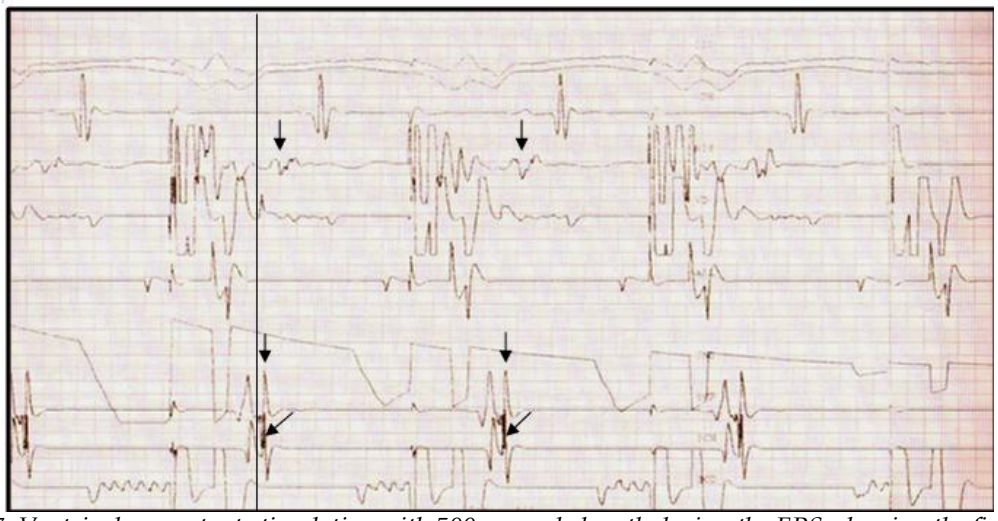


Figure 7. Ventricular constant stimulation with 500 ms cycle length during the EPS, showing the first atrial activation at the level of medium coronary sinus (mention that the distal cornary sinus did not register at the time,due to a technical problem). The arrows indicate the atrial activation; the angled arrowsshowing the first activation at the level of the medium coronary sinus- left origin of the Kent bundle.

A 6 FrenchBiosense ablation catheter was introducedthrough the arterial approach up to the mitral valve ring where we performed the anterior region mapping and established the optimal ablation target. The next step was to apply the radiofrequency energyat the optimal ablation target, the acessory pathway diagnosed as left anterior (positive delta wave in DI, aVL, V1, V2, V3, V4, V5, V6, medium coronary sinus first retrograde activation of the atria at the programmed ventricular stimulation).

Figure 8. Left anterior oblique incidence at the left side and postero-anterior incidence at the right, showing the positioning of the catheters: HIS- the quadripolar his-ventricle diagnostic catheter,CS- the decapolar coronary sinus cathetr, ABL- the ablation catheter positioned at the target point

The maximal values of the parameters used for ablation: maximal power 40 W, maximal temperature 50ºC.We performed twoablation lesions on the ventricular side having as reference the shortest atrio-ventricular interval and the QS wave in the unipolar recording, with consequent loss of the surface ECG preexcitation aspect. Recidive was observed after 15 minutes.Radiofrequency energy was applied for 60 seconds to the atrial side of the mitral annulus this time, resulting in permanent ablation of theaccessory pathway.

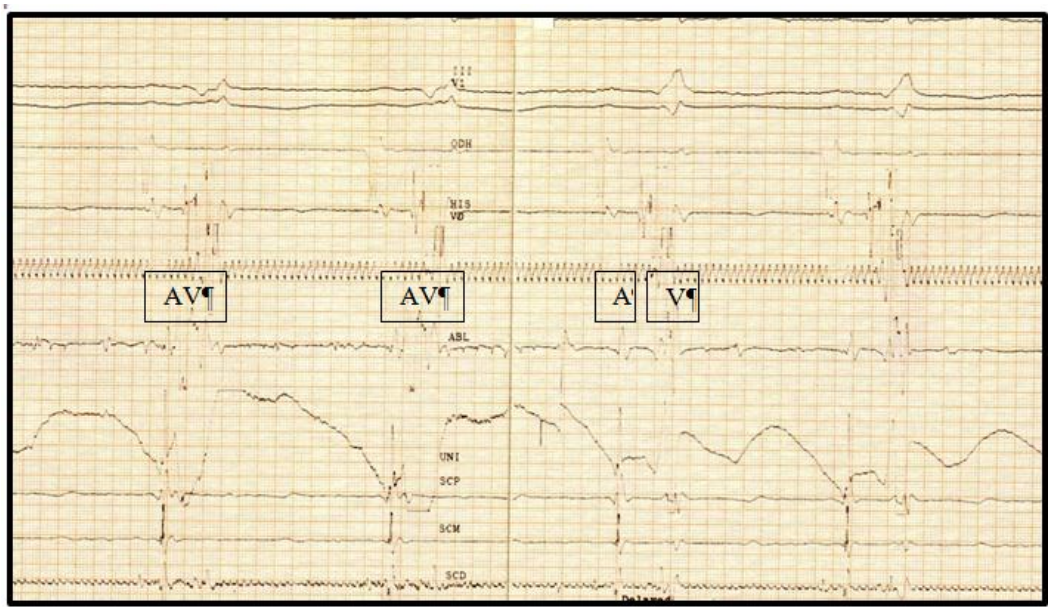


Figure 9. Optimal ablation target charcterized by the shortest AV interval in sinus rithm recorded by the ablation channel (ABL), QS registered by the unipolar channel (UNI). The third complex reveales the moment of ablation with the suddenprolongation of the AV interval and normalization of the QRS complexes and PR interval in the surface ECG reccording leads

After a 45 minutes waiting period we repeated the EPS observing complete atrio-ventricular dissociation and the absence of initiation of any type of tachycardia at the atrial and ventricular stimulation. We recorded the 12 lead ECG which demonstrated the dissapearence of the delta wave.

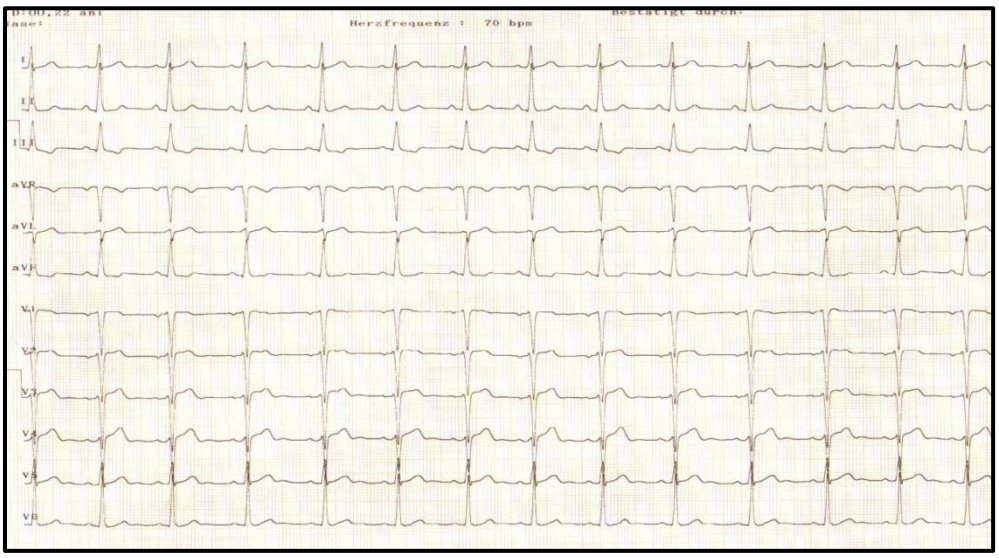


Figure 10. Twelve lead surface ECG after ablation showing the dissapearance of the delta wave, consecutive thinning of the QRS complex and normal PR interval

DISCUSSIONS

This clinical case is the proove of the WPW syndrome impredictibility in the context of lack of any tachyarrhythmia history and without any simptoms before the EPS. The electrophysiological exploration potentiated, in this case, by the patient's intentions to perform cyclism and occasionaly extreme sports (bungee-jumping), revealed extremely high sudden death risk otherwise announced by any manifestation.Sudden death can sometimes be the first manifestation of this syndrome. This is why we recommend electrophysiological testing regardless of the presence or absence of a history of tachycardia. Even if it is considered that the incidence of malignant WPW syndrome is higher in patients with syncope than in the asymptomatic patients, this case demonstrates that the assessment of characteristics of the accessory pathways should be mandatory in all patients, even at diagnosis or shortly after diagnosis.[5]

Retrospective studies have shown that anterograde conduction properties of the accessory pathway are of prime importance in the development of VF in patients with WPW syndrome. Other important factors considered risk markers for VF are documented orthodromic and antidromic tachycardia, the presence of several types of tachycardia in the same patient as well as the coexistence of multiple pathways. The group of patients which are at low risk for VFis characterized byintermittent pre-excitation and minimal RR interval greater than 220ms.[6]

In our case, the patient had anextremely short minimal RR interval (180 ms), which led to rapid conduction of AFthrough theaccessory pathway causing high ventricular frequency (sometimes above 300/min).Under these conditions, degeneration into ventricular fibrillation within less than one minute is the evidence of the importance of accessory pathway'seffective refractory period and of the minimal RR interval in the genesis ofsudden cardiac death. The atrial and ventricular stimulation protocol after ablation did no longer trigger any form of tachycardia.The delta wave disappearance was noted on the surface ECG and also the shortening of QRS complex from 140 ms to 90 ms and the prolongation of the PR interval from 80 to 140 ms (fig. 9).

The aspect of early ablation of the accessory pathway is also supported by the possibility of the change of its properties over time.In this light, an accessory pathway with initially benign features, under the influence of various factors can become malignant by shortening of the effective refractory period, being possiblein consequence thepotentiation ofVFand sudden death.The electrophysiological evaluation, mandatory in athletes presenting with this kind of pathology and which pottentialy saved our patient's life, wouldn't have been performed according to actual guidelines if the patient didn't decide to start practicing sports, especially extreme sports associated with high discharge of catecholamines.

CONCLUSIONS

Given the risk associated with this disease we suggest that any patient with WPW syndrome, symptomatic or not, to be at least fully explored by EPSin order to assess accessory pathway's properties and hence the risk of VF. We propose to evaluate not only symptomatic patients with a history of tachycardia but also patients without a history of tachycardia or syncope.We also recommend professional evaluation regardless of the risk groups, given that the first manifestation of this syndrome may be the sudden death.

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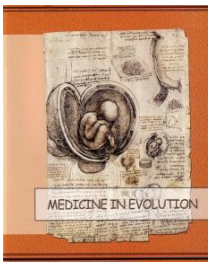
STUDY REGARDING QUALITY OF LIFE IN PATIENTS WITH INFERTILITY



ANA BENGESCU[1], COSMIN ILIE[2], ADRIAN RAȚIU[3], ANDREI MOTOC[2]

[1] PhD Student,"Victor Babeș"University of Medicine and Pharmacy
[2]Department of Anatomy and Embriology,"Victor Babeș"University of Medicine and Pharmacy
[3]2nd Obstetric and Gynecology Clinic,"Victor Babeș"University of Medicine and Pharmacy

ABSTRACT

In general, infertility is seen by individuals and the couples affected by it as pathological, but still, usually is seen as a private matter, that benefits from a large area of medical resources or, in case of adoption, of social resources.Despite all the recent studies on reproductive problems, certain aspects, certain important aspects as individual or couple's infertility are overlooked, and discussions regarding infertility as a real problem concerning public health are limited. The present study had the purpose to evaluate the quality of life in patients with infertility. Between January 2010 and January 2012 we studied health-related quality of life on 40 patients with primary and secondary infertility. The average emotional score of the included patients was 53,53, indicating a very powerful emotional issue. Female infertility is strongly associated with serious problems like low quality of life, stress, relationship problems with other family members, problems regarding sexual intimacy thus leading to infertility problems.

Key words: *infertility, quality of life, questionnaire*

Correspondence to:

Prof. Dr. Andrei Motoc
Address: University of Medicine and Pharmacy"Victor Babes", 2 E. Murgu Square, 300041 Timisoara, Romania,
Phone: +4 0722277806
E-mail address: amotoc@umft.ro

INTRODUCTION

Infertility represents a complex pathology with medical, psychological, social and economical implications.In the present time 10-15% from the general population has infertility problems. Recent studies have proven that the female factors are responsible for 50-80% of infertility causes, and the male ones are responsible for only 20-50%.

Recent demographic data has shown that Romania's population was in a continuous drop during the last decades. The reason can be found in the drop of life expectance – the general cause being aging and worsening of health in the general population. On the other hand the birth rate dropped during the last decades mainly due to the parent's wish to not have more than one or two children.

The quality of life was defined by The National Health Organization as the individual perception of their position in life from a cultural point of view and regarding their value system in which they live, in relation to their purposes, their expectances, their standards and personal problems.[1]

Measuring the quality of life is important for identifying different aspects of fertility issues associated with the quality of life.

The psychosocial studies have proven a series of negative reactions to infertility and the treatment associated with it that can affect the satisfaction of day to day life and the"feel good"state, the success of the treatment and the wish to continue treatment.[2-7]

Aim of the study

The present study had the purpose to evaluate the quality of life in patients with infertility. For this part we chose a sample of 40 patients that went to the gynecologist for sterility issues. They were asked to feel a questionnaire about quality of life especially created for patients with sterility issues.

MATERIAL AND METHODS

Between January 2010 – January 2012 we studies quality of life on 40 women with primary or secondary infertility, that went to 3 private gynecology clinics in Timisoara for investigations and/or treatment. To this purpose we used the questionnaire to evaluate quality of life in people qith fertility problems translated and adapted in Romanian since 2008. The questionnaire was made by the European Society for Human Reproduction and Embriology (ESHRE) and the American Society for Reproductive Medicine (ASRM). The questionnaire was anonymous and in addition to the part regarding quality of life it contained demographical data (age, environment, education, duration of infertility and it's type).

Answer categories: the questionnaire is made out of 24 items that make the main structure of the questionnaire. The complete questionnaire contains a section for patients that already started the infertility treatment that was not used in our study because patients completed the questionnaires before starting any type of treatment.

The answers are divided in 5 categories: (1) Emotional, (2) Mind/Body, (3) Relationships, (4) Social. The emotional category evaluated the impact of infertility on emotions, like sadness, resentment, etc. The mind/body category refers to the impact of infertility on physical health, cognition and behavior. The relationship and the social category qualtifies the impact of infertility on

the social aspects like social inclusion, the partner's expectancies and his support.

The scale of responses varies from 0 and 4. The higher the score, the better the quality of life is. The categories and scales are shown in the next table:

The response category	Scale
Evaluation	Very low (0), Low (1), Not good, not bad (3), Very good (4)
Satisfaction	Extremely unsatisfied (0), Unsatisfied (1), Not satisfied, nor unsatisfied (2), Satisfied (3), Very satisfied (4)
Frequency	Always (0), Very often (1), Often enough (2), Rarely (3), Never (4)
Intensity	Extremely (0), Very much (1), Moderately (2), A little (3), Not at all (4)
Capacity	Completely (0), Very much (1), Moderately (2), Not very much (3), Not at all (4)

Subscales and total scales

	Emotional	Mind/Body	Relationships	Social
Item	Q4R	Q1	Q6	Q5
	Q7	Q2	Q11R	Q10
	Q8	Q3	Q15R	Q13
	Q9	Q12	Q19	Q14R
	Q16	Q18	Q20	Q17
	Q23	Q24	Q21R	Q22

The questions signaled with R must be reversed before calculating the total amount

The total score

1. The first step is to reverse the scores where necessary.
2. The second step is to calculate the total scores (24 items).

To obtain the final value we multiply the total score with 25/k, where k is the number of items in that subscale. The final score varies between 0 and 100.

RESULTS AND DISCUSSIONS

Between January 2010 and January 2012 we studied health-related quality of life on 40 patients with primary and secondary infertility. The patients presented for infertility management in three private clinics in Timisoara.

We administered the health-related quality of life questionnaire for infertility and we analyzed the studied sample within the demographics variables.

Age distribution was the following: between 20 and 29 years old – 11 patients (27.5%), between 30 and 39 years old – 16 patients (40%), between 40 an 49 years old – 13 patients (32.5%).

Distribution in regard to their environment was: urban area – 24 patients (60%) and rural area – 16 patients (40%).

Distribution in regard to the level of education was: primary school – 4 patients (10%), secondary school – 7 patients (17,5%), high school – 11 patients (27,5%) and college – (45%).

Table 1. Patients' demographics

Variable		Number	Percentage (%)
Age (years)	*20-29*	11	27,5
	30-39	16	40
	40-49	13	32,5
Environment	*Urban*	24	60
	Rural	16	40
Education	*Primary school*	4	10
	Secondary school	7	17,5
	High school	11	27,5
	College	18	45
Infertility type	*Primary*	27	67,5
	Secondary	13	32,5

Table 2.Score quantification obtained at the questionnaire regarding quality of life in patients with infertility problems

Variable	Mean score	Standard deviation
Emotional score	53,53	18,16
Mind/Body score	59,37	22,72
Relationship score	48,36	10,84
Social score	60,83	24,01

We now can see that infertility can have a serious impact on the psychological status and also on the social one and the one regarding wellbeing of a person. As a result of their infertile status patients suffer physical and mental abuse, neglect, abandonment, economic deprivation and social isolation and in some cases exclusion from some social activities.

Now the studies can be divided in two categories: the ones that explore the possibility that infertility has psychological causes (the psychogenic hypothesis) and the ones that take into consideration the psychological consequences of infertility (the psychological consequences hypothesis).[4]Although the first hypothesis is rejected frequently there are important bibliographical sources that bring evidence that certain social factors like stress, anxiety or a weight loss can suppress the normal secretion oh gonadothrops leading to ovulation problems.[8,9]

Literature has identified a series of risk factors like psychological stress, smoking, alcohol and caffeine consumption, diet, obesity and insufficient physical exercise that can have a serious impact on infertility in the general population.[10-13]

Now in Romania there is no study that can evaluate quality of life in patients with infertility. Our study is made on a small sample and only in a certain area. We're in need of a multicentric study to correctly evaluate the social impact of infertility in a developing country.

We can see in the table showing the mean scores that infertility is a serious problem that can affect patients involved in all studied levels. The most affected aspect is that regarding the life partner. There are recent studies that reported the fact that infertile women have a great risk for sexual dysfunctions and that their dissatisfaction in their sexual life can often lead to stress regarding infertility.[14]

The existence of a real support in the community for these patients is extremely important. We should have specialized services only in this matter and the people in charge of this should be made aware to the emotional experiences of infertile couples. There

is a real need to advice infertile couples.

There should be a reset of basic relationships of these women and their natural habitat as part as couples management with infertility problems.

CONCLUSIONS

1. The used questionnaire (FertiQoL) was elaborated by The European Society For Human reproduction and embryology (ESHRE) and The American society of reproductive medicine (ASRM). The used questionnaire uses an evaluation scale from 0 to 100.
2. The average emotional score of the included patients was 53,53, indicating a very powerful emotional issue.
3. The mind/body score that refers to the infertility imact concerning physical health, cognition an behavior had an average value of 59,37.
4. The relationship and the social scores quantify the infertility impact on the social aspects like social inclusion, the partner's wishes and their support. The relationship area had the lowest score – 48,36, and the social one was 60,83. Practicaly, the social score was the least affected by the infertility issues and the relationship one was affected the most.
5. In conclusion female infertility is strongly associated with serious problems like low quality of life, stress, relationship problems with other family members, problems regarding sexual intimacy thus leading to infertility problems.

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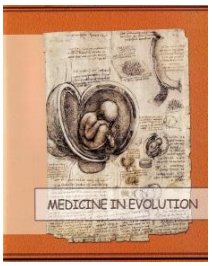
THE ROLE OF LAPAROSCOPY IN THE DIAGNOSIS OF POSSIBLE SECONDARY LIVER LESIONS IN THE ABSENCE OF A PRIMARY TUMOR



BREBU DAN, TARȚA CRISTI, DOBRESCU AMADEUS, LAZAR FULGER

"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania, Department of Surgery, Second Surgery Clinic of Timișoara County Hospital

ABSTRACT

Introduction: Another option for exploratory laparotomy on patients with liver metastasis and/or abdominal carcinomatosis in the absence of the primary tumor is minimally invasive surgery (MIS), also known as laparoscopic surgery. Some of the advantages of this technique are minimizing the rate of negative laparotomies, reduced morbidity, less blood loss and decreased hospital stay.

Case report: A 71-year old woman with multiple comorbidities comes to the emergency department because of abdominal pain, emetic syndrome and history of dark, tarry stools. After a close clinical and paraclinical examination, the incomplete results lead to the decision to perform a diagnostic laparoscopy in order to elucidate the diagnostic and to ensure the best possible therapy type.

Conclusions: On patients with liver metastasis and/or abdominal carcinomatosis in the absence of the primary tumor, laparoscopy might the best diagnostic and therapeutic tool in the management of those cases.

Key words: *laparoscopy, liver lesions, peritoneal carcinomatosis*

Correspondence to:

Dr. Dan Brebu
MD, PhD Student
Department of Surgery, University of Medicine and Pharmacy"Victor Babes"Timisoara, Romania,
Address: Iosif Bulbuca street, nr. 10, Timișoara, România
Phone: +40755012719
E-mail address: ***dr.brebudan@gmail.com***

INTRODUCTION

An alternative for opened exploratory laparotomy on patients with liver metastasis and/or abdominal carcinomatosis in the absence of the primary tumor is minimally invasive surgery, also called laparoscopic surgery and it has major advantages in comparison with classical approach: losing a reduced amount of blood, less postoperative pain, fewer and smaller scars, and a faster recovery. This surgical technique has an important impact on early perioperative morbidity [1], length of hospital stay [2], pain management, and it may improve the prognosis of these patients. Another significant role of laparoscopy in patients with liver metastases and/or peritoneal carcinomatosis is the possibility to perform a wedge hepatic resection [3] or to provide tissue biopsy and peritoneal fluid sampling. In addition, exploratory laparoscopy could be also used for therapeutic interventions [4], to guide the chemotherapy schemes by identifying the histological type of the tumor and applying a targeted therapy. Moreover, in the patients with severe condition, associated comorbidities and uncertain origin of the primary tumor, it might be the first surgical choice to elucidate the diagnostic.

CASE PRESENTATION

A 71-year old woman with multiple associated cardiac pathologies (single-chamber cardioverter-defibrillator, double disk mechanical mitral valve which has been done for an underlying mitral regurgitation, dilated cardiomyopathy, grade I degenerative aortic regurgitation, degenerative aortic stenosis, grade I functional tricuspid regurgitation, permanent atrial fibrillation, second degree essential high blood pressure), secondary pulmonary hypertension, long-term anticoagulant therapy, type two diabetes mellitus, renal lithiasis, right thyroid nodule and grade one obesity, presents at the emergency room with abdominal pain, emetic syndrome and history of dark, tarry stools (melena). Abdominal computed tomography (CT) scan revealed the following aspects on the liver: macronodular lesions with a diameter of approx. 6.5 cm, disseminated in the hepatic parenchyma, with hypodense aspect in all phases; the CT aspect can be suggestive for secondary disseminations. Colonoscopy confirmed the presence of multiple 3-4 mm polyps on the ascending colon and sigmoid colon. Polypectomy is not performed, the patient being under anticoagulant treatment. Upper gastrointestinal endoscopy did not reveal any lesion suggestive for a primary tumor. After a close clinical and paraclinical assessment, the findings were still not complete and thus it was decided to perform an exploratory laparoscopy in order to establish the diagnosis. This procedure revealed multiple tumors of the liver, with capsule expression (Fig. 1), disseminated in both liver lobes and multiple lesions on the diaphragmatic peritoneum, with a peritoneal carcinomatosis aspect (Fig. 2), serous peritoneal fluid - approximately 100 milliliters. After the thorough inspection of the entire peritoneal cavity, no obvious lesion can be identified as primary tumor.

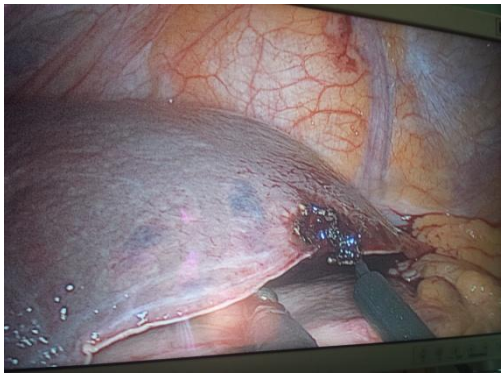


*Figure 1.*Aspect after hepatic wedge resection

*Figure 2.*Peritoneal carcinomatosis

A wedge resection is performed for a small peripheral hepatic tumor situated on the left liver lobe, segment III, and a perisigmoid lesion is excised for biopsy (Fig. 3). Moreover, peritoneal fluid is collected for the cytologic examination. The pathology examination confirms the presence of a subcapsular liver metastasis of a tubular adenocarcinoma with mucosecretions and unknown origin, most probably the digestive tract (stomach, hepatic ducts, pancreas etc.).

Figure 3. Small peripheral liver metastasis, tumor of peritoneal carcinomatosis and peritoneal fluid collected during laparoscopy

DISCUSSIONS

The secondary liver metastases of colorectal cancer are frequently met in patients diagnosed with this disease, this being a frequent cause of death for these patients[5]. Liver resection should be considered for patients with solitary liver metastases [6]. With an improved perioperative morbidity and mortality rate in the last twenty years,liver resection has become a feasible option for a growing number of patients with secondary metastases of colorectal cancer[7]. The combination between chemotherapy and liver resection is another option for the vast majority of the patients who initially show an inoperable disease [8]. With the advanced chemotherapy schemes, the resection rate reached 12% - 22% for this type of patients, with a 5-year survival rate of up to 35% reported after subsequent resection [9]. Despite the improvement of the imagery techniques, laparoscopy remains the best option for the identification of the peritoneal carcinomatosis lesions or small superficial liver metastases [10].

In this particular case, exploratory laparoscopy represents a real progress in the identification of a precise diagnosis, as well as in the restriction of the area related to the possible origin of the malignancy, aiming at establishing an efficient treatment. Peritoneal carcinomatosis represents a contraindication for liver resection and these patients may only benefit from adjuvant chemotherapy. Thus, the diagnostic laparoscopy was necessary and beneficial in this case, where the origin of the primary tumor is not known. A recent study presents some of the most important indications for exploratory laparoscopy as follows: staging of the carcinomatosis already diagnosed with imaging (CT scan and MRI), staging of carcinomatosis of dubious origin (biopsy), restaging after neoadjuvant chemotherapy, restaging during follow-up in the case of dubious imaging, and restaging after adjuvant chemotherapy [11,12].

CONCLUSIONS

A small wedge resection may be performed by laparoscopy, and it does not imply the same morbidity or mortality rate as does the open surgery. Thus, in certain situations, laparoscopymay be part of the diagnostic tools as a last variant, and sometimes it can also have a curative role.

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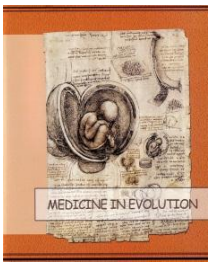
ANTHRACYCLINE INDUCED CARDIOTOXICITY: IS RISK STRATIFICATION POSSIBLE?



MIHAIELA VALCOVICI[1], LUCA CONSTANTIN[1], STEFAN IOSIF DRAGULESCU[2]

[1] Department of Cardiology,"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania
[2] Institute of Cardiovascular Disease,"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania

ABSTRACT

The cardiac dysfunction defined by the decrease of the left ventricle ejection fraction (LVEF) during chemotherapy was more clearly demonstrated after the use of anthracyclines. The risk stratification for cardiotoxicity justifies the use of the echocardiographic method (Tissue Doppler and STE- BASE STRAIN): an early diagnosis of myocardial modifications with defined prognostic involved; a prediction of the subsequent cardiotoxicity; a remote detection of the consequences of chemotherapy to anthracyclines: cardiomyopathy and cardiac failure.

Key words: *anthracycicline,- cardiotoxicity, -risck stratification*

Correspondence to:

Dr. Mihaiela Valcovici
Address: Department of Cardiology, University of Medicine and Pharmacy"Victor Babes", Timisoara, Romania,
Phone: +40731814818
E-mail address: mihaeladanielacardio@gmail.com

BACKGROUND

Beyond the cardiovascular complications induced by the neoplasic invasion, there were described a series of cardiovascular manifestations caused by chemotherapy and radiotherapy, respectively (1).

Anthracyclines, through a myocardial accumulation, dose-dependent effect, generates cardiac failure. The risk of cardiomyopathy increases with the cumulative increase of the dose of anthracyclines: 3% at the dose of 400 mg/m2, 7% at the dose of 550 mg/m, and 18% at the dose of 700mg/m2. We must underline that there are patients who, at the dose over 1 g/m2 have not developed cardiomyopathy, which involves the debate regarding the possible mechanisms involved in the cardiotoxicity pathogenicity (3).

ALGORITHM FOR THE DETECTION AND PREVENTION OF ANTHRACYCLINE INDUCED CARDIOTOXICITY

At this point of knowledge, the questions refer to:

a) Do we know the mechanism through which anthracyclines induce cardiac failure?

The mechanism of anthracycline induced cardiomyopathy is partially deciphered. It seems that mitochondrial injury and the oxidative stress could be responsible for the cellular apoptosis and the subsequent heart dysfunction manifested as heart failure (4). Anthracycline induced cardiotoxicity, in its acute and sub-acute form, can be early detected using imaging techniques, it is usually reversible with a good prognosis, and it does not require giving up the chemotherapy agent. It is cardiomyopathy type 1. In exchange, late cardiomyopathy has the aspect of dilated cardiomyopathy in adults, of restrictive cardiomyopathy in children respectively, which limits the prescription of the product (5). Cardiomyopathy type 2 is characterized by transtuzumab induced myocardial dysfunction; it does not relate to the use of the chemotherapy agent, and the lesions may be reversible. (6**)**. The risk factors are currently identified for the anthracycline induced cardiotoxicity: age over 70 years (7), the dose of mediastinal radiotherapy (8), the cumulative anthracycline dose, pre-existent high blood pressure and concomitant chemotherapy: taxane and trastuzumab.

b) Are there any persons subject to risk of developing chronic cardiotoxicity?

A series of studies state, based on the echocardiographic exploration, the existence of a sub-group of cardiovascular asymptomatic patients during the anthracycline treatment. In these patients, the picture of the cardiac failure intervenes late, after the treatment is stopped (9). This evidence justifies a new approach of the patient with neoplasic disease under anthracycline treatment, in the direction of the screening for cardiotoxicity (echocardiographic method), as well as the need to systematically and extendedly follow them.

c) The chemotherapy regime using anthracycline as adjutant agents: does taxane or trastuzumab influence or not the prevalence of the heart failure?

Ewer Sm et all claim that trastuzumab associated to anthracyclines increases the cardiotoxic effect through additive mechanism, on short term (10). Transtuzumab is responsible for the introduction of a mild form of cardiomyopathy (type 2),

without evident ultrastructural modifications, and with a good functional prognostic, due to the lesion reversibility.

The monitoring guides for anthracycline induced cardiotoxicity propose the left ventricle EF as parameter - golden standard for the analysis of the cardiac dysfunction. Belham M. et al propose a functional classification of cardiotoxicity (11), defined as:

- mild form: decrease of the EF > 10% of the base EF at rest, but with a final value > of 50%

- moderate form: decrease of the EF > 10% of the base EF at rest, with a final value < of 50% without symptoms (signs of heart failure)

- severe form: decrease of the EF > 10% of the base EF at rest, with a final value < of 40 % with symptoms of heart failure.

Among the non-invasive imaging methods, the echocardiographic assessment is accepted, according to the standard procedure (2D, M-Mode, and Doppler - ACC/AHA guidelines) (12) for the left ventricle: dimensions and ejection fraction.

Schwartz et al propose a monitoring algorithm in time of the ejection fraction, which could lead to a 4 times decrease of the risk of heart failure (13).

The United Kingdom National Cancer Reasheat Institute elaborated a guideline for the cardiotoxicity monitoring (14).

During the last decade, the research were focused on the strain echocardiographic use as more sensitive means for the early detection of the anthracycline induced cardiotoxicity. Pio M. et al prove with tissue Doppler at the level of the mitral annulus, the possibility of detecting cardiotoxicity intra-clinically (15):

- the decrease of the systolic peak (Sa) without the reduction of the ejection fraction supports the potential risk of developing anthracycline induced cardiotoxicity

- the significant decrease of the ejection fraction and of the systolic wave peak (Sa) are a sign of cardiotoxicity and they occur at a cumulative dose of approximately 1q50 mg/m2.

A new series of data specify that a correct quantification of the regional deformation of the left ventricle (Strain and Strain rate imaging) could sub-clinically identify the myocardial dysfunction before the occurrence of the LVEMF decrease (16).

A current review of the trials in two data bases (EMBASE) and (MEDERILINE) underline a new approach of the risk regarding anthracycline induced cardiotoxicity, the modification of the left ventricle geometry precedes the significant modification of the left ventricle ejection fraction (17): an early decrease with10-15 % of GLS by STE during therapy represents a good parameter for cardiotoxicity prediction. In the remote follow-up of the neoplasic patient, post-chemotherapy, the measurements of the global, radial and circumferential strain remain at an abnormal value even in the context of a normal ejection fraction, but without having a predictive value for a subsequent ventricular dysfunction.

In the end we wonder if there really exist preventive strategies for anthracycline induced cardiotoxicity and for its consequences? The answer is positively affirmative.

First of all, the progresses performed in due time lead to the possibility of risk stratification for anthracycline induced cardiotoxicity.

Secondly, the new echocardiographic techniques bring in additional data regarding the structural and functional modifications of the left ventricle.

Thirdly, the use of the association angiotensin converting enzyme inhibitor or receptor blocker with Carvedilol reduce the cardiotoxicity progression and it implicitly ameliorates the morbidity / mortality

indexes through heart failure in patients treated with anthracyclines (18). Moreover, the concomitant administration of an iron chelating agent - dexrazoxane - insures short-term protection without reducing the efficiency of anthracycline.

CONCLUSIONS

Recent data suggest the introduction of the genetic susceptibility study to anthracyclines, in the risk stratification algorithm for cardiotoxicity (19). So that, knowing the polymorphism of the genes mediating the metabolism, the transport, and the pharmacological activity of anthracyclines (doxorubicin), we could state the hypothesis of prescribing a customized treatment that could ameliorate in time the cardiovascular morbidity / mortality indexes.

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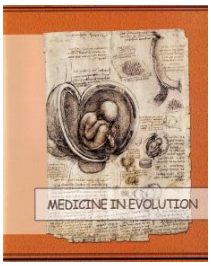
PULMONARY TUBERCULOSIS AND LUNG CANCER: A COMPLEX AND DANGEROUS CONNECTION



IONELA IOVAN[1], DORIN VANCEA[1], VOICU TUDORACHE[2]

[1]Hospital of Infectious Disease and Pneumology"Victor Babes"Timisoara
[2]"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania

ABSTRACT

Lung cancer and pulmonary tuberculosis (TB) are two major public health problems with potential clinical correlations. The co-existence has attracted attention for several years but the causal relationship is not well understood.

There are clinical evidence of increased lung cancer risk among individuals with TB. The risk may increase further with coexisting COPD or other smoking-related cancers.

Preexisting TB may be an independent risk factor and negative prognostic factor for lung cancer. Chronic inflammation associated with recurrent Mycobacterium tuberculosis infection, may initiate or promote pulmonary carcinogenesis. In contrast, cancer or chemotherapy induced immunosuppression, can lead to increased rates ofrecent tuberculosis infection in patient with lung cancer.

Due to high TB prevalence and radiological similarities, a large number of lung cancer patients initially get wrongly treated for TB. Clinicians need to maintain a high index of suspicion for simultaneous and/or misleading presentations.

Key words: *lung cancer, pulmonary tuberculosis, causal relationship*

Correspondence to:

Ionela Iovan
Hospital of Infectious Disease andPneumology"Victor Babeş"Timişoara
Address: Bld. 3 August1919,nr.4,ap.3,Timisoara,Timis,cod 300092
Phone: +40724817369
E-mail address: neagoe_ionela@yahoo.com

INTRODUCTION

Tuberculosis presents a global threat in both developing and developed countries. According to the World Health Organization, more than 2 billion people, equal to one-third of the world's population, are currently infected with tuberculosis bacilli.There were 8.6 million new cases and 1.3 million deaths attributed to TB in 2012 (including 320 000 deaths among HIV-positive people)[1].

On the other hand, the worldwide incidende oflung cancer was 1.8 million new cases (13% of all new cases) and 1.6 million deaths (19,6% of all deaths) in 2012[2].

HISTORICAL ACCOUNT

Although TB and lung cancer are very common diseases, there has been little attention to the pathophysiological and practical implications of their co-existence.

The association of TB with carcinoma was initially described ~200 years ago by Bayle who considered"cavitation cancereuse"as one of the various types of TB, without histological proof [3]. Pilliet and Piatot in 1897 made the 1th report of synchronous lung carcinoma and tuberculosis. Between 1850-1930 the association was considered to be less frequent and with no causal relationship because"TB killed the patients before lung cancer could develop in them".

Since 1930 many reports have been published in the literature refuting and supporting the causal relationship between TB and lung cancer. But this causal relationship is not well understood.

TB and lung cancer are two major public health problems associated with significant morbidity and mortality and potential clinical correlation. But epidemmiological or clinical correlation doesn't necessarily mean causality[4]!

RISKS

The risk of Cancers in patients with TB

Tuberculosis infections have been associated with increased incidence rates of lung cancer and non-pulmonary malignancies in case reports:

For males:

- within 1 year after TB diagnosis: head and neck, esophageal, colorectal, liver, lung cancers, melanomas, and Hodgkin's disease;
- 1 year post TB diagnosis: liver, biliary, lung, and bladder cancers.

For females:

- within the first year after TB diagnosis: leukemia, esophageal and lung cancers;
- 1 year post TB diagnosis: only for leukemia beyond[5].

The risk of TB in patients with Cancers

Head and neck and hematological cancers are significant risk factors for tuberculosis. In areas with relatively low prevalence of TB, the rate of TB among patients withhematologic neoplasms and head and neck cancer is > 100-200 cases/100,000 persons (≈40X the rate among the general population).

Solid tumors other than head and neck cancer do not have anincreased risk for TB[5] !!

Possible associations between Lung Cancer and TB

The association between TB and cancer can occur in several ways[4]:

1. A chance coincidence without any apparent relation. Is a rare situation.
2. Metastatic carcinoma developing in an old TB lesion. Also very rare.
3. Secondary infection with TB of lung cancer. Patients with lung cancer are vulnerable to develop active pulmonary TB (reactivation of latent or recent tuberculosis infection) due to immunosuppression and malnutrition induced by cancer or resulting from the use of intensive treatment modalities such as aggressive radio and chemotherapy.
4. Development of lung cancer on the background of aprevious tuberculous infection. Post TB scarring lesions evident on the baseline chest radiograph subjects, are associated withelevated lung cancer risk, specifically for occurrence of cancer inthe lung ipsilateral to the scar. It was hypothesised thatlocalised inflammatory processes associated with scarringpromote the subsequent development of lung cancer. Is the most frequent sitation:chronic progressive tubercle in which a carcinoma develops("ipsilateral lung scar cancer")[6].
5. Simultaneous development of both TB and lung cancer. Concurrent existence of TB and cancer causes diagnostic dilemma due to similarities in presentation leading to delay in the diagnosis and institution of appropriate therapy[4].

Risk of Lung Cancer in TB patients

Since a third of the world's population has been infected with TB, several studies have suggested an increased risk of lung cancer among people with TB. It is still uncertain if TB"causes"lung cancer, being impossible to infer causality based exclusively on clinical correlations.

Researchers from China and Taiwan Medical Universities selected 716,872 people with data from China's National Health Insurance program (4,480 in the TB cohort and 712,392 in the non-TB cohort). Results showed that patients with TB were 11 times more likely than non-TB patients to develop lung cancer (26.3 versus 2.41 per 10,000 person-years). Mortality was 6 times higher in the patients with TB than in the non-TB patients (51.1 versus 8.2 per 10,000 person-years). The Hazard Ratio (HR) for lung cancer risk in the TB cohort was 4.37 compared with those without TB. Combining tuberculosis with chronic obstructive pulmonary disease yielded an increase in the lung cancer risk HR to 6.22. The combination of TB and other smoking-related cancers resulted in an HR for lung cancer risk of 16[7].

The researchers wrote:"this study provides a compelling evidence of increased lung cancer risk among individuals with TB and the risk may increase further with coexisting COPD or other smoking-related cancers"[8].

Table I. The incidence and Hazard Ratio of Lung Cancer in TB cohort vs. non-TB cohort[7]

	TB-cohort	non-TB cohort
Incidence of lung cancer 10,000 person-year	26,3 11-fold higher	2,41
Mortality	51,1 6.23-fold higher	8,2
HR for lung cancer	4.37-fold higher	
HR for lung cancer (+ COPD)	6.22-fold higher	
HR for lung cancer (+other smoking related cancers)	16-fold higher	

How can TB promote Lung Cancer?

Although wordwide, infections are considered the cause of roughly 25% of cancers, in developed countries that number is closer to 10%. But how could an infection with Mycobacterium tuberculosis (MTB) lead to cancer? In tuberculosis there is an association of a chronic inflammatory process with a severe chronic lung infection with MTB.

1. The chronic inflammatory process is activating the alveolar macrophages which produce:

- reactive oxygen and nitrogen species, which can bind to DNA leading to DNA mutation andactivation of transcription factor which directly induced squamous cell metaplasia and angiogenesis;
- citokines (TNF-α, IL-6) which may directly activate the NF-kB pathway, inducing inhibition of apoptosis;
- epiregulin which is a potent growth factor for premalignant epithelial cells.

2. The severe chronic lung infection with MTB causes:

- extensive pulmonary fibrosis (IL-3, IL-4, and TNF-α);
- tissue repair with scars, associated with cellular proliferation ('scar carcinomas').

In tuberculosis, chronic inflammation associated with recurrent MTB infection, by inducing DNA mutation, cellular proliferation, angiogenesis, extensive fibrosis and scars, may initiate or promote lung carcinogenesis. Preexisting TB may be an independent risk factor for lung cancer[4,9].

The experimental model of lung carcinogenesis induced by chronic MTB infection

Squamous cell (SC) is a very rare type of lung tumor in mice. In an experiment made by Harvard Medical School, male mice were infected with 30–50 CFU of MTB strain Erdman by aerosol.

SC metaplasia of alveolar cells with malignant transformation surrounded by massive fibrosis associated with the necrotic TB lesion were observed in mouse lung chronically infected with MTB.

The lesions were found at 4 months post infection in 25% of TB-genetically susceptible mouse, after 5 months post infection in 100% of TB-genetically intermediate susceptible mouse and after 12 months post infection in 80% of TB-genetically resistant mouse.These SC carcinoma cells were adjacent to extensive inflammatory lesions, but clearly distinct from the surrounding fibrosis.

Table II.Appearance of SC metaplasia with malignant transformationin mice lungs

Months	TB-genetically susceptible mouse	TB-genetically intermediate susceptible mouse	TB-genetically resistant mouse
2	0/4 (0%)	0/4 (0%)	0/4 (0%)
4	1/4 (25%)	1/4 (25%)	0/4 (0%)
5		4/4 (100%)	0/4 (0%)
7		4/4 (100%)	2/4 (50%)
12			8/10 (80%)

There are experimental evidence that chronic TB infection in the lungs is sufficient to cause a multi-step transformation of cells associated with TB lung lesions. SC metaplasia is a frequent event specifically associated with chronic TB lesions in the lung which may progress towards the formation of SC carcinomas at later stages of the infection. MTB-inflicted lung tissue damage seems to accelerate the formation or accumulation of SC in the vicinity of old TB lesions (which represent an environment that is highly

conducive to tumor development) in the lungs. The researchers showed that coexistence of lung cancer with pulmonary TB documented in clinic and epidemiological studies, at least in some cases, is causal, not coincidental[10].

Risk of Lung Cancer in current smokers with pulmonary TB

The Seoul Male Cancer Cohort Study concludet that a history of TB is associated with an increased risk, RR=1.85 (95%CI 1.08-3.19) of lung cancer in current male smokers. The risk of TB history exhibited a synergistic interaction with daily amount, duration of smoking and total cigarette index, respectively. Therefore, a heavy male smoker with a past medical history of TB belongs to the group at high risk of lung cancer, and should quit smoking[11].

Risk of Lung Cancer in nonsmokers with pulmonary TB

Active smoking is a commun and confounding risk factor for lung cancer and TB, but an increased RR of lung cancer in TB patients may be found in the absence of any tabacco expure effect. To minimize the impact of cigarette smoking in TB patients, a number of studies have estimated lung cancer risks associated with nonsmoking status.

A systematic review of 37 case-control and 4 cohort studies (between 1966 and 2009) found in never smokers patients with TB, a statistically significant 1.78-fold increase in risk of lung cancer. The strength of this association increased to 2.93-fold after adjusting for lifetime environmental tobacco smoke exposure (passive smoking). The most significant association (RR=1.60) was observed related to adenocarcinoma. The increased lung cancer risk appeared greatest within the first 5 years after TB diagnosis (11-fold), but the risk for lung cancer remained 2-fold elevated for more than 20 years after TB diagnosis[12].

Lung Cancer histological type risk in TB smokers according to gender

In a Korean Study was examined the correlation between TB, cigarette smoking,gender and histological type lung cancer. Among males, the respective OR (Odds Ratio) for past and current history of lung tuberculosis was 3.21, 2.69 and 1.52, and for females was 2.40, 4.20, and 1.37 for squamous cell, adenocarcinoma, and small cell carcinoma. This findings provide additional evidence that tuberculosis is a potential risk factor for certain lung cancer histologic types and that women are more susceptible to the carcinogenic effects of tobacco[13].

Table III. Lung Cancer histological type risk in TB Smokers

	Past and current history of lung tuberculosis	
	Male (Odds Ratio)	Female (Odds Ratio)
Squamous cell carcinoma	3.2	2.4
Adenocarcinoma (ADK)	2.7	4.2
Small cell carcinoma	1.5	1.8

The survival of Non Small Cell Lung Cancer (NSCLC) patients with the presence ofTB lesions.

In a retrospective Chinese review of 782 NSCLC patients who underwent surgical resection was observed the associations between lung cancer survival and the presence of old pulmonary TB lesions. The median survival of squamous cell carcinoma patients with TB was significantly shorter than that of patients without TB (1.7 vs. 3.4 years, $p < 0.01$). The presence of an old pulmonary TB lesion is an independent predictor of poor survival in squamous cell carcinoma patients. The presence of TB did not impact the survival of the patients with adenocarcinoma[14].

In a Taiwanese study was examined the association between EGFR Mutation and TB in 275 patients

with adenocarcinoma of the lung. From ADK patients, those who had scar cancer and old TB lesions had a higher probability of having EGFR mutations, especially exon 19 deletions. Those patients with old TB lesions who had EGFR mutations (exon 19 mutations) survived longer than those who did not. These findings suggest that there exists a relationship between pulmonary TB and EGFR mutations in patients with adenocarcinoma of the lungs[15].

Risk of Lung Cancer among TB patients with AIDS

Previous reports describes significant increased lung cancer risk among persons withAIDS-associated tuberculosis. In an U.S. National Cancer Institute study was investigated whether AIDS and pulmonary tuberculosis affected the risk of subsequent lung cancer over 10 years after AIDS onset among 322,675 patients with AIDS whose records were linked with cancer registries in 11 U.S. regions.

In contrast with previous reports, lung cancer risk was not related to tuberculosis (HR=1.11, p=0.52) both overall or for specific lung cancer histologies. Although overall cancer risk was not associated with tuberculosis, significantly increased lung cancer risk was observed within the first year after tuberculosis diagnosis (HR=2.01, p=0.007), suggesting a non-causal association or a reverse causality (i.e., subclinical lung cancer facilitated the reactivation of latent tuberculosis infection)[16].

Aspects to consider for diagnosis of the TB + Lung Cancer association

Lung cancer should be suspected if there are changes (constitutional symptoms or radiograph or CT scanes) in a patient after months or years after TB infection.

Every effort should be made to diagnose MTB infectionn when lung cancer is detected to initiate antiTB treatment. Also, clinicians associate lung cancer with high case-fatality and start antitumoral treatment without detailed investigation. Altogether, this leads to delay in TB diagnosis and progression of disease. Antituberculous HIN prophylaxis should be started especially in patients withhematological malignancies or head and neck cancer and positve tuberculin skin test (≥5mm). For diagnosis, a combined approuch with tuberculin test and different interferon-γ releaseassays (unfortunately its sensitivity is very low in immunosuppressed patients)might be the best option[17].

In TB endemic countries, due to high TB prevalence and radiological similarities, a large number of lung cancer patients initially get wrongly treated for TB(a common medical error: lung cancer misdiagnosed as sputum negative TB). This can result in a delay in diagnosis and ultimately a delay in treatments for lung cancer[18].A lack of awareness and socioeconomic reasons have been cited as causes for these misdiagnoses[19].

CONCLUSIONS

There are evidence of increased lung cancer risk among individuals with tuberculosis.

The risk may increase further with smoking, coexisting COPD or other smoking-related cancers.

Clinicians need to be aware of the protean manifestations of TB and cancer and maintain a high index of suspicion for simultaneous and/or misleading presentations.

In addition, further research is required to determine if a TB infection, being similar to other chronic infections and inflammatory conditions, may facilitate carcinogenesis[20,21].

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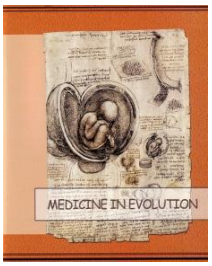
CURRENT CONCEPTS IN CERVICAL PATHOLOGY



IZABELLA DIANA ERDELEAN[1], DAN NAVOLAN[1], EUGENIA TAURESCU[1], DRAGOS ERDELEAN[1], DORU ANASTASIU[2], DORIN GRIGORAS[1]

[1]County Emergency Hospital Timisoara, Obstetrics and Gynecology Department,"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania
[2]Obstetrics and Gynecology Discipline III,"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania

ABSTRACT

The etiology of cervical cancer has undergone several stages.The evidence gathered concerning the natural history of the preinvasive cervical lesions shows that, if those lesions are not treated, they can progress into invasive cancer in a substantial proportion

The medical practice in treating patients with squamous intraepithelial lesions has changed over the years, along with the progress made in understanding the disease evolution and aetiology, and the progress in technology, ranging between two extremes, represented by the electrocautery and the total hysterectomy.In this context, the conization has both diagnostic and therapeutic value when dealing with the invasive lesions of the cervix.

The diagnosis and treatment files, the cytology and colposcopy examinations were studied for 126 cases with preinvasive lesions of the cervix that required surgical treatment which consisted of:

- *wide excision of the transformation area with the diathermy loop: 25 cases*
- *classic conization - 90 patients*
- *cervical amputation - 11 patients*

Studying the cytology of these patients we found that 73.56% had CII at the cytological examination, in other cases 28.73% being CII.

We also monitored the correlation between the BABEŞ – PAPANICOLAU cytological examination, the colposcopy and the result of the histopathological examination. We noticed a perfect concordance in 120 cases (95.24%), indicating cervical cancer only in 6 cases, representing4.76%.

The histological appearance of the fragments extracted by cervical conization showed:

- *61 patients - 48.41% - CIN I*
- *48 patients - 38.09% - CIN II*
- *17 patients 13.49% - CIN III.*

Key words: *colposcopy,cone biopsy,cytology,cervical lesion,H-SIL*

Correspondence to:

Dr.Erdelean Izabella Diana
Address: University of Medicine and Pharmacy"Victor Babes", County Emergency Hospital Timisoara, Hector Street 1
Phone: +40730024109
E-mail address: erdelean.izabella@gmail.com

INTRODUCTION

The etiology of cervical cancer has undergone several stages. Many population studies tried to establish a causal relationship between certain habits and ways of life and the cervical lesions occurrence (1). The precancerous lesions are very important for the carcinogenesis. The evidence gathered concerning the natural history of the preinvasive cervical lesions shows that, if those lesions are not treated, they can progress into invasive cancer in a substantial proportion (2, 3,4).

Today the viral theory, incriminating the HPV in more than 95% of cervical cancers cases, prevails in the etiology of cervical cancer (5, 10, 18).

The intraepithelial neoplasia concept (CIN) introduced by Richard in 1968 showed that all the dysplasia cases have a development potential (17).

The mitotic activity degree, the mature cells and nuclear abnormalities proliferation determine the neoplasia degree. The existing lesions at the squamous-cylinder junction have an important role in the cancer lesions genesis.

The medical practice in treating patients with squamous intraepithelial lesions has changed over the years, along with the progress made in understanding the disease evolution and aetiology, and the progress in technology, ranging between two extremes, represented by the electrocautery and the total hysterectomy (6).

In this context, the conization has both diagnostic and therapeutic value when dealing with the invasive lesions of the cervix.

The conization is performed (7,9):

• For all the patients with abnormal cytology and unsatisfactory colposcopy (squamous-cylinder junction, invisible lesion margins)

• For normal colposcopy, but persistent abnormal cytology or positive endocervical curettage

• For the colposcopic suspicion of occult or invasive carcinoma

• When there are significant cytocolpohystological discrepancies.

The conization is therapeutically suitable for:

• the treatment of histologically confirmed cervical intraepithelial neoplasia (CIN) in patients with unsatisfactory colposcopy

• the in situ AIS treatment of the endocervical adenocarcinoma.

From a technical point of view, the conization may be:

1. Classical conization, with the scalpel, the hemostasis being performed by applying Stumdfort threads.
2. Conization according to Mc Donald method
3. Conization according to Palmrich – Bielecki method
4. Conization according to Masterson method
5. Conization with the ultrasonic scalpel, which is a tool that cuts and coagulates by converting electrical energy into mechanical ultrasonic vibrations
6. The CO2 laser conization is a modern alternative to this procedure
7. The conization with the diathermy loop, which is an alternative to conventional or laser conization, being performed with a large loop, with a 2,5 / 2,5 cm diameter or with a medium-sized loop with which the transforming area is excised(13,14)
8. Cervical conization, using the"two cones"method (12).

The diagnosis of the cervical lesions is based on the tripod diagnosis of cervical lesions (cytology, colposcopy, pathology). The colposcopy which is complementary to the cervical cytology helps us locate the

changes indicated by the smear, to appreciate their seriousness and to take the most appropriate therapeutic decision for each case.(8)

Regardless of how the excisional surgery treatment is performed, the patient must be integrated in a medical short and long term surveillance system, the cytology, colposcopy and the prophylactic vaccination being very important in this system (1, 3, 10,17).

Among the modern diagnostic possibilities for the cervix dysplasia, besides the cytology and colposcopy, with the possibility of performing a targeted biopsy (colposcopically directed) the conization is a diagnosis and treatment method used predominantly for the dysplasia that is large and extended towards the cervical canal (5, 7,15).

Often the lesions located at the squamous - cylindrical junction in the endocervix are not suitable for biopsy, but can be diagnosed with the fragment extracted by conization (20, 21, 22).

At the same time, the cervical conization or even the cervical amputation represents for the benign dysplastic lesions and the premalignant lesions a therapeutic method which can be carried out in a single session (11, 19, 21). The histopathological detection of some invasive carcinoma lesions requires immediate radical treatment (1, 16, 18).

The diagnosis management and the therapy based on the histopathological examination of the cone removed by conization (12) implies the following procedures:

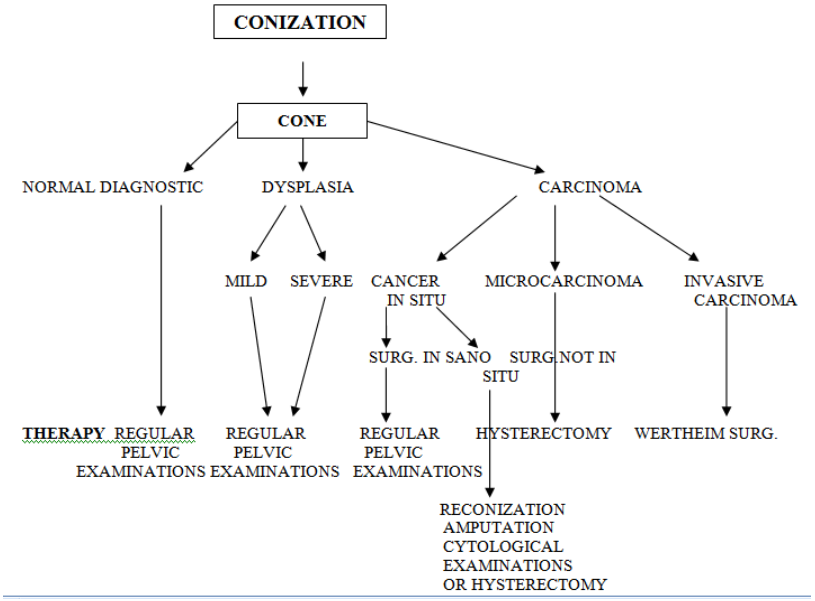


Figure 1. Algorithm of treatment in cervical lesions

Figure 2.The cervix after aplication of 3% acetic acid demonstrating an easily observed acetowhite cin 3 lession on the anterior cervix noted only following acetic acid application

Figure 3. An acetowhite high-grade lession gradually appears on the anterior lip of the cervix. An nabothian cysts with overlying dilated,but normal branching blood vessels,also on anterior and posterior lip

Figure 4. Leukoplakia of the cervix,demonstrating white,thinked,raised epithelium prior to the aplication of 3% acetic acid

MATERIAL PRESENTATION

The diagnosis and treatment files, the cytology and colposcopy examinations were studied for 126 cases with preinvasive lesions of the cervix that required surgical treatment which consisted of:

- wide excision of the transformation area with the diathermy loop (LLETZ technique): 25 cases, 19%
- classic conization - 90 patients - 71.42%
- cervical amputation - 11 patients 8.7%

According to the provenance, 96 (76.19) patients were from urban areas and the remaining 30 (23.8%) from rural areas.

The group distribution analysis, according to age, shows that the peak incidence is between 28-40 years - 90 patients representing 71%, the remaining 36 (29%) having ages between 41-50 years.

Studying the cytology of these patients we found that 73.56% had CII at the cytological examination, in other cases 28.73% being CII.

Performing the conization, we applied 4 standard non-absorbable threads instead of 2, which are applied in the original process. 6 weeks after the surgery we extracted the threads.

We also monitored the correlation between the BABEŞ – PAPANICOLAU cytological examination, the colposcopy and the result of the histopathological examination. We noticed a perfect concordance in 120 cases (95.24%), indicating cervical cancer only in 6 cases, representing4.76%.

From these cases, in 5 cases – representing 83.33% the invasive cancer was confirmed upon the histopathological examination of the uterus, after performing hysterectomy, in a single case, representing 16.67% obtaining a false negative result, reconfirming the histopathological result from the cone obtained by conization.

All the suspected cases, for which the total hysterectomy was performed were classified in the CIN III with H-SIL or carcinoma in situ category.

The histological appearance of the fragments extracted by cervical conization shows:

- 61 patients - 48.41% - CIN I
- 48 patients - 38.09% - CIN II
- 17 patients 13.49% - CIN III.

We specify that we have included all patients in the therapeutic management scheme for the preinvasive lesions of the cervix.

CONCLUSIONS

1. The conduct adopted by us for the non-invasive lesions of the cervix was an active one, implying a diagnosis as correct as possible of these lesions and their proper treatment.
2. We consider the electrocautery as an obsolete procedure, performing it only for a satisfactory colposcopy, on a cervix with extended ectopy that secreted mucus in a in a disturbing manner for the patient with normal cytology.
3. Regardless of the technique used for performing the conization, the healing was safe, but we prefer the classical conization in order to obtain a piece of cervix (cone) that allows us to perform a histopathological diagnosis as accurate as possible.
4. Performing the conization allowed an early diagnosis of invasive cancer in 5 cases that otherwise would have been omitted until a later stage.

5. In the H -SIL cases, at the histopathological examination of the cone obtained by conization, we prefer performing a total hysterectomy in cases where there is no interest for the obstetrical prognosis or the reconization, for young women without children, taking the final decision after the second histopathological result.

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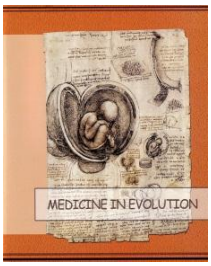
ANATOMO- IMAGISTICAL STUDY OF LIVER METASTASES IN COLORECTAL CANCERS



MARIUS TOBA[1], VASILE SARBU[1], CONSTANTIN IONESCU[1], CLARA MATEI[2], MIRCEA TAMPA[2]

[1]Faculty of Medicine, Ovidius University of Constanta, Romania
[2]"Carol Davila"University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

The aim of this study was to compare the results of the ultrasound examination and computed tomography (CT) techniques in preoperative staging of colorectal cancer, and to determine whether CT offers other benefits beyond ultrasound. The study was performed on a total of 243 patients, hospitalized in the Clinic of Surgery II Constanta County Hospital, from January 2007 till December 2011, diagnosed with colorectal cancer.

Ultrasound examination determined 30 (12.3%) patients with liver metastasis while CT 71 (29.2%) patients. The sensitivity rates for liver metastasis of those with ultrasound were 69%, and of those with CT were 78%. CT showed to give higher rates regarding the detection criteria, indicating the necessity of reviewing the clinical diagnosis in patients with colorectal cancer. Our study indicates that CT should be used as a first-line scanning technique in detecting liver metastasis in respect with ultrasound. Therefore, CT plays a key role in the screening of liver metastasis in colorectal cancer patients.

Key words: *colorectal cancer, liver metastasis, ultrasound, computed tomography*

Correspondence to:

Toba Marius
MD, Assistant Professor
Address: University str, 2nd Building, Constanta, 900470, Romania
Phone: +40722592424
E-mail address: marius.toba@anatomie.ro

INTRODUCTION

Colorectal cancer is one of the most common malignancies, after lung, liver and stomach cancer (1). Liver metastases develop most of the time in over 60% of patients with colorectal cancer, representing the most common cause of morbidity (2). Surgical resection is the modality of choice (3) and only 5 to 15% patients can benefit from surgery (4, 5).

Sometimes laboratory tests and chest radiograph are approach before surgery. The use of a routine abdominal ultrasound and computed tomography (CT) with or without contrast substance is now the standard protocols. However, the routine use of CT in colorectal cancer patients is still in debate (6, 7). It is well know that the preffered routine technique is surgery, and some studies showed that patients who undergo preoperative CT scanning before surgery help the decision to avoid it. Therefore, it would become necessary to introduce routine preoperative CT scanning in all colorectal cancer patients (8).

The study aims to compare the results of ultrasound and CT assessment on 243 patients diagnosed with colorectal cancer, as well as to determine whether CT offers any benefits beyond ultrasound in detecting liver metastasis.

MATERIAL AND METHODS

From January 2007 to December 2011, 243 patients treated in Surgery Clinic II Constanta Emergency Hospital diagnosed with colorectal cancer were evaluated for clinical outcome. Within this group, based on CT with contrast substance, were found a total of 71 patients, who were diagnosed with liver metastases. Inclusion criteria for the procedure were the patients who were not surgical candidates or who refused surgical resection.

Patients were assessed prospectively by preoperative abdominal CT after abdominal ultrasound. Ultrasound was carried out by one of the gastroenterologist from the hospital prior to CT. The ultrasound was carried out using a Toshiba Sonolayer unit (Japan) while CT was performed using a Somatom Spiral CT scanner (Germany). Scanning was performed after overnight while intravenous contrast agents were used and sequences were about 8 mm sections. CT scans were read by a radiologist and the evaluations were independent from ultrasound results.

Ultrasound and CT procedures were performed in standard form to assess the liver metastasis. All follow-up images were assessed for the development of new metastatic disease and ancillary peritumoral changes.

This study was approved by our institutional review board, and an informed consent was obtained from all patients before the procedure.

RESULTS

Total of 243 patients were diagnosed with colorectal cancer based on a pathological examination within a period of 60 months. The patients with colorectal cancer consisted of 145 men and 98 women at a mean age of 56 (range 30-72 years). During preoperative radiological evaluation, ultrasound determined 30 (12.3%) patients with liver metastasis while CT with contrast substance revealed 71 (29.2%) patients.

The patients with liver metastases did not show any characteristically

ultrasound appearance, and the number, differentiation degree, consistency, vascularization and the structure, varied from case to case (Figure 1).

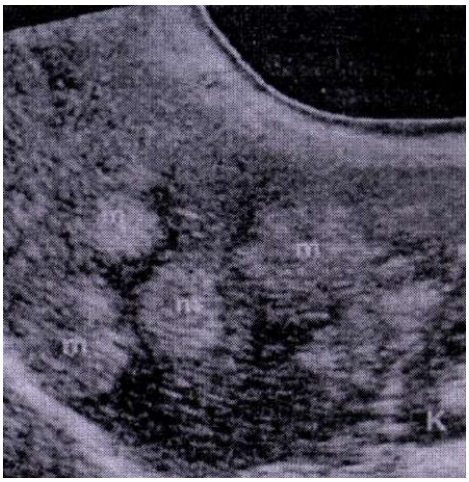


Figure 1. Ultrasound of hiperechogene metastases; primary tumor-colorectal

Interestingly, detection of liver metastasis showed to be more efficient with CT using contrast substance and the diagnosis of ascites with ultrasound. Therefore, ascites was reported in 12 (4.9%) cases without any other peritoneal metastasis. From 71 patients, 40.84% (29/71) patients had one metastasis, while 26.7% (19/71) had two, and 16.9% (12/71) had three metastases respectively. Above them, 50.7% (36/71) were located in the left hepatic lobe and 49.29% (35/71) in the right hepatic lobe.

Large sized metastases showed to have central necrosis and may mimic fluid formations, apparently benign ones. Moreover, metastases from melanoma and leiomyosarcoma appeared hipoechogene, multicentered, poorly bounded, showing central fluid necrosis developing an image like a 'bull's eye' and secondary malignancies in our study were revealed by CT (Figure 2).

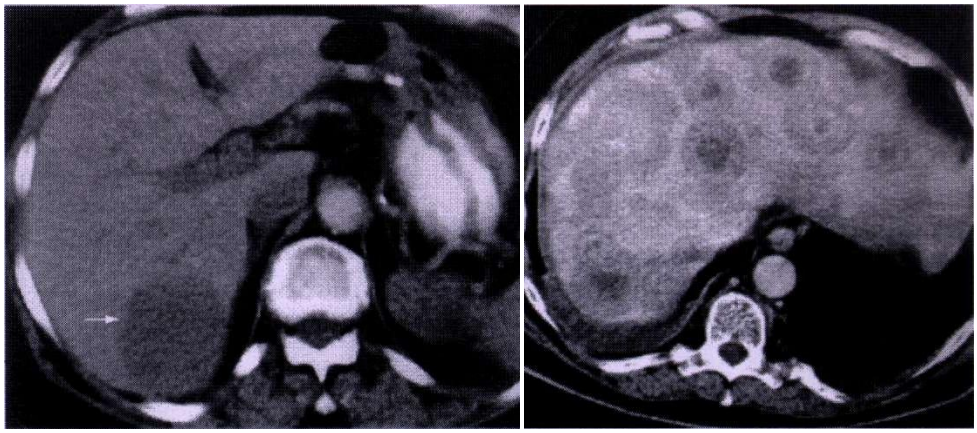


Figure 2.CT scanning with contrast substance of spontaneous liver metastases.

The difference between CT without contrast substance and CT with contrast was the fact that the first serve to see the location of the tumor, specifying the number, and establishing the structure of spontaneous lesions (i.e. fatly inclusions, fluid content and calcifications), and the second one, establishes the vascular structures in the tumor.

Therefore, metastases from the patients varied in size and those with less than 1 cm in diameter remained unnoticed, taking into consideration the partial volume effect which was not identified, requiring further examinations. In most cases, after using CT with substance contrast, the metastases remained hipodense, and by setting the contrast showed to be as a peripheral ring around the central hipodense area, in both arterial and portal phase.

In our study, large metastases showed to have area of necrosis inside, which appeared in colon carcinomas (Figure 3).

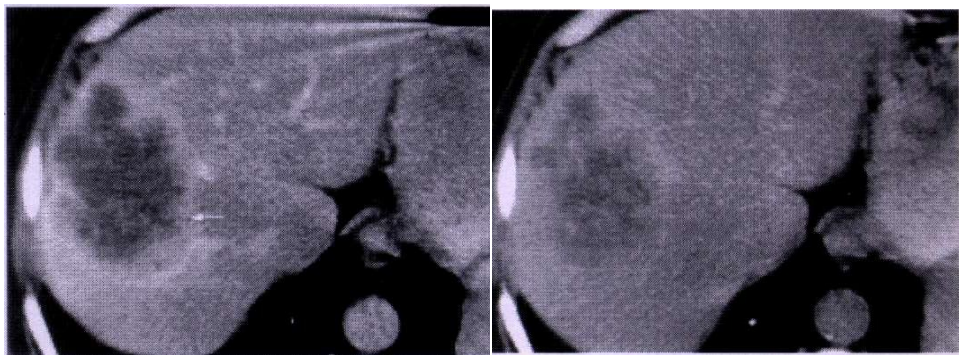


Figure 3.CT scanning: liver metastases in colon carcinoma

On the other hand, small metastases, marginal, intense hiperdense, hipercatching, was observed in renal cancer (Figure 4).

Ovoid metastases with fluid content and calcifications, powdery on the entire surface occurred in pancreatic cancer (Figure 5).

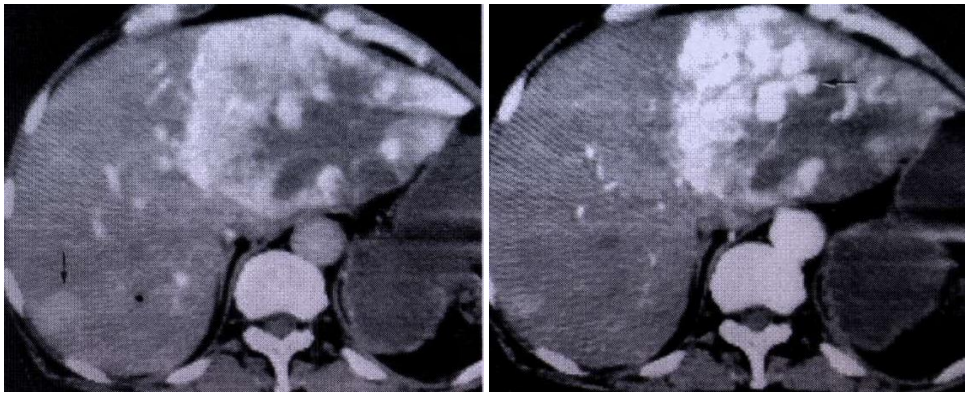


Figure 4. CT scanning: liver metastases in renal cancer

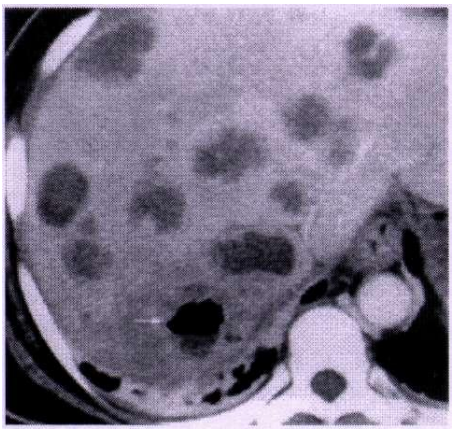


Figure 5. CT scanning: liver metastases in pancreatic cancer

DISCUSSIONS

Colorectal cancer metastases, the most common malignant tumors of the liver, could imply the surgical resection, sometimes the only prospect for cure (2, 3). However, the number of patients suitable for resection is very limited if we take into consideration the unresectable location, extrahepatic metastases, advanced liver cirrhosis and comorbidities (4).Although colorectal cancer is often considered as a single entity, staging of colorectal cancers differ depending on primary tumor location (i.e. rectum or colon).

In many countries, most patients with colon cancer performed staging with abdominal CT scanning before surgery (9). Despite extensive regular use of CT, many studies have showed that in a small number of cases, preoperative CT scanning alters the chosen treatment (10-12). One study conducted on 108 patients, found that CT was a poor staging method in their case, staging only 48% of patients (13).

The use of CT in colorectal liver metastasis was showed to have a higher sensitivity (36-100%) and specificity (74-100) (6, 11). Reporting to our study, the sensitivity rates were 78%. Although CT with or without contrast substance is useful in detection of liver metastasis, sensitivity of CT decrease with liver metastasis. Moreover, ultrasound examination showed to give similar disadvantages with CT for detecting small and diffuse liver metastasis (12).

The first general criteria for incurability are not represented by the detection of the metastasis. Therefore, it is known that there is no adverse effect on survival (14). In our study, undetectable liver metastasis with ultrasound showed superficial small lesion. In contrast with ultrasound, CT did alter neither the superficial lesions nor the liver procedures.

We can state that preoperative liver scanning by both techniques was useful for liver metastasis, but CT with contrast substance can determine surgery decision-making.

CONCLUSIONS

Nowadays, the treatment of colorectal liver metastases is in rapid evolution. Comparing to ultrasound, CT indicate to highlight space location lesions and diffuse liver lesions. Our results revealed the fact that CT should be used as a first-line scanning technique in detecting liver metastasis from colorectal cancer patients in respect with ultrasound.

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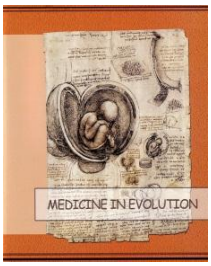
USING INJECTABLE DERMAL FILLERS FOR THE AGEING FACE IN DERMATOLOGY



MIRCEA TAMPA[1], CLARA MATEI[1], TEODOR POTECA[2], ISABELA SARBU[3], VASILE BENEA[3], SIMONA ROXANA GEORGESCU[1], ROXANA OANCEA[4]

[1]„Carol Davila"University of Medicine and Pharmacy, Bucharest, Dermatology Department
[2]„Carol Davila"University of Medicine and Pharmacy, Colentina Hospital, Bucharest, General SurgeryDepartment
[3]„Victor Babes"Hospital for Infectious and Tropical Diseases, Bucharest, Dermatology Department
[4]„Victor Babes"University of Medicine and Pharmacy, Timisoara, Department I MD

ABSTRACT

The process of ageing conducts to various alterations in the facial aspect; in the context of population ageing, the methods for imporving the aesthetic aspect of the ageing face lead to a improved quality of life for more and more patients. Dermal filler are cutting edge medical products designed for soft tissue augmentation, with an overall good profile in terms of efficacy and safety. Filler injections stand for one of the most common minimally invasive procedures for facial rejuvenation and sculpturing. The present paper presents the available products for facial soft tissue augmentation, the procedure of filler injection, as weel as the indications and adverse effects of dermal fillers.

Key words: *dermal fillers, ageing skin, rejuvenation*

Correspondence to:

Clara MATEI
MD, PhD
Address:"Carol Davila"University of Medicine and Pharmacy, 37 DionisieLupu Street, Bucharest
Phone: +40758040765
E-mail address: matei_clara@yahoo.com

INTRODUCTION

Ageing leads to various changes in facial aspect, comprising ultraviolet damage of the skin (alteration of skin texture, elasticity, color and tumescence), depletion of subcutaneous fat tissue, changes in intrinsic muscles of the facial expression, sagging due to alteration of various structures that holds fat into place-such as malar fat ptosis, and remodelation of cartilaginous and even bone structure of the face (1,2).

Dermal fillers are a category of injectable substances and/or mixture of chemical compounds used in medical practice for rejuvenation and/or correction of facial defects. Their effects are consequent to their capacity of volume augmentation in target areas; the mechanism of action vary between filler agents: however, either by attracting water in the target region (e.g. hyaluronic acid may attract water in a measure of 1000 times its weight) or by fibroplasia, neocollagen formation and the mechanic filling effect, filler agents augment the tissues and create a rejuvenating effect (1,3).

Employment of modern skin filler agents in dermato-cosmetology dates back in the beginning of the XXth century, when paraffin oil was used; in 1953 Baronders uses liquid silicone as a filler agent, a compound whose usage for this purpose was banned by the Food and Drug Administration in 1991, due to the increased incidence of side effects. Collagen was first approved for skin injections in 1981, and in 1996 the first fillers containing hyaluronic acid were released on market and approved by regulatory organisms in the European Union. A wide panel of chemical compounds based on polymeric mixtures were subsequently released, therefore in present days the dermatologists may rely on a large spectrum of products for filler injections (3-5).

Currently, filler injecting is among the most frequently used minimally invasive procedures for rejuvenation of the ageing face (6). The 2012 Plastic Surgery Statistics Report issued by the American Society of Plastic Surgeons states a major increase in the usage of soft tissue fillers by 5% in 2012 as compared to the previous year; soft tissue augmentation is placed on the second place as most used cosmetic minimally-invasive procedure, after botulinum toxin injections; fillers injections are more frequently employed that chemical peels, laser hair removal and microdermabrasion (7).

The advantages of facial filler injections consist in the short duration of the procedure, the short required down-time and the good profile of safety and efficacy of the filler agents.Several products are available for skin augmentation; while their mechanism of action varies widely, as well as their chemical structures, all these products have in common the ability to fill the tegumentary areas where they are injected.

FILLER AGENTS CLASSIFICATION

Filler agents can be classified in respect to several factors, the most important of which is the duration of the effect. Therefore, in respect to effect persistence, filler agents can be divided into:

-biodegradable fillers – dermal fillers made from materials that can be metabolized by the body-a category that can be further divided into rapid biodegradable (temporary biodegradable, effect less than 12 months: collagen, hyaluronic acid) and slowly biodegradable/semipermanent fillers (1-2 years of effect persistence:

poly-L-lactic acid, calcium hydroxyapatite, polyvinyl alcohol)

-non-biodegradable fillers (permanent fillers): silicone, polyacrylamide, polyalkylimide)

-various combinations (such as bovine collagen and PMMA-polymethylmetacrylate) (1,3,4,8)

Currently, the most common used compound for filler injections is hyaluronic acid, a polysaccharide naturally encountered in normal dermis (2). Hyaluronic acid fillers have the same mechanical and structural properties as normal dermis, therefor the biocompatibility of the products containing hyaluronic acid is enchanced, while the rate of adverse reaction is lower (1,2). A wide variety of products containing hyaluronic acid are available; the concentration of hyaluronic acid in these product may vary, depending on the producer as well as on the product destination (e.g. thinner products are designed for lip augmentation, as opposed to more concentrated products, designed for mid-face augmentation and correction of facial asymmetries)(1,4).

INDICATIONS FOR DERMAL FILLER INJECTIONS

Filler injections are usually employed in cosmetic dermatology for(2,3,9-11)(Figure 1):

-correction of various static skin folds caused by ageing of the skin, such as glabellar rhytids, nasolabial folds

-correction of labiomental creases

-correction of the periorbital rhytids and tear trough deformity

-correction of temporal hollows

-correction of depressed scars, including acne scars

-augmentation of lips for cosmetic purposes,

-alteration of nose and/or chin anatomy

-ptosis of the midface (loss of midfacial volume)

-correction of lipoatrophy (e.g. in HIV positive patiens)

-correction of facial symmetry

-other aesthetic purposes (e.g. hand rejuvenation, even penile augmentation).

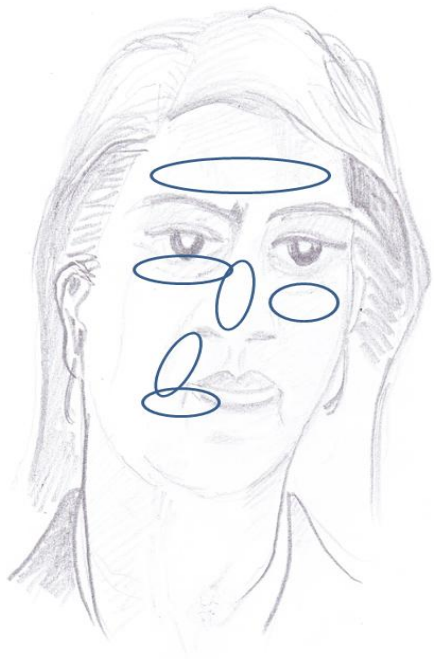


Figure 1. Schematic depiction of the areas of potential injection of dermal fillers in the ageing face (tear trough, nose, midface, nasolabial folds, labiomental folds and lips)

THE PROCEDURE OF INJECTING THE DERMAL FILLERS

Cleansing of the face, with total removal of the make-up is mandatory before the procedure, in order to avoid foreign body insertion during skin penetration by the needle. The injection per se bears a moderate risk of local blood vessel injuries and may require the discontinuation of anticoagulant medications in order to decrease the risk of bruising. The pain that accompanies the procedure is perceived in a variate manner by the patients. However, usually some form of anesthesia is employed, in order to reduce unnecessary emotional disconfort to the patient. Anesthesia might be topical (e.g. EMLA-eutectic mixture of local anesthesics: 5% lidocaine and 5% prilocaine, tetracaine gel) or in rare cases might be a form of cryoanesthesia or vibratory anesthesia. Nerve block anesthesia is a efficient form of anesthesia, and, in respect to the anatomic area targeted for the procedure of filler injection, might be: supraorbital, supratrochlear or zygomaticotemporal nerve block (periorbital region, zygomatic region), mental nerve block (for chin and lower lip procedures) or infraorbital nerve block (in case of procedures that target the lower lip). The approach for the nerve block may be either percutaneous or intraoral (for example, for mental nerve block in case of injection of filler agents in the lower lip)(1,12).

The injecting technique may vary, depending on the augmentation effect that is wanted, the specific dermal filler used and the anatomic particularities of the topographical region that is targeted; most used injection techniques are linear threading, serial puncture, fanning and cross hatching) (8).

SAFETY AND ADVERSE EFFECTS

Various adverse effects may accompany the procedure; most adverse reactions are transient and mild to moderate; however, in rare cases serious adverse reactions may occur, leading to permanent functional and cosmetic deficits (13,14). The commonlyencountered adverse reactions include pain, erythema, oedema, brusing and common skin infections. Formation of granuloma and/or sterile abcesses (foreign body granuloma may occur independent of the used filler agent, with an estimated incidence between 0.01 and 1%)may also occur (13). Foreign body reactions caused by filler injections are unique and can be differentiated from one another microscopically; the morphologic aspect of the foreign materials themselves (i.e.dermal fillers) can also offer an important clue that may permit a retrospective diagnosis in a patient (15).Allergic reactions are also possible; e.g. bovine collagen injections require pre-testing by injecting in the skin of forearm with 72 hours beforehand, for allergic reactions exclusion; however, allergic reactions may accompany filler injections, independent of the employed compound (1,4). Bruising may be limited if blunt cannulas are used, and if patient head is elevated throughout the entire procedure and up to 24 hours following the injections (13). Oedema occurs independent of the specific dermal filler, and usually dissipates within the first week after the treatment (13).

Lumps and nodules may also form after filler injection; in case of lumps appeared after hyaluronic acid injections, hyaluronidase injection is able to dissolve the formed subcutaneous nodules and to correct excessive quantities of injected filler, partially reversing the augmentation effect of hyaluronic acid injection (16).

Vascular compromise (if the dermal filler is injected ina vessel may create obstruction and ischemia, which in rare cases may lead to skin necrosis and even blindness-retrograde flow of an intravascular thrombus into the retinal artery) may also occur, in rare cases; skin necrosis is more frequently encountered in filler injections in glabellar region; skin necrosis is a immediate complication and could be recongised by an increased pain felt by the patiens as well as by the blanching of the tegument in the treated area(4,8). Paresthesia may also occur, if a nerve is pierced accidentaly during the procedure (13).

Temporary biodegradable filler agents are usually accompanied by short term adverse reactions, whilst the permanent fillers may lead to permanent complications (vascular occlusion, filler migration); moreover, although permanent fillers are cheaper for the patient (requiring a lower number of interventions that biodegradable fillers), there is the risk that filler placement would become inadequate after a few decades interval, due to alteration of facial structures with ageing. Therefore, permanent filler injections are recommended to be avoided, at least in patients addressing for the first time for facial soft tissue augmentation (1,2,4).

Least but not last, certain dermal fillers may also impede radiologic/imagistic explorations; Feeney et al. have shown that dermal fillers containins calcium hydroxyapatite are hyperattenuating on computer tomograph examination, hypermetabolic on positron-emission tomography, of intermediate signal intensity on magnetic resonance and may be considered as a potential cause of a errors on imaging exams of the patient (17).

CONCLUSIONS

Facial soft tissue augmentation using dermal fillers is a frequently-used procedure worldwide, aiming to reduce the effects of ageing and to improve the aesthetic aspect of the face. Biodegradable filler agents are efficient and safe, as long as the indications and the techniques are followed in a correct manner. Basic knowledge of the facial anatomy is required for the injector, in order to ensure a proper anesthesia, an adequate volume correction and the avoidance of intravascular injection. There is a large panel of dermal fillers of variate chemical structure available for the practicing physician; as most side effects are preventable with proper planning and technique, knowledge regarding the particularities of each product, the anesthesic procedures and the adequate injection techniques may conduct to good cosmesis and improved results, considerably enhancing the quality of life of the ageing patiens.

Conflicts of interests

None declared. All authors have contributed to this work.

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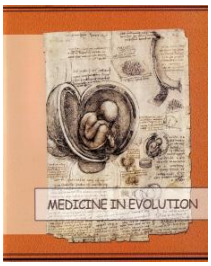
MALE INFERTILITY-CYTOGENETIC FINDINGS IN A COHORT OF PATIENTS FROM WESTERN PART OF ROMANIA



MIRELA COSMA[1,2], SIMONA FARCAS[1], MONICA STOIAN[1], DANIELA AMZAR[3], NICOLETA ANDREESCU[1], MARIA PUIU[1]

[1]Discipline of Genetics, University of Medicine and Pharmacy, Timisoara, Romania
[2]Swedish Convenant Hospital, Medical Education, Chicago, USA
[3]Discipline of Endocrinology, University of Medicine and Pharmacy, Timisoara, Romania

ABSTRACT

The aim of this study was to evaluate the frequency and the type of chromosomal anomalies in male from couples with infertility. We done this study over a period of 10 years and included a large number of patients from the Western part of Romannia. The study lot included 518 male patients with ages between 18 and 52 years old referred for genetic analysis between 2005-2014. Cytogenetic analysis was done using peripheral blood cells following the standard procedure.We did not report here the polymorphic variants including chromosomal satellite associations, anomalies of the long arms/satellites of acrocentric chromosome. 42 patients presented an abnormal karyotype: 26 cases with numerical and structural anomalies of the gonosomes, 16 cases presented structural aberrations of the autosome chromosome. For the future, we consider that the cytogenetic and molecular investigations of the patients with infertility will provide valuable insights into the etiopathology of the infertility and will allow development of targeted treatments for patients.

Key words: *cytogentic analysis, male infertility*

Correspondence to:

Nicoleta Andreescu
Address: Discipline of Genetics, University of Medicine and Pharmacy"Victor Babes", 2 E. Murgu Square, 300041 Timisoara, Romania
Phone: +4 0256204476
E-mail address: nicollandreescu@yahoo.com

INTRODUCTION

Infertility represents one of the most important problems affecting couples at reproductive age. Infertility was defines as couple's failure to conceive after having sexual intercourse without contraception for 1–2 years [1]. The incidence of infertility rate is estimated between 8% [2] to 24% [3] and the contribution of male factors to infertility is about 30–50% [4].

There are several well documented causes of male infertility including anatomic and functional anomalies of the male genitalia, exposure to different chemicals, drugs, radiations, systemic disorders, and genetic aberrations [3]. A comprehensive evaluation in cases of male infertility should include an attentive documentation of patient and family history, physical examination, spermogram, endocrinology evaluations, conventional and molecular cytogenetic analyses.

Genetic causes of male infertility include numerical chromosomal anomalies, balanced cytogenetic rearrangements, microdeletions of Y-chromosome.[5, 6]. Genetic anomalies can lead to infertility by interfering in different physiological processes, by altering hormone sintesisand spermatogenetic function [7].

The genetic causes of male infertility were investigated in several studies. A meta-analysis done in order to establish the frequency of autosomal anomalies in cases of male infertility found a rate of 3,5% for infertile males as compared with 0,42% for general male population [8-12].

Apart autosomal anomalies, aneuploidies as Klinefelter syndrome (KFS) are a frequent cause of male infertility. Klinefelter syndrome is one of the most common aneuploidy and have an incidence of 1/600 cases in newborn males [13]. The incidence of Klinefelter syndrome in cases of male infertility is significantly higher than in general population [14]. In cases with Klinefelter syndrome was recorded a severe alteration of spermatogenesis with arrest of spermatogenesis at the primary spermatocyte stage, but occasionally subsequent stages of sperm development are observed [15].

This paper aims to present our experience in testing infertile males for chromosomal abnormalities. This study includes a large lot of patients from the Western part of Romania and the results are representative for this population.

MATERIAL AND METHODS

The study lot included 518 male patients with ages between18 and 52 years old referred for genetic analysis between 2005-2014 to the Genetic Laboratory from the University of Medicine and Pharmacy"Victor Babes"Timisoara and the Genetic Laboratory from the Hospital"DumitruPopescu"Timisoara.

Cytogenetic analysis was done using peripheral blood cells following the standard procedure. The lymphocytes were incubated for 72 hour in medium with phytohemagglutinin stimulation. The cells were blocked in metaphases by using colchicine, hypotonized in KCl solution and fixed with a mix of methanol and acetic acid (3:1 proportion). For banding we used GTG technique and a minimum of 30 metaphases were analyzed for each patient. In cases with mosaicism this number raised up to 100 metaphases.

The cytogenetic result for each patient was noted in accordance with the International System for Human Cytogenetic Nomenclature [6]

For several cases, molecular cytogenetic analysis was done. We used fluorescent in situ hybridization in order to better characterize the chromosomal anomalies found. Were followed the protocol indicated by the probe's manufacturer and used fluorescent probes (Abbott) corresponding to region of interest.

RESULTS

The cytogenetic results are presented in Table I. Out of 518 male patients tested to rule out cytogenetic causes of male infertility, 476 (91.9%) patients had a normal karyotype. We did not report here the polymorphic variants including chromosomal satellite associations, anomalies of the long arms/satellites of acrocentric chromosome.

Table I. Karyotyping results for the study lot

Karyotype	No of cases
46,XY	476
47,XXY	7
46,XY/47,XXY	3
46,XY/47,XYY	1
46,XY/47,XYY/49,XYYYY	1
46,XdelY	13
46,Xdup(q21)Y	1
46,XY, inv(9)	10
45,XY,trob(21;21)	1
45,XY,trob(13;14)	1
46,XY,t(5;18)	1
46,XY,t(1;11)	1
46,XY(4;16)	1
46,XY/46,XY,t(1;8)	1

42 patients presented an abnormal karyotype: 26 cases with numerical and structural anomalies of the gonosomes, 16 cases presented structural aberrations of the autosome chromosome. The most frequent anomaly of the gonosome chromosome was the deletion of the Y chromosome, followed by 47,XXY or variant karyotype (mosaic 46,XY/47,XXY) (Figure 1).

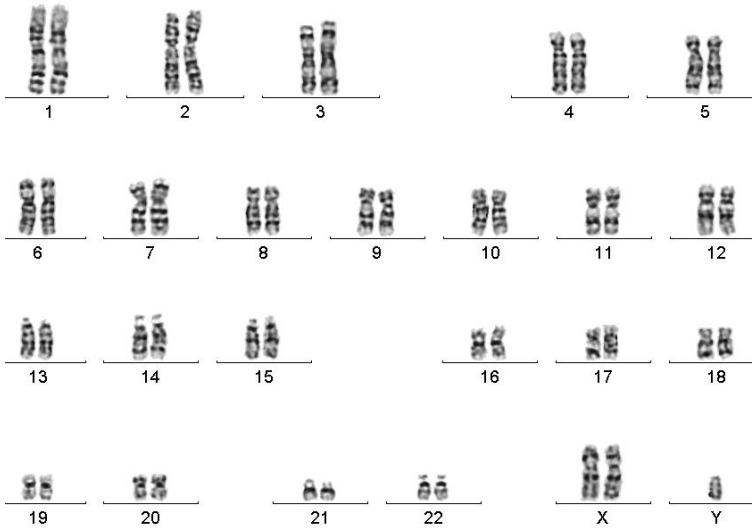


Figure 1. 47,XXY karyotype

Of the autosomal abnormalities, the most frequent anomaly found was the inversion (pericentric or paracentric) of chromosome 9 (Figure 2).

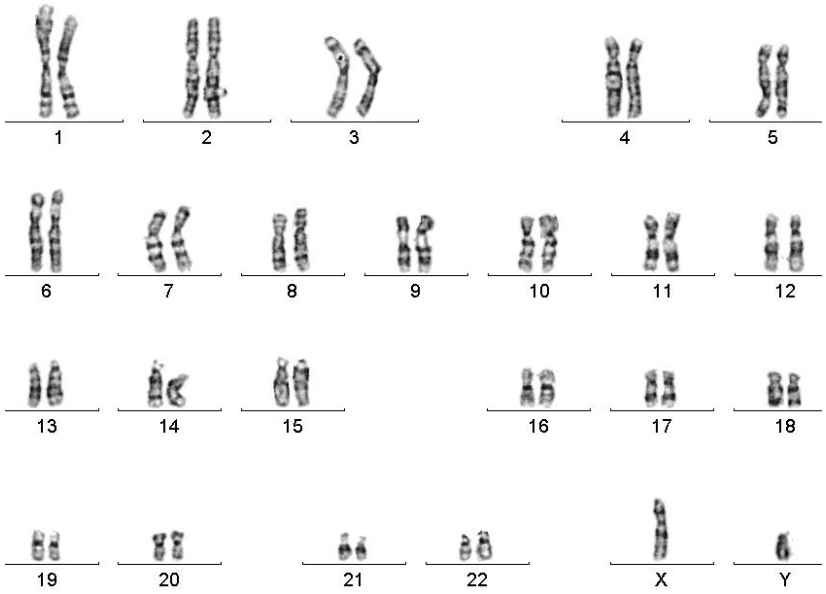


Figure 2.Male karyotype exhibiting pericentric inversion of chromosome 9

Translocations of the autosome chromosome were found in 6 cases (Figure 3, 4), 2 cases presented robertsonian translocation (Figure 5), while the rest of the cases were reciprocal translocation involving autosomes.

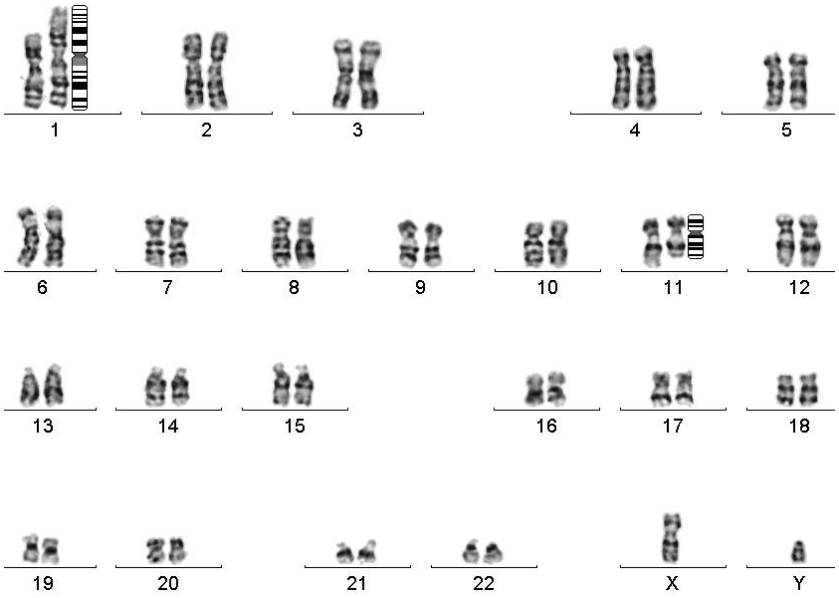


Figure 3.Male karyotype presenting a translocation between chromosomes 1 and 11

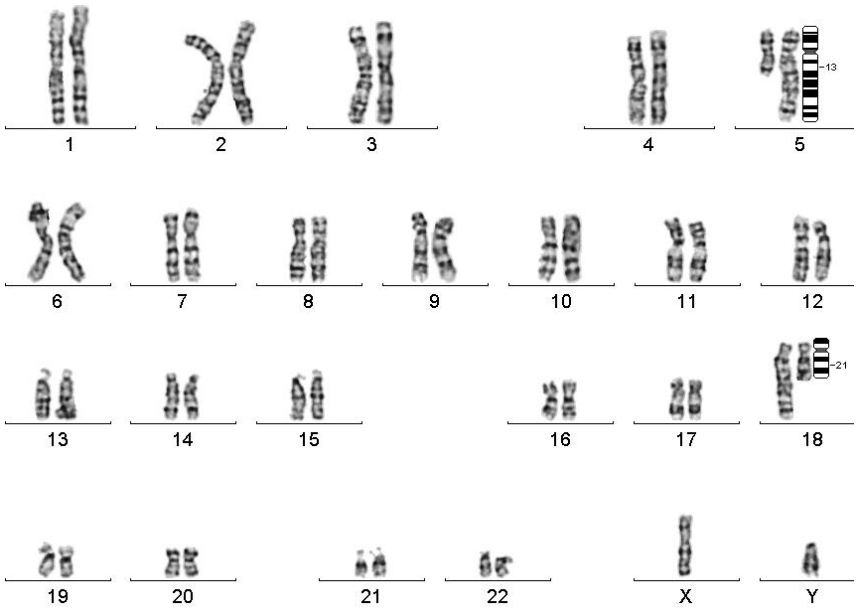


Figure 4. Male karyotype with a translocation between chromosomes 5 and 18

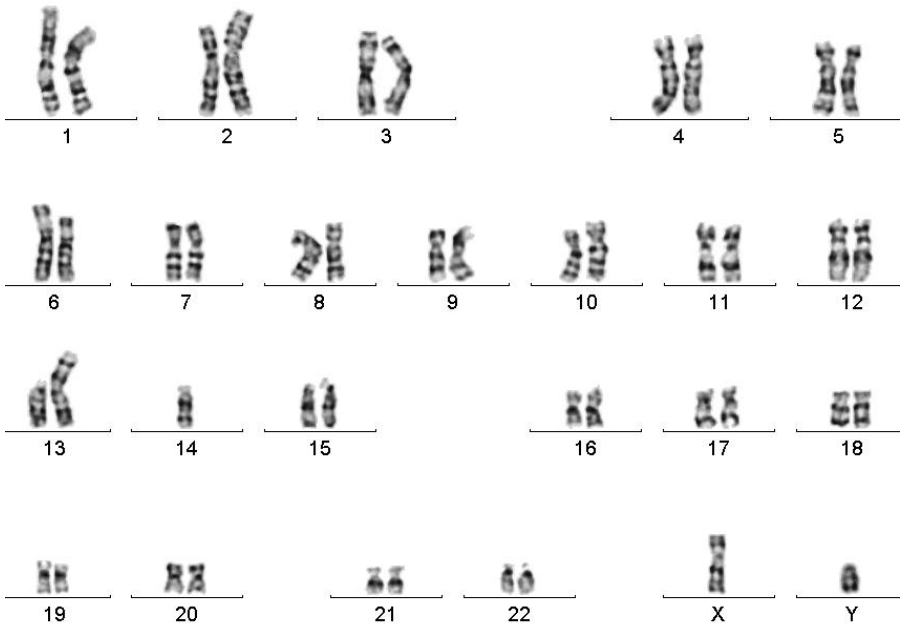


Figure 5. Robertsonian translocation between chromosomes 13 and 14 in a male karyotype

DISCUSSIONS

The aim of this study was to evaluate the frequency and the type of chromosomal anomalies in male from couples with infertility. We done this study over a period of 10 years and included a large number of patients from the Western part of Romania. The results of the study bring valuable information regarding the chromosomal aberrations in unselected males referred for cytogenetic evaluation due to infertility.

Cytogenetic investigations are of great importance in characterizations of male infertility causes, the role of different cytogenetic anomalies is well documented, but still there are under debate the clinical significance of some chromosomal variants [16].

Numerical chromosomal imbalances found in this study involved exclusivelygonosomes, the cases with extra chromosomes X, consistent with Klinefelter syndrome,

being the most frequent aneuploidies identified. The frequency of Klinefelter syndrome in general population is about 0.11%, while in cases of male infertility, the frequency of Klinefelter syndrome is reported to be between 4.9% and 11.4% [17].

In this study the frequency of Klinefelter syndrome was 1.9%, lower than reported in other studies. A possible explanation could be the criteria of inclusion in the study, we analyzed unselected infertile males, and this study did not included only patients with azoospermia or oligospermia. Another aspect is the age of the patients included in the study. All the male patients included in this study were above the age of 18 and the reason for investigation was the reproduction failure. The study did not included male patients under 18 years old.

Y chromosome anomalies represent another cytogenetic aberration found in the study lot. Numerical anomalies of the Y chromosomes were found in 2 cases, the frequency being 0.38%, significantly lower than the aneuploidies involving chromosome X. 13 patients presented deletions of the Y chromosome, aberration considered of clinical importance as these abnormalities are expected to have an impact on male fertility since many male fertility factors are located on the Y chromosome.

On the structural aberration group of autosomes anomalies, the most frequent defect were the inversions followed by the translocations. This group of anomalies classified as balanced chromosomal rearrangements included 16 patients (3.09 %).

There are several studies regarding the role on chromosome inversions in cases of infertility. Inversions of chromosome 9 were considered minor chromosomal rearrangements without phenotype effects, but in the frame of recent reports that found correlations between these chromosomal variants and infertility, recurrent pregnancy loss, deceased infants, a special attention should be paid in these cases [18]. The implications of chromosome 9 variants in infertility are also sustained by the observation that about 30% of carriers of those variants were evaluated due to infertility [19-21]. Another important aspect to mention is the fact that heteromorphisms were correlated with increased chromosomal instability, congenital abnormalities, and cancer [18].

The role of these aberrations in male infertility depends on the type of rearrangement and the effect on male fertility might have different etiologies.

For Robertsonian translocation was reported an incidence of 0.1% in general population, while in infertile males, the incidence was about 0.7% [22].In cases with Robertsonian translocations it was reported that these rearrangements interfere with the XY bivalent forming. There is also a risk for abnormal meiotic recombination and failure of sperm development [23].

Reciprocal translocations have a frequency of 0.09% in general population, but a higher incidence (1.4%) was reported for infertile men [17].

Carriers of reciprocal translocations might have alterations of spermatogenic function, sperm cells were found in spermatocyte stage, not overcoming meiosis I. It was observed that in cases of reciprocal translocations, different quadrivalent or trivalent structures are formed and there is an increased risk for unbalanced gametes formation [24]. The risk for unbalanced gametes formation depends on the chromosomes involved in the rearrangement and the position of the break-points [25].

Translocations leads to changes in gene positions and disruption of several genes can appear during the

rearrangement. The consequence of those events is the alteration of the spermatogenesis and abnormal spermogram [26]. In patients with reciprocal translocations were documented the effects on spermatogenesis consisting in azoospermia, oligozoospermia and infertility [26].

For these cases, analysis of meiotic process can bring additional valuable information in order to provide accurate genetic counseling. An option for these patients is to perform genetic preimplantation diagnosis after the *in vitro* fertilization.

CONCLUSIONS

In this study, 8.1% of the patients referred for cytogenetic investigations due to infertility, presented a chromosomal abnormalities. Cytogenetic investigations are reliable tools for infertile patients' evaluation and should represent one of the mandatory analyses in cases of reproduction failure. Identification of chromosomal anomalies, facilitate a good management of the couple with reproduction failure.

For the future, we consider that the cytogenetic and molecular investigations of the patients with infertility will provide valuable insights into the etiopathology of the infertility and will allow development of targeted treatments for patients.

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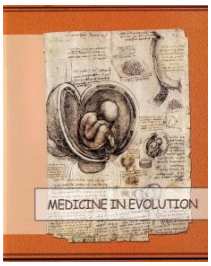

IMMUNOHISTOCHEMICAL MARKERS FOR DIFFERENTIATION BETWEEN KERATOACANTHOMA AND SQUAMOUS CELL CARCINOMA OF THE SKIN

CARMEN MITRACHE[1], MIRCEA TAMPA[2], CARMEN ARDELEANU[3], ALICE RUSU[4], IRINA TUDOSE[4], CLARA MATEI[2], SIMONA ROXANA GEORGESCU[2]

[1]„Medical CenterHumanitas", Bucharest, Dermatology Department
[2]„Carol Davila"University of Medicine and Pharmacy, Bucharest, Dermatology Department
[3]General PathologyDepartment, „Onco Team Diagnostic", Bucharest
[4]„Victor Babes"Hospital for Infectious and Tropical Diseases, Bucharest, Dermatology Department

ABSTRACT

Keratoacanthoma and squamous cell carcinoma are both cutaneous tumors that share multiple clinical and histopathological characteristics, in the same time exhibiting a different evolutional pattern. In this respect, while keratoacanthoma regresses spontaneously, squamous cell carcinoma of the skin extends progressively and may even metastasise; moreover, in rare cases, keratoacanthoma may evolve into cutaneous squamous cell carcinoma. The present article focuses on the factors that conduct the evolution of keratoacanthomatowards transformation into squamous cell carcinoma, instead of spontaneous regression; moreover, this paper aims to establish several differencies between keratoacanthoma and squamous cell carcinoma based on immunohistochemical markers, assessing further the possibility of using these markers in the diagnostic of these tumors.This article focuses on analyising and discussing 4 immunohistochemical markers: CD4, CD8, CD30 and CD117.

Key words: *keratoacanthoma, squamous cell carcinoma, immunohistochemical markers*

Correspondence to:

Mircea Tampa
MD, PhD
Address:"Carol Davila"University of Medicine and Pharmacy, 37 DionisieLupu Street, Bucharest
Phone: +40758040752
E-mail address:tampa_mircea@yahoo.com

INTRODUCTION

Keratoacanthoma and its variants are subject to major clinical and histological heterogeneity.In respect to clinical and histopathological characteristics, keratoacanthoma presents multiple resemblings to squamous cell carcinoma. While some authors consider keratoacanthoma as a benigh tumor, others classify it as a subtye of cutaneous squamous cell carcinoma. However, in current medical practice, keratoacanthoma is usually rather treated, intead of being left aside and expected to resolve spontaneously [1].This hinders the correct evaluation of natural evolution of the lesions diagnosed as keratoacanthoma. Moreover, specialty studies failed to find a reliable marker for the differentiation between keratoacanthoma and squamous cell carcinoma. As in both situations the tumoral lesions may evolve into agressive squamous cell carcinoma, at present times the relationship between keratoacanthoma and squamous cell carcinoma of the skin still remains unclear, therefore further researach in this fields appears as necessary [1].

Objectives

We have undergone research on several cellular markers –of both tumoral and inflammatory infiltrate appartenence- aiming to find the cellular context that leads to the regression of keratoacanthoma; we have also aimed to find the cause and the factors that conduct in some cases towards an agressive evolution, and, furthermore, we have tried to assess whether these factors depend on the tumor, the host or the inflammatory infiltrate.

The immunohistochemical markers chosen for this study were assessed in both keratoacanthomas and squamous cell carcinomas, with the goal of finding a correlation between their presence and weight dependent of the phases of tumoral development and the tumoral evolution. Also, we aimed to establish a differentiation pattern between keratoacanthoma and squamous cell carcinoma, based on the analysed immunohistochemical markers.

RESULTS AND DISCUSSIONS

CD4+ lymphocytes (T helper) and **CD8+** lymphocytes (cytotoxic T cells) are present in intlammatory peritumoral infiltrate of keratoacanthoma and squamous cell carcinoma, in variable proportions, dependent of the evolutive stage of the tumor (Figure 1, Figure 2).

In *early* stages of tumoral development of keratoacanthoma, the infiltrate is moderate, localised mostly at the interface between the lesion and the reticular dermis. The infiltrate is made up mostly of CD3+ lymphocytes (approximately 14 T cells for every B lymphocyte). B lymphocytes CD20+ are localised in nests under the dermo-epidermal junction. In this stage, a predominance of CD4+ T lymphocytes (considered to be non-supressor, CD4/CD8=5:1) was also described [2]. At the peripheral zone of the lesion CD68+ macrophages are aslo found.

As the lesion progresses and the typical aspect of filled crater is achieved, important alterations in the inflammatory infiltrate can be observed. T lymphocytes are predominant, although CD20+ B cells are more numerous than in the previous stage (CD3:CD20 =8:1) [2].

Later on, the keratoacanthoma exhibits an extreme behaviour, developing the tendencies shown in the early stages: the B lymphocytes are more numerous than before, although

never as numerous as T lymphocytes (CD3: CD20 = 4:1) and CD4+ T lymphocytes are as numerous as CD8+ lymphocytes[3]. In this stage, some macrophages CD68+ may be observed in the fibrosis area at the base of the tumor.

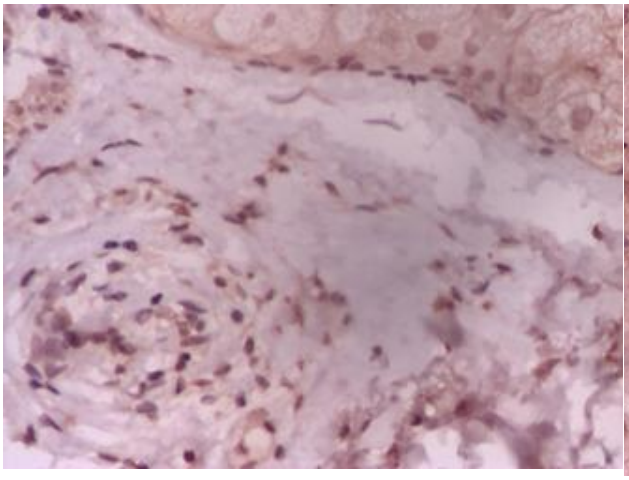

Figure 1. Immunohistochemical staining. CD4+ lymphocytes in keratoacanthoma. 20x magnification

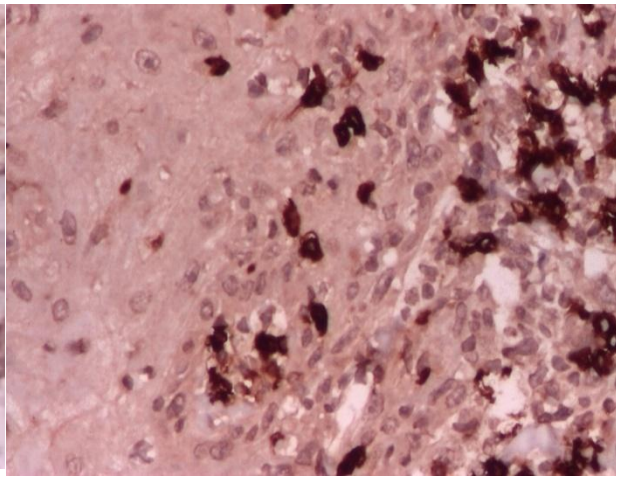

Figure 2. Immunohistochemical staining. CD8+ lymphocytes in keratoacanthoma. 20x magnification

In the stage of keratoacanthoma regression, both CD4+ and CD8+ lymphocytes are found more abundent in the tumor, with a predominance of CD8+ cells over CD4+ cells, while the regression follows its course.

These findings seem to demonstrate the principal role of cytotoxic T cells in destroying the tumoral cells of keratoacanthoma[4, 5].

CD30 is a protein member of TNF (tumoral necrosis factor) receptor family on the surface of the cell; it stands as a tumoral marker and a receptor expressed on T or B activated cells (and not on non-activated cells) (Figure 3). CD30 cellular marker is also known as Ki-1 or Ber-H2 [6]. CD30 is a lymphocytic activation marker initially described in Hodgkin lymphoma with Reed Sternberg cells [7]. However, CD30 + cells are also present in inflammatory infiltrate of numerous non-malignant dermatoses.

CD30 is also a positive regulator of apoptosis; moreover, it has been proven that CD30 limits the proliferative potential of CD8+ autoreactive effector T cells and protects the host against autoimmunity [6].

There exists a correlation between the considerable reduce in the number of CD30+ lymphocytes and the maintainance of a high number of CD8+ lymphocytes ih the regression phase of the keratoacanthoma, permitting to CD8+ cells to exhibit their cytotoxic effect, beneficial in this situation, unlike squamous cell carcinoma, where these cels are better represented. The presence of CD30 on the surface of the cells has been more accurately studied in haematologic tumors, than in solid tumors [8, 9].

In 2008, Fernandez-Flores published a study evaluating the presence of CD30+ in both dermal inflammatory infiltrate in regression keratoacanthomas and well-differentiated squamous cell carcinomas. Both the percent and quantity of CD30+ cells in each lesions were assessed. In squamous cell carcinomas, CD30+ cells were more numerous [10]. Although the exact role of these cells in keratoacanthoma evolution remains unknown, they seem to dissappear in the precess of regression of the tumor[10].

It is also possible to exist a breach in keratoacanthoma evolution that leads to regression, and when these

condition is not fulfilled, the keratoacanthoma may progress towards profound metastasing squamous cell carcinoma [11].

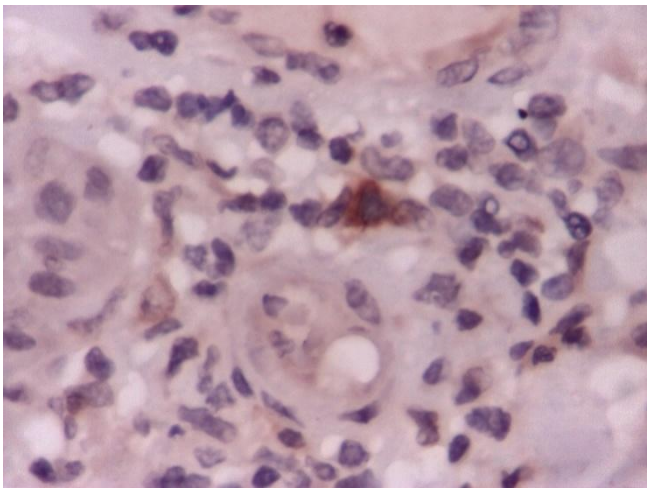

Figure 3.Immunohistochemical staining. CD30+ lymphocytes in keratoacanthoma. 40x magnification

CD 117is an important marker, used to identify several types of precursos haematopoetic cells in bone marrow.

The mast cells are important components of immune system in vertebrates. They are found in almost every body tissue and they stationate at the entry points in the organism, playing a sentinel role; therefore, they can be found in dermis, in the intestinal mucosa and submucosa, in the conjunctival membrane of the eye, in pulmonary alveolae and in respiratory branches.As components of the immune system, the mast cells become more numerous in the inflammatory areas in atopic, malignant conditions[12, 13, 14].

The peritumoral inflammatory microenvironment (Figure 4, Figure 5) is composed of immune cells, stromal cells, endothelial cells tht assure a proper environment for the tumoral growth and invasion [15-18].This also represents a barrier for the immune response of the host against the tumor, and, therefore, a target of cancer immunotherapy [19].The accumulation of mast cells in tumoral microenvironment is associated with a defective prognosis in agressive cancers, whilst a high effector T cells density in the tumor is associated with a favorable prognosis [19].

The role of the mast cells in cancer seems to be very complex and up to present times, not entirely understood. Recent proofs support the idea that these cells also influence the angiogenesis and tumoral invasion, as well as the immunological supression, and have a major contribution to the immune supression in the peritumoral microenvironment [19].

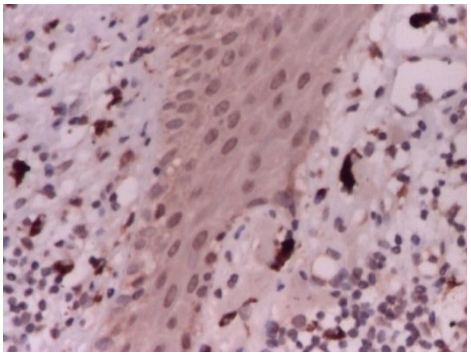

Figure 4. Mast cells in peritumoral infilatrate in keratoacanthoma, CD117+, 20X magnification

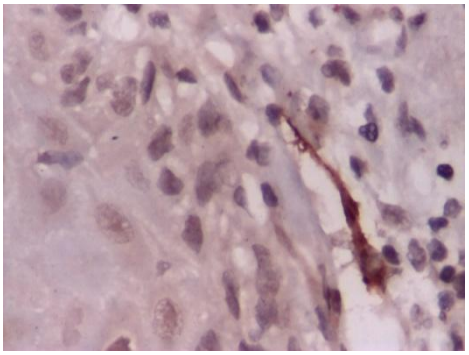

Figure 5. Mast cell, CD117+, 40X magnification

We have tested only the completely excised tumors, consisting of 15 keratoacanthomas and 7 cutaneous squamous cell carcinomas.

The skin tumors were selectioned in the „Victor Babes"histopathological laboratory and personal practice, while the immunohistochemical determinations were performed in Onco Team Diagnostic laboratory.

Out of the 15 analysed keratoacanthomas, 2 have presented an advanced tumoral regression pattern at histopathological examination, consisting of flattened crater, very low inflammatory infiltrate, displaced in some areas by fibrosis (Figure 6).

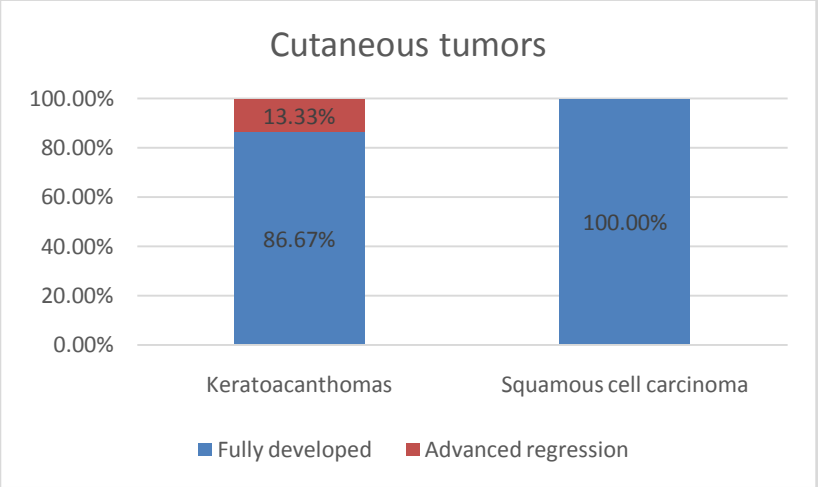

Figure 6. Overwiew of the studied skin tumors

The immunohistochemical staining for CD30 determination has shown a proportion of CD30 situated between 1% and 5%; the lower proportions (<1%) have corresponded to the keratoacanthomas in regression stage. However, the CD30+ lymphocytes were found in higherproportions, situated between 1% and 10% in the specimens of squamous cell carcinomas (Figure 7).

CD117 analysis has shown the presence of the marker in all squamous cell carcinomas tested but one, whilst CD117 was present in only 66.66% in keratoacanthomas (Figure 8).

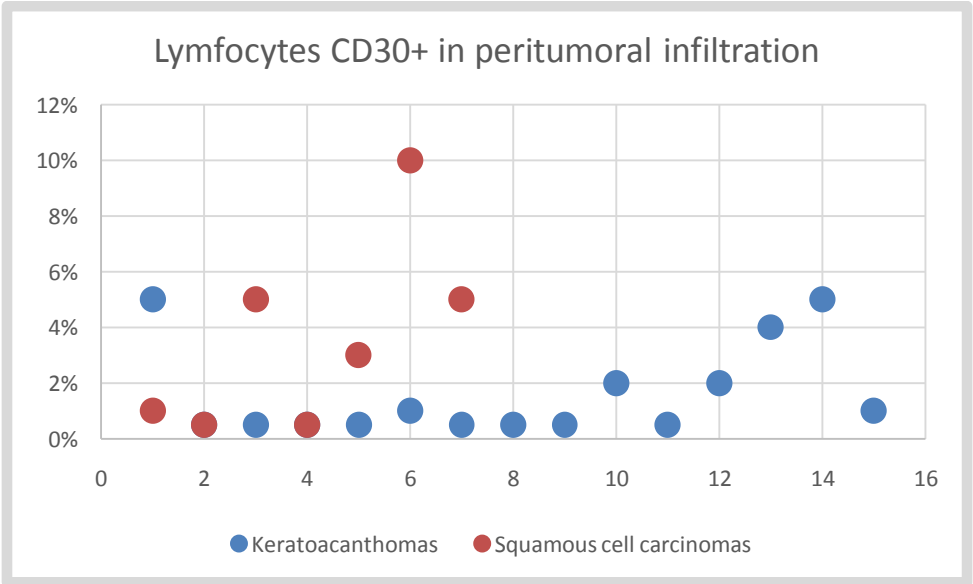

Figure 7. CD30 + lymphocytes present in higher percentages in infiltration of carcinoma unlike keratoacanthomas

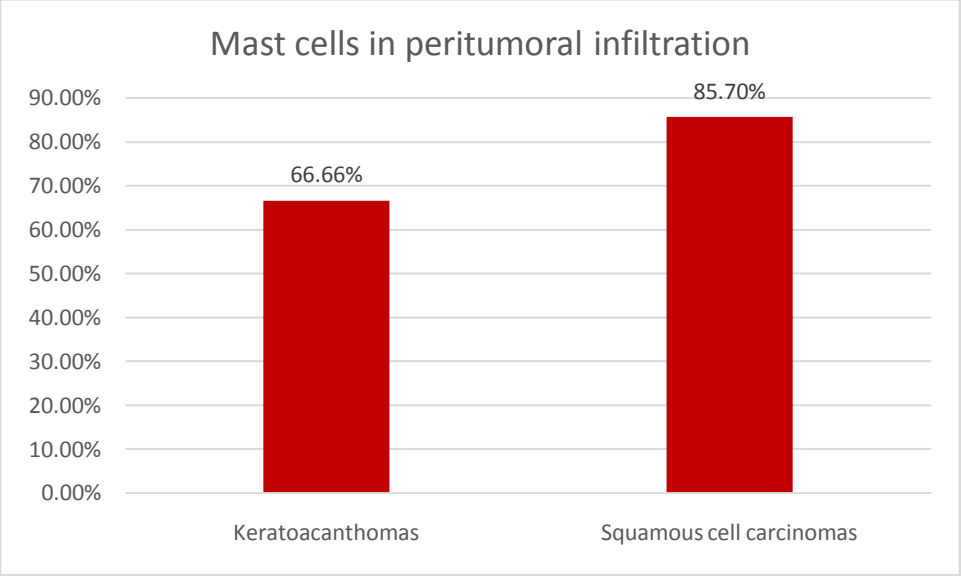

Figure 8. Infiltration of mast cells present in a majority of carcinomas, in contrast to keratoacanthomas

As for CD8+ lymphocytes, they were detected in a significantly higher proportion in the peritumoral infilatrate in keratoacanthomas (40-90%), as compared to squamous cell carcinomas (only 30%-60%).

CONCLUSIONS

CD30+ lymphocytes, present in the lowest percent in regression keratoacanthomas, represent a source of investigation towards understanding their involvement in the regression of keratoacanthomas; also, remains to be established whether CD30+ lymphocytes represent one of the factors that lead to tumoral regression or it represents a phenomenon secondary to regression initiated by other factors.

On the other hand, the presence of mast cells in a significantly lower percent in the inflammatory infiltrate of keratoacanthomas, as compared to that of squamous cell carcinomas, represent a factor of positive prognosis, permitting the immune system of the host to react against the tumor.Considering the cytotoxic function of CD8+ cells, their presence in a significant higher percent in keratoacanthoma may raise the hypothesis of a beneficial role of these cells in the evolution towards regression, instead of invasion and agressiveness.

Up to present date, there has not been identified a reliable marker for differentiation between keratoacanthoma and squamous cell carcinoma; further studies in this field are necessary.

Conflicts of interest

None declared. All authors have contributed to this work. The article is part of author Carmen Mitrache PhD thesis.

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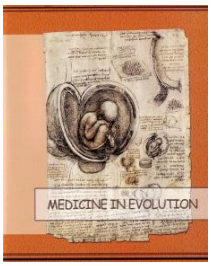
NEAR INFRARED SPECTROSCOPY AS AN INDICATOR OF HYPOXIC ISCHEMIC INJURY IN PREMATURE INFANTS



NICOLETA IONIȚA[1,2], MIRABELA ADINA DIMA[1,2], ALINA ELENA AGOSTON-VAS[2], C. ILIE[1,2], C. MUNTEAN[2]

[1]"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania, Department of Obtetrics-Gynecology and Neonatology
[2]Clinical Emergency Hospital – Bega Universitary Clinic, Timișoara, România a

ABSTRACT

Near Infrared Spectroscopy (NIRS) technique is based on the optical properties of the brain tissue due to the natural chromophores, hemoglobin, deoxyhemoglobin and cytocrome oxidase with different characteristic absorption spectra in the visible and near-infrared wavelength range.To convert the changes in absorbtion and attenuation in concentration of the chromophores it is used the Modified Lambert Law [2]. There are different NIRS devices available:FORE-SIGHT, INVOS, NIRO, InSpectra, O2C, OM-220, OxiplexTS, TOx, TRS-20.

Non-invasive methods of investigation are very useful in the NICU. NIRS is a non-invasive and real time technique which provides information about cerebral tissue oxygenation and cerebral blood flow.

There are several studies which demonstrate that ultrasound scanning alone does not provide useful information about early injury in the brain. This is also our aim to demonstrate that observing regional cerebral oxygenation (rSO2) simultaneously with cerebral ultrasound gives a helpful hand in choosing the most appropriate therapeutic procedures and establish an early diagnose in order to prevent the onset of irreversible brain damage. From a number of 144 preterm newborn infants (gestational age < 32 weeks) admitted in our NICU during January 2013 – May 2014, we chose for our study 70 of them, having an average gestational age = 29,057 weeks (24-32 weeks) and the average birth weight = 1334,286 g (400-2150 g). NIRS has organ and region specificity, it indicates regional perfusion and metabolism, it is not temperature, pulse or blood flow dependent [4] which is an advantage comparing to the classic methods of oxygen monitoring like pulsoximetry and blood gasses. It is very easy to use, it does not stress the infant and we can place nCPAP or conventional ventilation during the monitorization. Other investigations like blood pressure and blood gases show the status of the systemic oxygenation, but the values do not indicate cerebral oxygenation. Using NIRS we have a real time result, as previously explained, so we can have in time a cerebroprotective intervention.

Key words: *Near Infrared Spectroscopy,Pulsoximetry (SpO2), cerebral oximetry (rSO2), INVOS*

Correspondence to:

Nicoleta Ioniță
Address: Clinical Emergency Hospital – Bega University Clinic, 12 Victor Babes St, Timișoara, România
E-mail address: ionita_nicoll@yahoo.com

INTRODUCTION

Near Infrared Spectroscopy (NIRS) was first described by Jobsis in 1977 using the results obtained from studies on laboratory animals. First reported studies on cerebral oxygenation in newborn infants (a lot of 3 newborns) belong to Brazy, Darrell, Lewis, Mitnick and Jobsis from 1985 [1]. First quantitative measurements were reported by Reynolds and colleagues (Edwards et al., 1988; Reynolds et al., 1988; Wyatt, Cope, Delpy, Wray & Reynolds, 1986) who monitored sick newborn infants and the changes in regional hemoglobin concentrations, cerebral blood flow and cerebral blood volume. This technique is based on the optical properties of the brain tissue due to the natural chromophores, hemoglobin, deoxyhemoglobin and cytocrome oxidase with different characteristic absorption spectra in the visible and near-infrared wavelength range.To convert the changes in absorbtion and attenuation in concentration of the chromophores it is used the Modified Lambert Law [2]. There are different NIRS devices available:FORE-SIGHT, INVOS, NIRO, InSpectra, O2C, OM-220, OxiplexTS, TOx, TRS-20.

Objectives:

In the Neonatal Intensive Care Unit (NICU) we face preterm infants having a characteristic pathology. They are a very vulnerable category of patients being sensitive to allminor changes in their management. Moreover, their brain is very vulnerable to all changes due to the extrauterine life and so to the variation in oxygenation; this is a major concern because it involves their neurodevelopmental outcome. Non-invasive methods of investigation are very useful in the NICU. NIRS is a non-invasive and real time technique which provides information about cerebral tissue oxygenation and cerebral blood flow. It is known that cerebral hypoxic ischemic injury is a major cause of permanent neurodevelopmental disability in preterm infants [3]. Portable ultrasound devices are highly effective at identifying cerebral hemorrhage and hypoxic-ischemic encephalopathy (EHIP). There are several studies which demonstrate that ultrasound scanning alone does not provide useful information about early injury in the brain. This is also our aim to demonstrate that observing regional cerebral oxygenation (rSO2) simultaneously with cerebral ultrasound gives a helpful hand in choosing the most appropriate therapeutic procedures and establish an early diagnose in order to prevent the onset of irreversible brain damage

PATIENTS AND METHOD

From a number of 144 preterm newborn infants (gestational age < 32 weeks) admitted in our NICU during January 2013 – May 2014, we chose for our study 70 of them, having an average gestational age = 29,057 weeks (24-32 weeks) and the average birth weight = 1334,286 g (400-2150 g). Most of them were born by cesarean section and needed cardiopulmonary resuscitation in the delivery room (VPPO2 100%, orotraheal intubation, external cardiac massage and medication). We excluded from our study lot the infants having congenital heart malformations or any other kind of malformations, and those for whom we had no parental approval.We noted the gestational age, birth weight, Apgar score at 1/5/10/20minutes, the need for resuscitation, maternal and fetal pathology, if they needed any type of suplimentary oxygen or conventional ventilation, the cardiac

and cerebral ultrasound aspects. We continuously monitored peripheral oxygenation (SatO2), blood pressure, heart rate and respiratory rate right after birth. Pulsoximetry is a method which is routinely used in NICU but it seems that it doesn't give sufficient data regarding cerebral oxygenation which is our major concern in this study. We monitored cerebral oxygenation using an INVOS 5100 (Somanetics) device, neonatal sensors for cerebral monitoring, the data was stored on a memory stick attached to the INVOS monitor and then processed on a laptop IBM Think Pad T410; data was processed using SPSS Statistics 17.0. We performed cerebral ultrasound using a Logiq E device. For ethical principles we asked for written consent of parents. We placed the NIRS sensors over the right cerebral hemisphere, after rigorously cleaning the skin surface. We excluded the newborn infants having hemangiomas on the frontal area, bruises or other lesions. We monitored cerebral oxygenation in our preterm newborn infants 3 hours after birth and during 24 hours. It has to be taken in consideration that in the first 10 minutes of life newborn infants and especially preterm infants have physiologically low oxygen saturation. The reference limits were established between 55-85%. The nurses from NICU were trained in using the INVOS device; they had to select the events and mark them on the monitor. We selected the following events: miscellaneous, physical assessment, oral and endotracheal tube suction, repositioning, feeding, seizures, intravenous bolus and sedation.

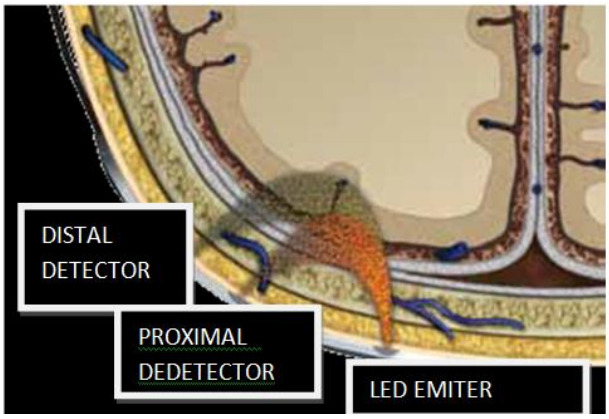


Figure 1. NIRS sensors functioning principle

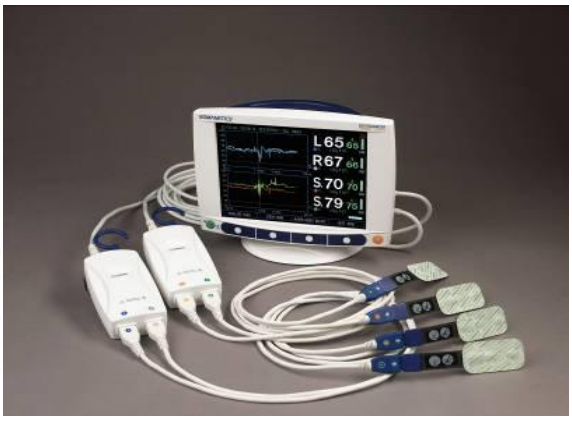


Figure 2. INVOS 5100 device

RESULTS AND DISCUSSION

The preterm infants included in the study lot were in need of cardiopulmonary resuscitation in the delivery room; median Apgar score 1/1'; 3/5', 6/10'; 7/20'. Pulsoximetry in the first 5 minutes after birth showed a SatO2 < 20% in the majority of the cases. After resuscitation SatO2 reached 50-60%. During the first hours after birth, blood pressure, heart rate, respiratory rate, SatO2 and blood gasses showed impaired general condition: hypotension, tachycardia or bradycardia, tachypnea, metabolic and respiratory acidosis, capillary refill time > 3 seconds. After specific oxygen and drug therapy the infants were stabilized; they received suplimentary oxygen, nCPAP, orotraheal intubation and conventional ventilation as needed, thermic comfort, hemodynamic support, metabolic, fluid and electrolytic correction so the values of peripheral oxygenation increased between 80-92%.We considered starting the NIRS cerebral oxygen monitoring in order to establish the impact of EHIP on the

neurodevelopmental outcome of the preterm infants. We noticed low regional cerebral oxygen values (rSO2) < 60% in the infants diagnosed by cerebral ultrasound with EHIP. The presence of EHIP means a reduced blood flow in the cerebral tissue, so a persisting low oxygenation which influences the appearance of the intraventricular hemorrhage (IVH). When we first applied the sensors the device registered a baseline value, after that we set the reference limits as we previously mentioned (55-85%). In 54% of the infants we had a severe form of EHIP and values of rSO2 < 50% in the majority of the monitoring time and the most of them developed 2nd and 3rd degree IVH; average rSO2 values = 76%; in 14% of the infants the cerebral oxygenation was under the critical limit of 45% and they developed 4th degree IVH and periventricular leucomalakia (PVL); average rSO2 = 61%. Variations of over 10% beside reference limits are pathologic. We diagnosed IVH and PVL by cerebral ultrasound performed periodically during their stay in the NICU. The rSO2 curve decreased when the preterm infants had low heart rate, low blood pressure, high respiratory frequency, metabolic and respiratory acidosis or seizures. The degree of cerebral tissue oxygenation is also influenced by external factors like the interventions of the nurses; rSO2 values decreased when repositioning the infant or other kind of physical assement, suctioning of the oral cavity or endotraheal tube, administering intravenous bolus or sedatives and other medication; the oxygenation curve increased during blood transfusions. In each of these situations we noticed variations of the cerebral oxygenation on the INVOS monitor, but in the majority of the cases we had nor or late variation in the periferic oxygenation or the values did not match.

Figure 3. INVOS report of a cerebral oxygenation record in a premature infant during 16 hours

Figure 4.Cerebral ultrasound aspect of EHIP and PVL

CONCLUSIONS

Pulsoximetry (SpO2) is a noninvasive method used routinely in the NICU to determine systemic oxygenation, the quantity of O2 delivered to the tissues; it needs detection of arterial pulse and blood flow. It is not conclusive for appreciating cerebral oxigenation compared to INVOS. NIRS for regional cerebral oximetry (rSO2) is a noninvasive method which it is not routinely usedin the NICU, it determines in the capillaries the balance between the quantity of O2 which is delivered to the tissue and the quantity which is utilized; there is no need for pulse or blood flow detection. NIRS has organ and region specificity, it indicates regional perfusion and metabolism, it is not temperature, pulse or blood flow dependent [4] which is an advantage comparing to the classic methods of oxygen monitoring like pulsoximetry and blood gasses. It is very easy to use, it does not stress the infant and we can place nCPAP or conventional ventilation during the monitorization. The oxygen values registered using NIRS must be interpreted in the clinical context (blood pressure, blood gasses, peripheral oxigenation). NIRS is a very reliable method of investigation, real time and as the devices are portable, we can monitor at bedside. We can monitor also the regional oxygenation placing the sensors on the kidneys, gut, liver and muscles area [4]. Cerebral hypoxia and hiperoxia are feared events in the NICU because they are involved in increasing mortality and morbidity of infants. Hiperoxia shows especially in the newborn infants with hypoxic ischemic injury in the phase of cerebral reperfusion, due to a lower metabolism in critical patients who are not receiving supplementary oxygen; these events are correlated with a poor prognosis [5].Cerebral ultrasound is also a noninvasive method used to identify and to diagnose cerebral injury and for long term investigation of cerebral development, but it is not useful if we intend to prevent the occurrence of the lesions. Other investigations like blood pressure and blood gases show the status of the systemic oxygenation, but the values do not indicate cerebral oxygenation. Using NIRS we have a real time result, as previously explained, so we can have in time a cerebroprotective intervention.

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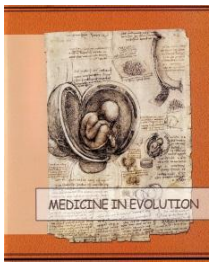

COMPARATIVE STUDY ON COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) USE BY PATIENTS IN ROMANIA AND HUNGARY

OVIDIU JUPANEANT[1], GABRIELLA HEGYI[3], CORINA SERBAN[1, 2], ANCA TUDOR[1], SIMONA DRAGAN[1,2]

[1]University of Medicine and Pharmacy"Victor Babeş"Timişoara, Romania
[2]Center for Interdisciplinary Research, University of Medicine and Pharmacy"Victor Babes"Timisoara, Romania
[3]Pecs University of Medicine, Head of the CAM Department, Pecs, Hungary

ABSTRACT

Background and aim: *Complementary and Alternative Medicine (CAM), as utilized by European citizens, represents a variety of different medical systems and therapies based on the knowledge, skills and practices derived from theories, philosophies and experiences used to maintain and improve health, as well as to prevent, diagnose, relieve or treat physical and mental illnesses. The purpose of this study was to compare the CAM use by patients in both Romania and Hungary using a modified form of NAFKAM I-CAM-Questionnaire.*

Material and method: *The study included 252 Romanian and 105 Hungarian patients, in order to compare the CAM used. The data was collected from seven CAM practices in Romania and from eleven CAM practices in Hungary. All participants completed the modified I-CAM-Q once, in their own country's language.*

Results: *The education levels of patients registered significant differences between the two countries ($\chi 2$ test, $p=0.002$, $a=0.01$). The proportion of gymnasium and high school graduates was significantly higher in Romania compared to Hungary (Z test, $p=0.038$ for gymnasium level and $p=0.002$ for high school level). It was observed that Romanian both women and men address an acupuncturist in a significantly higher proportion than other CAM practices ($p<0.001$). The Romanian men go in a significantly higher proportion to the phytotherapist than the Hungarian ones ($p=0.007$). Hungarian men address in a significantly lower proportion a phytotherapist, compared to other CAM practices ($p<0.001$).The number of visits to Acupuncture was significantly higher for both men and women in Hungary ($p<0.001$) comparative to Romania.*

Conclusions: *Modified NAFKAM I-CAM-Questionnaire indicated that the most used CAM method in Romania is acupuncture, while phytotherapy is the less addressed CAM method in Hungary.*

Key words: *Complementary and Alternative Medicine (CAM), patients, questionnaire, Comparative study, acupuncture, phitotherapy, holy unction*

Correspondence to:

Anca Tudor
Lecturer
Address: University of Medicine and Pharmacy"Victor Babes", 2 E. Murgu Square, 300041 Timisoara, Romania

INTRODUCTION

The use of complementary and alternative medicine (CAM) is becoming increasingly popular in European countries and the United States (US). Only few population-based studies have investigated the use and acceptance of a variety of classical and alternative methods, including their possible determinants (1).

The first national survey conducted between 1997-2002 in the US on the prevalence of CAM use revealed that the most commonly used CAM modalities were herbal therapy (18.6% of US adults), relaxation techniques (14.2% of US adults) and chiropractic (7.4% of US adults). Among CAM users, 41% used two or more CAM therapies, overall use for the 15 most common therapies representing about 72 million US adults yearly (2).The use of herbs, vitamins, and other complementary and alternative natural health products continued to be highly prevalent in the US in the next decade, particularly among individuals diagnosed with cancer and other chronic illnesses (3-5).

In Europe, a recent review on CAM use and acceptance of CAM among the general population and medical personnel reported a prevalence between 5% and 74.8% and finding a higher utilization of homeopathy and acupuncture in German-speaking countries (6). Previous surveys conducted in UK, Germany and Italy found that 10% to 70% of the total population use CAM therapies each year (1, 7-9).

Recently, CAMbrella, a coordination action funded within the Framework Programme 7, was aimed to address the prevalence of CAM use in Europe from population-based studies, and to determine which therapies are used for which conditions, considering the fact that, according to the European Information Centre for Complementary and Alternative Medicine, more than 100 million EU citizens regularly use CAM (10).

The only data concerning Romania, also available on the CAMbrella website, was derived from two Omnibus studies regarding CAM use by patients. The first study,"Habits and attitudes towards treatments in Romania"was developed as part of GfK Omnibus, a survey on a national representative sample. The research was applied to a sample of 1636 respondents from urban and rural areas aged 15 years and over, from 12 to 23 January 2009. The second Omnibus-type survey made by Totem Communications between May-June 2009 on a nationally representative sample of 1213 people aged over 15 years (574 men and 639 women) with a margin of error of ± -3%,showed that 2% of subjects have addressed a natural or alternative treatment in the last 12 months.

From the data available for Hungary, it results that about half of the population uses CAM, with the most common users being women, middle-aged people, well-educated individuals, people in high positions with high income, and city dwellers. There seems to be a significant trend towards an increased use of CAM.

The conclusions of the systematic review conducted within the CAMbrella project by S Eardleyet al were that heterogeneity and poor quality of studies available at present do not allow pooling in a meta-analysis. The authors also suggested that a valid questionnaire on CAM use variable for different countries would increase the accuracy of data collection (11).

The International Questionnaire to measure use of Complementary and Alternative Medicine (I-CAM-Q) was considered a good starting point for measurement of CAM use within the CAMbrella project (12). The questionnaire was translated into four

EU languages (Romanian, Italian, Spanish and Dutch). Pilot studies to validate the questionnaire were performed on 50 respondents in several centers in UK, Romania, Italy, Spain and the Netherlands. A number of problematic items and layout difficulties were identified across countries. Therefore, the investigators recommended several developmental modifications before using the I-CAM-Q in any major survey, considering that without these modifications the questionnaire has low face validity and acceptability (13).

The purpose of the present paper was to develop a modified version of the I-CAM-Q and to apply it in selected CAM-user patient populations in Romania and Hungary.

MATERIAL AND METHODS

In this study, the modified I-CAM-Questionnaire was applied on 252 Romanian patients, and 105 Hungarian patients, in order to compare the CAM use by patients in both countries. The data was collected from seven CAM practices in Romania and from eleven CAM practices in Hungary. All participants completed the modified I-CAM-Q once, in their own country's language. All the data were collected at the University of Medicine and Pharmacy Victor Babes, Timisoara, Romania. Ethical approval was obtained as necessary in Romania and Hungary.

The original NAFKAM I-CAM questionnaire has four sections. In the first two sections the patients asked about addressing the providers of: Manual therapy, Homeopathy, Acupuncture, Herbal medicine (Phytotherapy), Spiritual healing, Holy Unction, and to the providers of these CAM treatments. In the third section they were asked about using: herbs, vitamins, minerals, homeopathic remedies and other supplements; and last, in the fourth section, the patients were asked about their spiritual practices.

Translation of the questionnaire into Romanian and Hungarian following the European Organization for Research and Treatment of Cancer (EORTC) procedure (translation into the target langue from the original questionnaire language and retranslation back to the original language) was completed by March 2012. Difficult terms and issues from each country were discussed in consultation with the I-CAM-Q authors. Items were translated to overcome local variation and misunderstanding in therapies across countries; e.g. 'chiropractic' as 'manual therapy' in Romania. 'Spiritual healing' was the most difficult term, considered a religious matter in some EU countries; therefore, where necessary, respondents were given written definitions. Definitions were added for some countries where the researchers thought particular terms would be poorly understood (e.g., spiritual healing). All of these, because the original NAFKAM I-CAM questionnaire was not validated after the Pilot I-CAM-Q Study, because it was too heavy to be applyed and to be understood by the patinents. The same difficult terms and issues appeared in: Romania, Hungary, Netherlands, Spain and England.

Self-Complete participants completed and delivereddocument copies of the questionnaires by hand.

Statistical analysis

Data from each participating country were collected into a single data file and the statistical analysis was realized in Excel and SPSS version 17. Basic descriptive statistics for the entire sample and for each country separately were produced to describe the respondents' characteristics and responses to each item on the modified I-CAM-Q. Quantitative analysis focused on the extent to which

respondents followed the instructions on the modifiedI-CAM-Q and the extent of missing data. The total missing data was summed across all commensurate items within each modifiedI-CAM-Q question, for each different language version of the I-CAM-Q.For numeric variables the central tendency and dispersion indicators were calculated, and comparisons between variables were made using the ANOVA test (in the case of comparison between multiple sets of values) and the t-test of significance for variables. Frequency tables were done for nominal variables. The comparisons and associations were done using the $\chi 2$ compliance test.

RESULTS

he characteristics of age and sex of the study groups are presented in table 1.

Table 1. The characteristics of the study groups

	Romania	Hungary	p
Age	48.32±15.42	47.03±13.06	0.460
Sex (M/F)	98/154	37/67	0.631

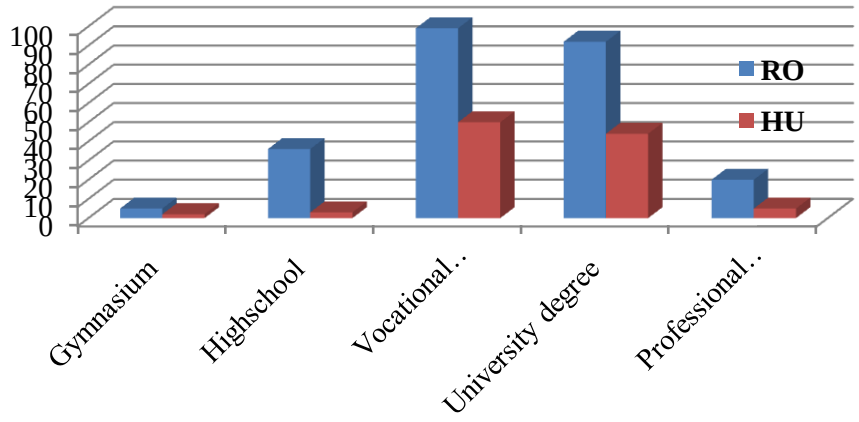

Figure 1. The differences in educational levels of respondents from both countries

The education levels of patients registered significant differences between the two countries ($\chi 2$ test, p=0.002, α=0.01). The proportion of gymnasium and high school graduates was significantly higher in Romania compared to Hungary (Z test, p=0.038 for gymnasium level and p=0.002 for high school level).

Table 2.CAM use by disease categories in Romania and Hungary

Nr.	Medical Specialties	Frequency	Percent	Cumulative percent
1	Internal Medicine	121	32.44	32.44
2	Cardiovascular diseases	51	13.67	46.11
3	Oncology	14	3.75	49.87
4	Rheumatology	75	20.11	69.97
5	Urology & Nephrology	12	3.22	73.19
6	Obstetrics and Gynecology	18	4.83	78.02
7	Psychiatry	60	16.09	94.10
8	Surgical Specialties	22	5.90	100.00

The addressability to main CAM therapies in both countries i.e. chiropractic, homeopathy, phytotherapy and acupuncture as percentageis represented in table 2.

It was observed that Romanian women go in a significantly higher proportion to acupuncture than to the other CAM practices (p<0.001). Using Z test it was noticed that the Hungarian women go in a significantly lower proportion to phytotherapy, in comparison with other practices, and in a significantly higher proportion to acupuncture (p=0.006, as comparison to chiropractic, p=0.031, as comparison to homeopathy and p<0.001 as comparison to phytotherapy).

Table 2.The percent of addressability to main CAM treatments of women

	Romanian	Hungarian	*p*
Consulted a CAM physician in the last 12 months (No/Yes)	24.5/75.5	35.1/64.9	0.279^{ns}
Number of visits to family physician in the last 12 months	2.37±1.74	2.21±1.93	0.447^{ns}
Visits to a chiropractician (No/Yes)	81.6/18.4	73/27	0.245^{ns}
Number of visits to a chiropractician in the last 12 months	3.17±2.46	4.10±2.69	0.376 ^{ns}
Visits to a homoeopathist (No/Yes)	70.8/29.2	73.1/26.9	0.749^{ns}
Number of visits to a homoeopathist in the last 12 months	1.69±0.82	2.39±1.69	0.073^{ns}
Visits to phytotherapist (No/Yes)	69.4/30.6	91.9/8.1	0.007
Number of visits to a phytotherapist	3.13±5.18	3.00±2.00	0.571^{ns}
Visit to an acupuncturist (No/Yes)	38.3/61.7	55.2/44.8	0.026
Number of visits to an acupuncturist in the last 12 months	2.26±1.96	8.79±5.83	<0.001

Using ANOVA test, significant differences were found between the number of visits of the Romanian women to the four CAM practices (*p*=0.042). Their visits to the Chiropractor are significantly more often than the visits to the other CAM practices (*p*=0.009, as comparison to homeopathy, p=0.008 as comparison to phytotherapy and p=0.049 as comparison to acupuncture), then more often to acupuncture comparative with homeopathy (p=0.017) and phytotherapy (p=0.011).

Table 3. The percent of addressability to main CAM treatments of men

	Romanian (n=98)	Hungarian (n=37)	*p*
Consulted a CAM physician in the last 12 months (No/Yes)	24.5/75.5	35.1/64.9	0.279^{ns}
Number of visits to family physician in the last 12 months	2.37±1.74	2.21±1.93	0.447^{ns}
Visits to a chiropractician (No/Yes)	81.6/18.4	73/27	0.245^{ns}
Number of visits to a chiropractician in the last 12 months	3.17±2.46	4.10±2.69	0.376^{ns}
Visits to a homoeopathist (No/Yes)	74.5/25.5	62.2/37.8	0.202^{ns}
Number of visits to a homoeopathist in the last 12 months	2.04±0.84	4.64±7.48	0.251^{ns}
Visits to phytotherapist (No/Yes)	69.4/30.6	91.9/8.1	0.007
Number of visits to a phytotherapist in the last 12 months	3.13±5.18	3.00±2.00	0.571
Visit to an acupuncturist (No/Yes)	35.7/64.3	48.6/51.4	0.236^{ns}
Number of visits to an acupuncturist in the last 12 months	2.46±2.05	9.11±8.89	p<0.001

As frequency, Romanian men address an acupuncturist in a significantly higher proportion, compared to other CAM practices (p<0.001). Hungarian men address in a significantly lower proportion aphytotherapist, compared to other CAM practices (p<0.001) (Table 3). Using unpaired t-test, it was observed that the Hungarian men use more often acupuncture than chiropractic (*p*=0.033) (Table 3). Furthermore, using Mann-Whitney nonparametric test it was observed that the number of visits to Acupuncture, it is significantly higher for the Hungarian men (p<0.001). Using $\chi 2$ test, it was noticed that the Romanian men go in a

significantly higher proportion to the phytotherapist than the Hungarian ones test (p=0.007).

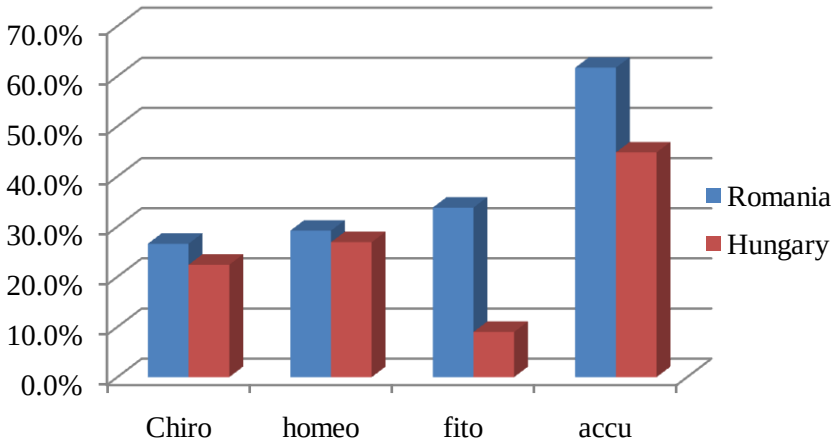

Figure 2. The differences between Romania and Hungary in terms of addressability to CAM methods

Significant differences were found between the number of visits of the Hungarian women to the four CAM practices (ANOVA test, p=0.038). These women use significantly more often acupuncture comparative to chiropractic (p=0.038), phytotherapy and, respectively, homeopathy (p<0.001).

The proportion of the Hungarian women who use Acupuncture is significantly lower than the proportion of the Romanian women–χ2 test, p=0.026; for men, this proportion difference is insignificant (χ2 test, p=0.236).Moreover, the proportion of the women in Hungary that address to the herbalist (phytotherapist) is significantly lower than the proportion of the Romanian ones (p<0.001).

The number of visits to Acupuncture was significantly higher for both men and women in Hungary, as shown by the Mann-Whitney nonparametric test, p<0.001.

Analysis of degrees of satisfaction in patients addressing CAM providers

The Romanian men were significantly more pleased about the results of visits to CAM providers (χ2 test, p=0.001) (fig.2).Also, Romanian women were significantly more pleased regarding the visits to CAM providers (test χ2, p<0.001), compared with Hungarian women (fig.3).

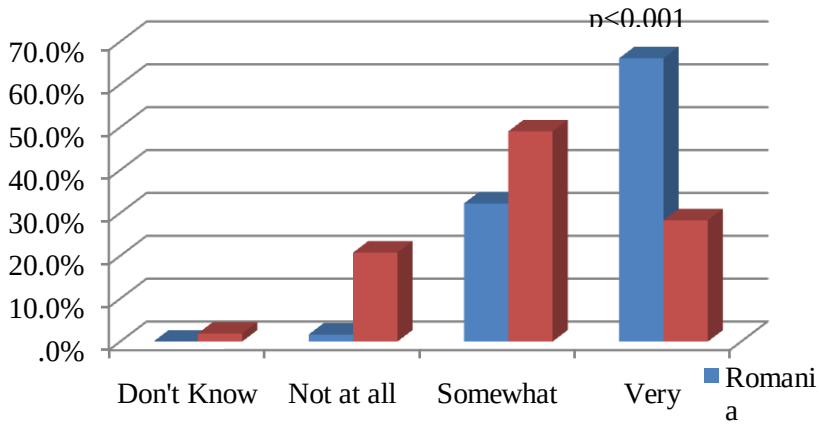

Figure 3. Comparative level between Romania and Hungary in terms of satisfaction in female patients after visit to CAM providers

It was noticed that the Hungarian men are satisfied in a greater proportion by homeopathy than chiropractic. (Z test, p=0.032).The Hungarian women have a greater degree of satisfaction regarding acupuncture sessions than regarding homeopathy (Z test, p=0.029).The proportion of the Romanian men who address to The Holy Unction is significantly higher comparative to the proportion on the Hungarian ones (χ2 test, p=0.002).

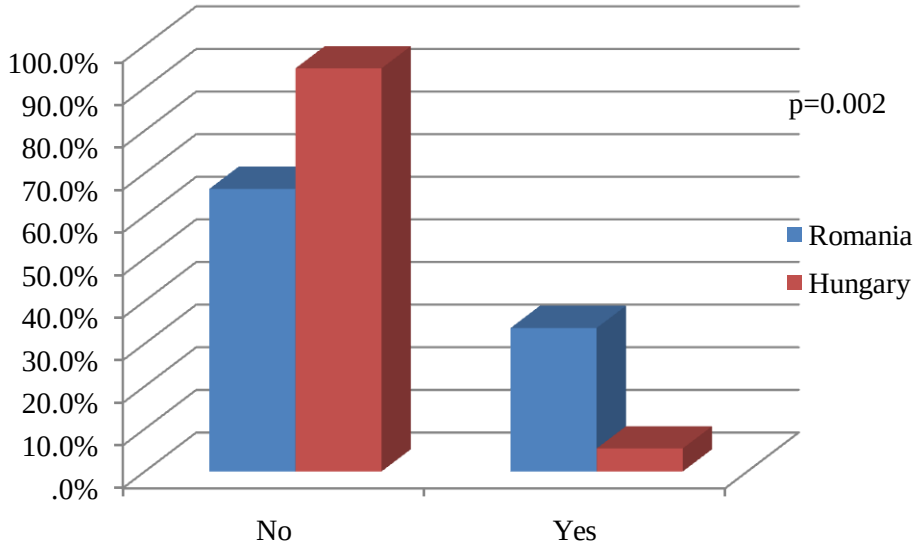

Figure 4. The satisfaction degree of men in both countries

The satisfaction degree of the Romanian men who were very pleased by the beneficial effects of The Holy Unction is significantly more high than the satisfaction degree of the Hungarian ones - χ2 test, p<0.001.The proportion of the women in Romania that address to The Holy Unction is significantly higher than the proportion of the Hungarian ones (– χ2test, p<0.001). And finally, the number of visits to The Holy Unction is significantly higher for the Romanian women – Mann-Whitney nonparametric test, p=0.005.

DISCUSSIONS

The International Questionnaire to measure the use of Complementary and Alternative Medicine (NAFKAM I-CAM-Q) raised some problems –in the previous publications-as a candidate for measuring the CAM use. The questionnaire was built to be usable in different languages, cultures and ethnic groups, by having a number of exact and stable, well-known items to be used on all versions of it, and also the option to adapt extra items if necessary – depending on the cultural and religious beliefs of the people- to observe the most common forms in CAM.I-CAM-Q has been used before in several published studies. To this day, very few of the psychometric tests of the I-CAM-Q have been published. While it is important to understand a questionnaire's measurement properties (reliability and validity), a useful step is to ensure that item wording and instrument design facilitate the potential to collect exact data. When people respond to questionnaires, they are engaging in a complex task. Think aloud methods can provide a view on these processes and help researchers to improve data by modifying items, and options for the answers.

In order to improve the applicability of the I-CAM-Q, we conducted a comparative study incorporating guided questionnaire to understand the properties of the I-CAM-Q ina population who may never have used CAM in both Romania and Hungary. The authors wished to observe how adults understood and evaluated the validity of the questionnaire. The aims of this comparative study were to evaluate the feedback of the new method of applying the I-CAM-Q on the participants, in order not to register so many errors and missing data like before. We also wished to investigate the feasibility of using a self-complete delivery mechanism to measure CAM prevalence across the EU. The specific objectives were to translate the questionnaire into two European languages-Romanian and Hungarian, to generate preliminary data and to analyze them.

In Romania the law of CAM is very permissive regarding the practice of different therapies, although there are no accredited trainers and no official certification for many of them. Furthermore, training and accreditation are not well regulated for non-MD practitioners. There is no official institution for training and control of non-MD CAM practitioners. In Romania, for example, the Questionnaire was applied on patients in 2011 and 2012. Also, there were some interviews taken to 10 patients, in which the limitations of this questionnaire were revealed. The respondents from Romania found it confusing and difficult to have to recall from a twelve month period whether they had used a modality and then switch to recalling over a 3 month time period reporting how many times they had used it. A number of people from each country couldn't remember how many times they had seen a practitioner at all.One person in the Romania summed up this problem by saying it was difficult to remember, people didn't keep account of how many times they'd been to a doctor etc.Another person said that twelve months was a long time to think back over.

On the Romanian version, missing data was most common for the self-care practices. The Romanian version consistently produced the largest proportion of incorrect responses and respondents had a strong tendency to tick more than one reason for using each provider.

The research results on the relationship between social factors and attitudes toward CAM and conventional practitioners are equivocal. Moreover, some investigators hypothesized a relationship between social factors and attitudes toward providers, with CAM being more attractive to socially and economically marginalized groups. A study conducted in the general US population evaluated the relationships between selected sociodemographic factors and attitudes toward CAM. It was noticed that age was positively related to favoring one's conventional medical doctor and subjects who reported using CAM reported significantly less confidence in their conventional doctors than individuals who did not (14).

Also in our study it was observed that the education levels of patients registered significant differences between the two countries ($p=0.002$, $\alpha=0.01$). The proportion of gymnasium and high school graduates was significantly higher in Romania compared to Hungary (Z test, $p=0.038$ for gymnasium level and $p=0.002$ for high school level).

A new cross-sectional study evaluated the CAM use by 400 older adults in Germany. Using a questionnaire,the investigators recorded demographics, current use of CAM, medical diagnoses, users' opinions and preferences. 61.3% of respondents used 35.5% dietary supplements, 33.3% herbal medicines

and 26.8% external preparations.A total of 30.3% of them used CAM based on recommendations, 20.0% by friends or family and 10.4% by pharmacists, 27.3% by own initiative and 25.8% by doctors' prescription. 64.9% of participants preferred a combination of CAM and conventional medicine and 58.7% perceived a good effect medicine. 57.9% of them didn`t know side effectsof CAM preparations used (15). In our study, Romanian both women and men address an acupuncturist in a significantly higher proportion than other CAM practices ($p<0.001$), while the number of visits to Acupuncture was significantly higher for both men and women in Hungary ($p<0.001$) comparative to Romania.As a novelty, the study demonstrated that the proportion of the Romanian men who address to The Holy Unction is significantly higher comparative to the proportion on the Hungarian ones ($p=0.002$).

CONCLUSIONS

Modified NAFKAM I-CAM-Questionnaire indicated that the most used CAM method in Romania is acupuncture, while phytotherapy is the less addressed CAM method in Hungary.

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Conflicts of interests

No conflicts of interests are to be declared by the authors.

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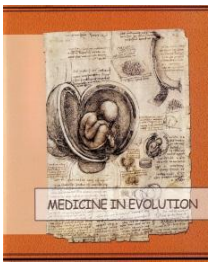

THE IMPACT OF CYTOMEGALOVIRUS REACTIVATION/INFECTION INHEMATOPOIETIC CELLS TRANSPLANT RECIPIENTS

URTILA PATRICIA[1, 2], MARGIT SERBAN[2], ESTERA BOIERIU[1, 2], ADA BALAN[1,2], EMILIA URSU[2], CRISTIAN JINCA[1, 2], LAURA PESCARU[2], FLORIN URTILA[1, 3], SMARANDA ARGHIRESCU[1, 2]

[1]"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania
[2]Children's Emergency Hospital"Louis Turcanu"Timisoara
[3]City Emergency Hospital

ABSTRACT

Introduction*Cytomegalovirus (CMV) infection, reactivationand disease are significantmorbidity and mortality risk factorsinhematopoietic stem cells transplantation (HSCT). The persistent controversial association between the effect of donor/receptorserostatus and HSCT outcome were reviewed and analyzed on our patients.*

Aim and objectives: *Weidentifiedthe risk factors that resulted in CMV reactivation or infection after allogeneic HCST. Also we investigated the possible correlation between the receptor/donor CMV serostatus and post-transplantreactivationof CMV infection assessed by polymerase chain reaction (PCR) assay.*

Material and method: *This is a retrospective study on forty-eight patients who underwent allogeneic HSCT at Children's Emergency Hospital"Louis Țurcanu, during the period 2008-2014. Data were obtained from patient's record files and from transplant data registry. CMV infection was investigated pre-transplant by ELISA method and post-transplant by PCR technology.*

Results: *We identified fourteen cases of CMV reactivation after allogeneic HSCT, representing one third of all recipients of HSCT. The highest incidence of CMV reactivation was observed among the high risk groupreceptor (R)/donor (D) IgG positive pairs (R+/D+ and R+/D-). Twenty five percent of recipients with CMV seropositive grafts experienced early reactivation. No case of suspected CMV disease was observed. No related CMV mortality after HSCT was assesed in this study.*

Conclusions: *In summary, our data suggest the roles for both virus as well as CMV specific immunity in the graft. This observation can be useful for donor selection, aiming an optimal post HSCT outcome.*

Key words: *hematopoietic stem cell transplant, CMV infection/reactivation, CMV serology*

Correspondence to:

Patricia Urtilă
Address: University of Medicine and Pharmacy"Victor Babes", Timisoara, Romania,
Phone: +40753957777
E-mail address: patriciaurtila@yahoo.com

INTRODUCTION

Cytomegalovirus (CMV) continues to cause major complications after hematopoietic stem cells transplantation (HSCT). In contrast to the fact that, usually, primary CMV infection is asymptomatic or is expressed as an infectious mononucleosis-like syndromein the immunocompetent adults.

As other herpes viruses, CMV remains lifelong in granulocyte-monocyte lineage. After seroconversion, this infection is biologically recognized by a continuous presence of CMV immunoglobulin G (Ig G) in the plasma. The percentage of latent CMV infection, reflected by serologic evidence in general population,ranges between 40% (France, Germany) to 100% (Uganda,Philippines), depending on socioeconomic and geographic factors (1).

The cellular sites in which CMV is carried during the latency period and his potential reactivation are still incompletely understood.In the immuno-competent host, the presence of CMV in CD34+ bone marrow progenitor cells and circulating monocytes is one of the hallmarks of latent infection.When talking about immuno-compromised individuals, the reactivation or primary CMV infection can have severe consequences, including fatal CMV disease. There are many risk factors for CMV disease: T cell depletion, graft versus host disease (GvHD), myeloablation, and so one, but the CMV serologic status of the recipients versus donor seems to be the most important risk factor in allogeneic HSCT patients (2, 3).

Determination of this donor/recipientCMV serostatus is used as a standard diagnostic routine for HSCT. The presence of CMV IgM antibodies is relevant for active/reactivation ofinfection. A latent donor CMV infection is argued by CMV IgG positivity; the grafts or the blood products from those individuals are potential infectious for immunosupressedrecipients. In the group ofrecipientCMV IgG positive/donorCMV IgG negative (R+/D-)pairs, a high mortality due to bacterial and fungal infection was observed(4, 5, 6).

Another study using European Blood Marrow Transplant (EBMT) registry concluded that CMV IgG seropositive recipients grafted from unrelated, CMV IgG seropositive donors (R+/D+) had a good improvement post transplant,a low transplant related mortality, compared with those receiving seronegative grafts. In this case, the donor's CMV memory has the potential to favor post allogeneic HSCT immune response (4, 7).

The lowest transplant CMV mortality and morbidityis reported for the situation of negative CMV serology for both recipient and donor (R-/D-), because, probably, there is no latent form of this viral infection. In the latter situation, thehigh risk for transfusion-associated CMV infection was substantially reduced by usage of CMV seronegative and/or leucodepleted (LD) blood products. Those two strategies are quite equivalent in preventing transfusion associated CMV infection after HSCT. Also, in order to prevent CMV infection via donor's graft to seronegative recipient, it is recommended the usage of seronegative graft when possible (4, 8, 9).

The incidence of post-transplant CMV infection depends on intensity and duration of immunosuppression correlatedto both donor andrecipient serostatus.

Aim and objective

Confronted with these aspects, we analyzed the impact of recipient/donor serostatus on morbidity after HSCT focusing on the risk for primary CMV infection,

reactivation of latent CMV infection, occurrence of CMV disease in connection with the characteristics of recipient and HSC donor.

PATIENTS CHARACTERISTICS AND METHOD

Forthy-eight patients (female/male:18/30, 15 respectively 33 below and above 18 years of age) were retrospectively reviewed.

These patients underwent allogeneic HSCT during the period ofFebruary 2008 to May 2014 at the Bone Marrow Transplant Department, in Children's Emergency Hospital"Louis Țurcanu". The grafts received were from related (*n* = 37) and unrelated (*n* = 11) donors. Thirty-six patients had hematological malignancies: acute lymphocytic leukemia (ALL; *n* = 16), acute myeloid leukemia (AML; *n* = 15), chronic myeloid leukemia (CML; n = 2) myelodysplastic syndrome (MDS; *n* = 2), juvenile myelomonocytic leukemia (JMML, *n* = 1) and three had non-Hodgkin lymphoma (NHL). Other patients were transplanted because of anemias (aplastic anemia n = 5; beta-thalasemia n = 1), other hematologic disorders (hemophagocytic lymphohistiocytosis, HLH, n = 1) and immunodeficiencies (chronic granulomatous disease, CGD n = 2). Most of the patients received myeloablative (MA) conditioning regime (n = 43). Out of 48 patients that underwent allogeneic HSCT, the most common indications of HSCT were for ALL (33,33%), followed by AML (31,25%) and anemia (aplastic anemia and betha-talassemia) (12,5%). All those patient characteristics are summarized in table 1.

Table 1. Patients demographic and characteristic data

Allo-HCST		**Number**	48
Age		Children≤ 18 yrs Adults> 18 yrs	19 29
Recipient gender		Male Female	30 18
Diagnosis		ALL AML CLL MDS JMML NHL HLH Anemias Immunodeficiencies (CGD)	16 15 2 2 1 3 1 6 2
Type ofHSC donor		Sibling Unrelated	37 11
Conditioning regimen		MA Non MA	43 5
CMV IgG serostatus		**Recipients** CMV IgG negative CMV IgG positive	 3 45
		Donors CMV IgG negative CMV IgG positive	 8 40
Recipient/Donor CMVIgG serostatus	**Positive (46)**	R+/D+ (high risk) R+/D- (high risk) R-/D+ (intermediate risk)	39 6 1
	Negative (2)	R-/D- (low risk)	2

We investigated transplant related factors that could influence the risk of CMV reactivation: age, sex, underlying disease, pre-transplant conditioning regimen, type of donor and the recipient and donor CMV serostatus. Analyzing the previous exposure to this virus, recipient/donor pairs were classified in high, intermediate and low risk.Recipient and donor positive IgG (R+/D+) and recipient positive/donor negative IgG (R+/D-) were included in high risk group. Intermediate risk group was represented by recipient negative/donor positive IgG (R-/D+), and low risk by those with negative CMV serology (R-/D-).

Recipients CMV viral load was assessed by quantitative real time polymerase chain reaction (PCR) assayduring the post-transplant period. Reactivation of CMV infection was defined by CMV DNAlevel above 100 copies/ml and without involvement of any systemic or organ functions. CMV disease was considered in the situation of symptomatic CMV reactivation: gastrointestinal, pulmonary or eye manifestations.On the time interval above 100 days post HSCT was defined early CMV reactivation and late, thereafter.

All statistical analysis were performed using SPSS software, version 20.0 (Paired Samples Test). A probability level of 5% ($p < 0.05$) was considered statistically significant.

RESULTS

CFrom the point of view of CMV status of all recipient-donor pairs, 45pairswith recipient IgG CMVpositive (39 pairs R+/D+ and 6 pair R+/D-),were included in high risk patients group (93,75%). Intermediate risk patients included one R-/D+ serostatus (2,08%). Two R-/D- pairs (4,16%) pairs were classified as low risk group-figure 1.

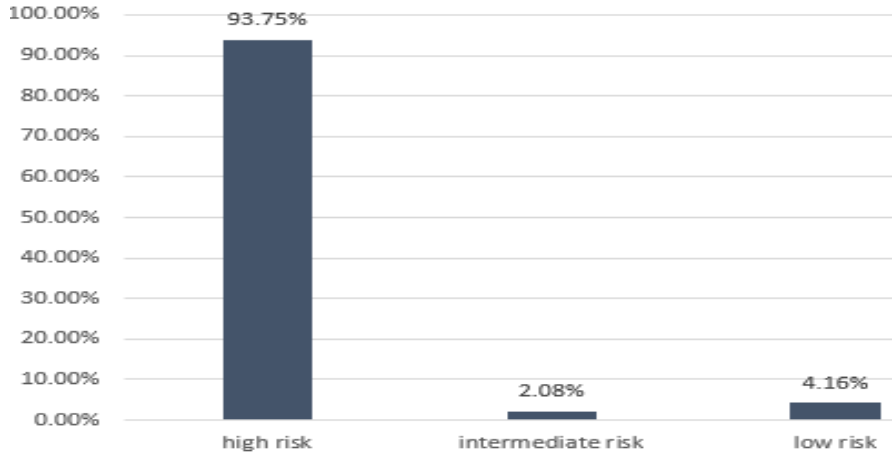

Figure 1. Distribution of CMV risk groups

Recipient age, conditioning regimen, CMV status of the recipient and donor are factors that could influence the risk of post transplant viral reactivation.

Fourteen cases (30,43 %) of the IgG positive allogeneic transplanted patients with CMV reactivation (>100 copies/ml)were retrospectively identified in our study (*p=0,005*). CMV reactivation was observed in 41,37% patients who were over 18 years of age at the time of HSCT (12/29 versus 2/17 at the age bellow 18 years, *p=0,006*); 31,7% had a conventional myeloablative transplant (13/43, versus 1/5 in non myeloablation, *p=0,001)* and a unrelated donor source

(45,45%) (5/11 versus 9/35 sibling donor, *p= 0,253)*.

Reported to recipient and donor serostatus, 30,76 % of CMV reactivations were R+/D+ and33,33% of R+/D- (*p=0,002*) (table 2).All of patients with CMV reactivation belonged to high risk group (14/46, 30,43 %)- figure 2.

Table 2. Reactivation of CMV infection afterallogeneic HSCT patients and their characteristics

Patients characteristic			**Total of allo-HSCT patients**	**Totalof IgG positive R/D pairs**	**Patients with post-transplant reactivation of CMV infection**	**Patients with no post-transplant reactivation of CMV infection**	***p* value**
Number(%)			48	46	**14(30,43)**	**32(69,56)**	**0,005**
Age		≤ 18 yrs > 18 yrs	19 29	17 29	**2(11,76)** **12(41,37)**	15(88,23) 17(58,62)	**0,006**
Sex		male female	30 18	28 18	**9(32,14)** **5(27,77)**	19(67,85) 13(72,22)	**0,253**
Diagnosis		ALL	16	15	6(40,0)	9(60,0)	
		AML	15	15	6(40,0)	9(60,0)	
		AA	5	5	1(20,0)	4(80,0)	
		BT	1	1	1 (100,0)	0	
		CLL MDS JMML NHL HLH CGD	2 2 1 3 1 2	2 2 1 3 1 1	0 0 0 0 0	2(6,25) 2(6,25) 1(3,12) 3(9,37) 1(3,12) 1 (3,12)	
Type of HSC donor		related	37	35	**9(25,71)**	26(74,28)	**0,253**
		unrelated	11	11	**5(45,45)**	6(54,54)	
Conditioning regimen		MA	43	41	**13(31,7)**	28(68,29)	**0,001**
		Non MA	5	5	**1(20,0)**	4(80,0)	
R/D CMV serostatus	Highrisk	R+/D+	39	39	**12(30,76)**	27(69,23)	**0,002**
		R+/D-	6	6	**2(33,33)**	4(66,66)	
	Intermediate risk	R-/D+	1	1	0	1(100,0)	
	Low risk	R-/D-	2	0	0	0	

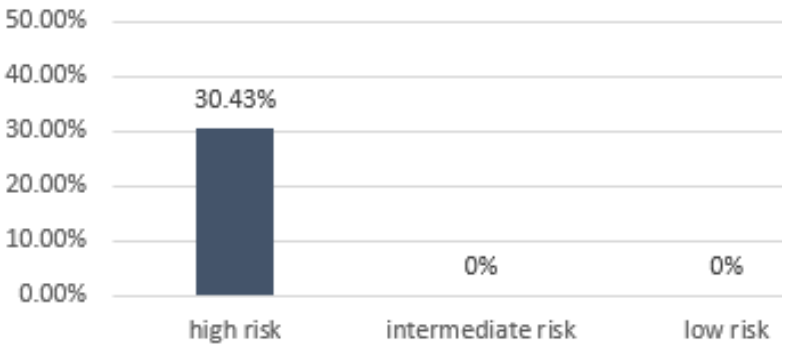

Figure 2. Distribution of CMV reactivations in R/D CMV risk groups

From all patients, 25% of recipients that received CMV seropositive grafts, experienced early CMV reactivation(*p= 0,003*). Only 2 patients with positive CMV serology R+/D+ had late CMV reactivation (5,12%;*p=0,001*) –table 3.

Table 3. Early and late CMV reactivation-correlation with CMV serostatus

Patients		**EarlyCMV infection**	**Late CMV infection**	***p*value**
Total (%)		**12(25,0)**	**2 (4,16)**	**0,003**
R+/D+	**39**	**10 (83,33)**	**2 (5,12)**	**0,001**
R+/D-	6	2(16,66)	0	0,175

A more frequent occurrence of early CMV reactivation was observed in patients receiving a CMV positive graft (83,33%) than in patients receiving CMV negative graft(16,66%).

No CMV related mortality and also no documented CMV disease were identified in our study. This can be explained by application of post-transplantation viral monitoring and CMV preemptive therapy.

DISCUSSIONS AND CONCLUSION

CMV infection or disease remains one of the most frequent post allogeneic HSCT complications and recipient CMV serostatus is one of the most important risk factors for CMV reactivation (10, 11, 12).

In our study one third of all patients (30,43%, *p=0,005*) developed CMV reactivation at a median of 52 days (range, 12-182 days) post HSCT, followed by initiation of preemptive therapy with ganciclovir. Mostly of CMV reactivations occurred mostly in CMV positive patients grafted from CMV positive or negative donors. Floor L. Pietersma et al. suggested thathigher viral incidence reactivation among seropositive recipients may be caused by the reactivation of the donor stains. CMV specific T-cells from the seropositive graft can interfere with the severity of viral reactivation. This transferred immunity from the received graft can be protective, leading to mild CMV reactivation (13).

However, the usage ofIgG seropositive grafts only forseropositive recipients, remains controversial.In order to benefit of the donor's transferred immunity, some studies are recommendingselection of R+/D+ pairs in case ofunrelated donors,in non-T-cell-depleted HSCT, but this strategy is not universally adopted(7, 14, 15).

Our retrospective study showed that CMV reactivation occurred only in high risk group patients (R+/D+, R+/D-). Large, especiallymulticenter studies are needed toanalyze the impact of CMV seropositive patients and/or donors and a rigorous monitoring is recommended to be used to prevent CMV disease among HSCT.

In summary, our data suggest the roles for both virus as well as CMV specific immunity in the graft. This observation can be useful for donor selection, aiming an optimal post HSCT outcome.

Acknowledgements:

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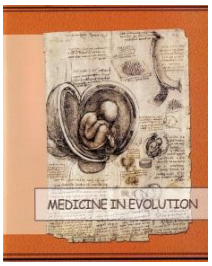
DIABETES MELLITUS, AN EPIDEMIOLOGICAL APPROACH USING ARAD COUNTY DATABASE



DANA NEGRU[1], MARIANA NAGY[2], LAURA NICOLESCU[1], GHEORGHE FURAU[3], ROXANA FURAU[3], CRISTIAN FURAU[3], TEODORA OLARIU[3], IOANA RUCSANDA JURCA[3], VICTOR TOMA[3]

[1]Arad Public Health Department
[2]Arad „Aurel Vlaicu"University
[3]Arad"Vasile Goldis"West University

ABSTRACT

Obiectives. *Determining the prevalence of diabetes mellitusof Arad County areas by type, to identify clusters with high prevalence.*

Material and Methods:*Retrospective study of Arad diabetes mellitus database, registered cases between 2006-2014, usingBesag-Newell's R Method, ClusterSeer® program.*

Results.*There were 26346 cases of diabetes mellitus, representing a prevalence of 6.12%, with peak in 2006 and declining, the minimum for 2013 being in ratio to maximum / minimum of 2.68. Average age at detection is 60 years with a standard deviation = 11.476 Std.Dv., no gender differences. Type 2 diabetes represents 98.61% of the cases, no gender differences. Statistically significant differences occur in the age of onset, type 1 occurring in young adults, with average age 42.27 years, while type 2 occurs at a mean age of 60.30 years (p=0.000). Cluster analysis reveals diabetes mellitusin 42 statistically significant clusters. Diabetes mellitus affects six of one hundred in Arad, under global morbidity of 8.3%. Patient distribution is uneven in Arad county, for some clusters prevalence being higher than average rate of 6.12% for all types of diabetes. There are some regions where prevalence reaches 14.33% to 11.09% for women and men, which is almost twice the prevalence for both genders.*

Conclusions. *Statistical analysis methods for morbidity are very useful in transmissible and non-transmissiblediseases epidemiology by identifying differences in the disease geospatial distribution, simple comparison of attack rates being not equally relevant; Besag-Newell method permits additional scanning and comparison of attack rates based on population density in a region, including graphical illustration, contributing to decisions of health professionals.*

Key words: *cluster, prevalence, Besag-Newell method, diabetes mellitus*

Correspondence to:

Dana Negru
Address: Arad Public Health DepartmentStr. Spitalului, nr.2-4, Str. Unirii, nr.10
Phone: +40257254438
E-mail address: dananegruarad@yahoo.com

INTRODUCTION

Diabetes mellitus defines a metabolic disorder with multiple etiology,characterized by changes in carbohydrate metabolism, lipid and protein, resulting a deficiency in insulin production or cell-insulin resistance or both, defining element being high level blood sugar [1].Diabetes mellitus represents 90% type 1 [2], affecting 8.3 percent of the adult population, with equal rates for gender [3]. The disease doubles the risk of death [4], is the eighth leading cause of death worldwide [5]. Today, 400 million patients are diagnosed in the entire world and it is likely that this number will grow to 600 million over the next 20 years [6]. Diabetes mellitus is defined as elevated blood glucose levels for an extended period of time [7], which causes frequent urination, intense hunger and thirst. Untreated, diabetes mellitus can complicate [8] with acute diabetic ketoacidosis or hyperosmolar coma. Long-term serious complications are cardiovascular, kidney failure, foot ulcers and eye disorders [4]. The pathogenesis is due to either the inability of the pancreas to synthesize insulin, as in type 1, or in inability of the cells to respond adequately to insulin produced, as in the type 2 [9]. A third form of diabetes, gestational, can occur in pregnant women without prior history of diabetes, which develops high blood sugar levels during pregnancy and resolves after delivery[13].

Aims: Determining the prevalence of diabetes mellitus by type, its regional distribution, even or uneven, knowing that the determinants of health, as overeating and sedentary behavior, has a major influence on health, to identify sanogenousfactors in low prevalence region, while regions with high prevalence must enter into the attention of general practitioners[12].

MATERIAL AND METHODS

Retrospective study performed on the electronic database of all diabetic patients detected between 2006-2014 in Arad County, by type of disease, gender, age and place of residence, total 26364 patients. Criteria for inclusion in the study were diagnosed as metabolic disease according to ms.ro Guide for the care of patients with diabetes, and residence in Arad. Data processing has followed the principles of non-transmissible disease epidemiology statistics, using classical methods for describing and evaluating statistical effect for significant differences between variables. We used Besag-Newell's R Method, ClusterSeer® [10] to assess geospatial distribution of cases for spatial clustering; null hypothesis asserts that the disease distribution is even, and denial null hypothesis of uneven distribution of disease states, with the probability P observed statistical tests obtained by comparing them with the null distribution. This gives the estimate of the likelihood of disease occurrence in clusters / nests under the null hypothesis uniform distribution.

RESULTS

Systematic data set defines the group of patients with diabetes type 1 and 2 from the point of view of gender and average age at diagnosis, disease type and year of diagnosis, Table 1, 2 and 3.

Table 1. Frecvency by gender, average age diagnosis

Gender	frequency	percent	Average age diagnosis	Std. Deviation
F	14566	55.3	61.42	11.147
M	11780	44.7	58.35	11.649
Total	26346	100.0	60.05	11.476

Average age at detection is 60 years,lower for men (58.35 years) and higher in females (61.42 years), ratio F/M 1.23.

Table 2. Frecvency by gender, average age diagnosis and types

tip	frequency	M	F	percent	Average age diagnosis	Std. Deviation
dz1	365	172	193	1.4	42.27	15.432
dz2	25981	11608	14373	98.6	60.30	11.212
Total	26346	11780	14566	100.0	60.05	11.476

For Type 1 percent is1.4% of the disease, the gender ratio being 1.12 for women. For type 2 ratio is 1.23 for women.

Table 3.Frecvency by types, annual incidence for new cases and gender

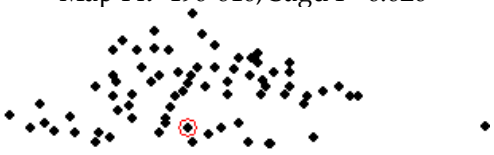
year	frequency	%	dz1	Annual incidence for new cases % dz1	dz2	Annual incidence for new cases % dz2	F	M
2006	5007	19	65	0.02	4942	1.15	2595	2412
2007	4358	16.5	102	0.02	4256	0.99	2345	2013
2008	3984	15.1	22	0.01	3962	0.92	2323	1661
2009	3561	13.5	58	0.01	3503	0.82	2006	1555
2010	2695	10.2	33	0.01	2662	0.62	1502	1193
2011	2112	8	30	0.01	2082	0.48	1155	957
2012	1849	7	19	0.00	1830	0.43	1044	805
2013	1868	7.1	23	0.01	1845	0.43	1078	790
2014	912	3.5	13	0.00	899	0.21	518	394
Total	26346	100	365	0.08	25981	6.04	14566	11780

Annual incidence for type 2 is maximum for the first three years of analyzed period with decreasing trend, the period prevalence being6.04%, below the world average.

Spatial Cluster Analysis reveals uneven distribution for diabetes mellitusin 42 statistically significant clusters for chosen cut-off k, 0.05 alpha level, as follows: k=490-610, Sagu P=0.02, Map I; k=645 to 720, P=0.041 Fantanele-Vinga, Map II; k=730, Lipova, P=0.047, Map III; k=750 to 755, P=0.046 Lipova-Sistarovat, Map IV; k=890-955, Fantanele-Sagu-Vinga P=0.0401, MapV; k=1080-1200, P=0.035 Fantanele-Vinga, Map VI; k=10500, 10700, Arad, P=0.0056, Map VII; k=10900-11000, Arad-Livada, P=0.0003, Map VIII; k=11100-11200, Arad-Livada-Sofronea P=0.014, Map IX; k=11300-11400, Arad-Livada-Sagu-Sofronea-Vladimirescu, P=0.018, Map X; k=11500, Arad-Fantanele-Livada-Sagu-Sofronea-Vladimirescu, P=0.006, Map XI; k=11600, Arad-Fantanele-Livada-Sagu-Sofronea-Vladimirescu-Zimandu Nou, P=0.009, Map XII; k=11800, Arad-Fantanele-Iratosu-Livada-Sagu-Sofronea-Vladimirescu-Zimandu Nou, P=0.002, Map XIII.

Map I k=490-610, Sagu P=0.020

Map II k=645-720, Fântânele-Vinga P=0.041



Map IIIk=730, Lipova, P=0.047

Map IV k=750-755, Lipova-Sistarovat P=0.046

Map V k=890-955, Fântânele-Sagu-Vinga P=0.040

Map VI k=1080-1200, Fântânele-Vinga P=0.035

Map VII k=10500, 10700, municipiul Arad, P=0.005

Map VIII k=10900-11000, municipiul Arad-Livada P=0.0003

Map IX k=11100-11200, municipiul Arad-Livada-Şofronea P=0.014

Map X k=11300-11400, municipiul Arad-Livada-Şagu-Şofronea-Vladimirescu, P=0.018

Map XI k=11500, municipiul Arad-Fântânele-Livada-Sagu-Sofronea-Vladimirescu, P=0.006

Map XII k=11600, municipiul Arad-Fântânele-Livada-Sagu-Sofronea-Vladimirescu-Zimandu Nou, P=0.009

Map XIII k=11800, municipiul Arad-Fântânele-Iratosu-Livada-Sagu-Sofronea-Vladimirescu-Zimandu Nou, P=0.002

Diabetes mellitus affects six of one hundred persons in Arad county,under global morbidity and 3.67% of patients are persons under 40 years. Patient distribution is uneven in Arad county, 44.78% of residents being affected in clusters with higher rate of 6.12%. There is a cluster prevalence of 14.33% for women and 11.09% for men, almost twice the prevalence for men and more than twice the average prevalence for women.

DISCUSSIONS

Diabetes mellitus type 2 is pandemic"due to lifestyle, aging, urbanization, which result in changes in diet, adopting a sedentary lifestyle and obesity development. The prevalence of diabetes varies significantly depending on the population studied, age, gender, socioeconomic status and lifestyle. Although diagnostic methods and monitorising of risk populationwere improved at least 30% of cases are undiagnosed for diabetes type 2"[1]. Chronic complications (mainly cardiovasculary) may be present in 50% of casesat diagnosis and once appeared lower quality of life, functional capacity, patient autonomy, increase the number of days of hospitalization, the clinic visits and expenses for medication [11]. Diabetic patient gradually becomes not interested in professional and family life. Mortality rate are double for them, more than70-80% because cardiovasculary complications.Reducing these serious consequences of diabetes is possible through: early detection of people with risk for diabetes, treating patients according to international evidence-based treatment protocols, prevent the onset of chronic complications by systematically monitoring and specific treatments in collaboration with cardiologists, nephrologists, neurologists, ophthalmologists.Nursing a diabetic person must also involve psychological assistance, to improve family, social and professional insertion. [11]."The cost of diabetes increases 3-5 times if there are complications of chronic micro-andor macroangiopathy. The bottom line is that preventing chronic complications of diabetes improves clinical impact of therapeutic and psychosocial illness and reduce cost."[1].

Statistical analysis methods which identify differences in geospatial distribution for morbidity are essential, simple comparison of attack rates being equally relevant;Besag-Newell method permits additional scanning and comparison of attack rates based on population density in a region, including graphical illustration, contributing to decisions of health professionals.

CONCLUSIONS

Statistical approach in this paper uses the methods implemented in the program ClusterSeer®, specific software that has proven effective for the study of diseases. Monitoring population at all ages must be supplemented by additional screening measures ofpersons living in rural regions whereprevalence rates are above average, especially in the clusters identified. Medical measures should be supported by systematically informationof persons in order to maintain their normal Body Mass Index, to know the sanogenous role of exercise and diet, as well as measures to avoid acute and chronic complications of this disease. Statistical analysis methods are very useful in epidemiology of communicable and

non-communicable diseases by identifying differences in the spatial distribution.

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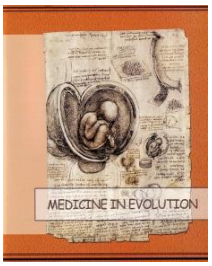
CANCER STATISTICSUSING SPATIAL CLUSTERS' METHODS



MARIANA NAGY[1], DANA NEGRU[2], IOANA RUCSANDA JURCA[3], VICTOR TOMA[3]

[1]Arad „Aurel Vlaicu"University
[2]Arad Public Hralth Department
[3]Arad"Vasile Goldiş"West University

ABSTRACT

Introduction. *Cancers arethe leading causes ofdeathin the world(13% ofall deathsin 2008), mortality is given bylung, stomach, liver, colon and breast cancer mainly. Overa quarter ofdeaths arepreventable with behavioralriskcancellationand diet: high Body MassIndex,low-fiber diet, inactivity,smoking, alcohol. Cancerscaused byviralinfection(HBV/ HCV, HPV)are responsible for20% of deaths in developingcountries. By2030cancerdeathswill reach13.1 milliondeathsworldwide.*

Hypothesis*. Studyingcancerusing statistical methodswithdedicated programsfor communicable and non-communicable diseases we can identifyclusters and, ideally, modifiable healthhazards.*

Materialand methods*.We usedBesag-Newell's R Method, ClusterSeer®applied on Arad cancer database in order to determinethe yearsof residence, gender, affected age groups, deathand survivalrates, to identifysignificantgeospatialdifferencesforsome entities, the gender proportionandcancerprevalence.*

Results. *Annual distributionincreasedsteadily sincethe '70s, with a peakin2008/1729cases and have a decreasingtrendafter 2008, to annual average ofyear2002/697cases. Annualtrendfor new casesanddeaths isrisingandcan not be explainedonly byaging.Averageage forall casesis59.7148, Std. Dev. =14.0076, which indicates exposure tobehavioral orenvironmentalhazards ofyoung adults. Forall cases, thehazard rateisslightly higherfor men/0.55, which indicates that theyare at riskbefore thetime of death,Relative Risk ofdeath comparedwith womenbeing0.6573(95% CI0.6321to0.6835, P<0.0001). South Westregionof AradCountyrecordsthehighest prevalence.*

Conclusions*. Oncetheareas withhigh prevalenceof allcancers including the rare ones are identified, the next step has to be the identification ofhazardsto whichwe canintervene.*

Key words: *cluster, prevalence,Besag-Newell Method, cancer*

Correspondence to:

Mariana Nagy
Address: Arad „Aurel Vlaicu"University, B-dulRevoluţiei nr. 77, 310130 Arad, România
Phone: +40257283010
E-mail address: mariana.nagy@uav.ro

INTRODUCTION

Cancers arethe leading causes ofdeathin the world(13% ofall deathsin 2008), mortality is given bylung, stomach, liver, colon and breast cancer mainly, withnotable gender differences. Inadults, 30% of deaths arepreventableby changingbehavioral anddietaryrisks: high BMI, low fiber diet, inactivity,smoking, alcohol. Cancerscaused byviralinfection(HBV/ HCV, HPV)are responsible for20% of deaths in developingcountries. By2030cancerdeathswill reach13.1 milliondeathsworldwide.[1]

Aftercardiovascular diseases, canceris the second/sometimes even the leading cause of death. Inthe Third World itseems to be a muchlowercancerincidenceandmortality due toinfectious diseasesorplagueswhich are dominant, but withmalariaand tuberculosis' control measures is expected thatcancer will increase inthe future.

Distribution ispandemic[2], theannualincidenceforall cancers is different, which shows thatthere are createdconditionsworldwide for cancerclustering.

The mostimportantrisk factor for cancer isage[3], an incresing lifespanbeing followed by increasedincidence ofcancer.Yetone third ofcancers anddeathsworldwidecan be prevented throughinterventionsonmodifiable risk factors: smoking -associated withlung cancer, mouthandthroat, alcohol - associated withoral cancer, esophageal, breast, liver, etc., low-fiber diet andno exercise- associated withcolon, breast, etc., obesity - associated withcolon, breast, endometrial, unprotected sex- associated withcervical andanalcancer. Men withcancer havetwice asmanymodifiablefactorsthan womenfortheir diseases.

Lifestyle and environmental factors influence the risk of cancer (eg, hormone substitutes that increase the risk of breast cancer), exposure to ionizing radiation, UV or occupational pollutants (eg asbestosis which causes pleural or peritoneal mesotelioma, or benzene which leads to leukemia). Most deaths from cancer due to occupational exposure to hazards arising in developed countries.

MATERIAL AND METHODS

A cluster is defined as the occurrence of cases over the expected number in a population group in a geographical area within a specified period of time. It is”authentic”especially if it's a certain type of rare cancer or not specific to age groups. Between 5% -15% of suspected cancer clusters are statistically semnificative.A cancer cluster is a statistical event that may or may not have any reason other than chance.[4].

Among the statistical methods, we have chosen Cuzick-Edwards test and Besag-Newell method to detect possible clustering (grouping) of a sub-population or a population which unevenly developed disease. Besag and Newell method is a spatial analysis of the data group level detecting local and regional clusters. [5, 8]. Null hypothesis H0: Poisson distribution of a disease is assumed as normal. When contradicts the hypothesis H0: there are deviations from the Poisson distribution (considered normal). If in a given spatial area, where densities are higher than normal occurrence expected (after Poisson), it is considered that the area is a region cluster. Were considered each of the 75 regions included in the dataset. Scanning proximity region is processed until circular window centered on the region includes a number of cases proposed by the

researcher (k – cutoffsize) and is a comparison of thepopulation within a circular window with the rest of the population. The population of the interior is compared to average value or expected disease frequency. If the frequency is within the window above expectation, we can considere that is acluster around that region.

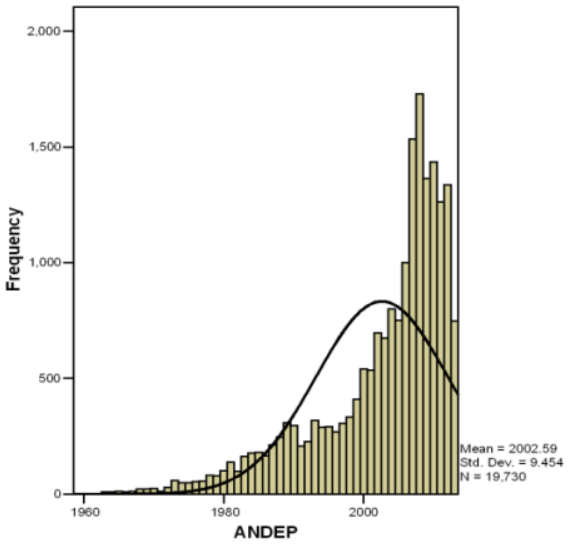
AIMS. Establishing statistically significant clusters for prevalent cancers. We were using *SPSS 14.0 for Windows*, *MedCalc* and *ClusterSeer*® on Arad tumor disease database to determine the years of residence, gender, age groups affected, death and survival rates to identify significant geospatial differences for some entities, the gender ratio and cancer prevalence"in toto". The algorithms used were chosen based on multivariate normal distribution patterns and density.

The measurements used were: cancer prevalence on all entity types, age of onset, location for residence more than 10 years; Attack rates by region, by age below 60 years / over 60 years; Survival rates after diagnosis; Mortality rates by gender; death risks, hazard rate attributable to gender.Type of study: Retrospective, geospatial, descriptive andanalytical for cancer.

For signs of cancer clustering tests were used Besag-Newell's R, the spatial scan statistic, Whittemore's test, Moran's I [6, 7].

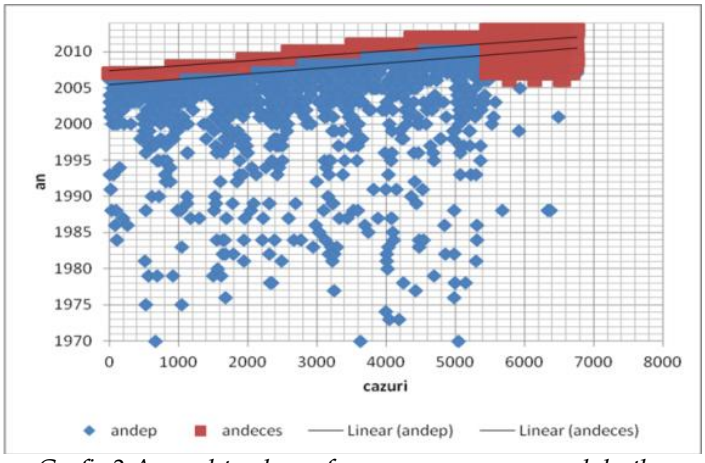
RESULTS

Cancer is recorded in Romania starting 1974, first as pilot system, a system in which Arad county was not a part and then generalized. County cancer registry was conducted electronically after 2005 in Arad and contains all cases. Annual detection frequency is increasing, with an average around 2002. Histogram in Figure 1 shows the annual distribution which increases steadily in the ´70s, with the peak in 2008 (1729 cases), decreased after 2008 and tends annual average of 697 cases, as registred in 2002.



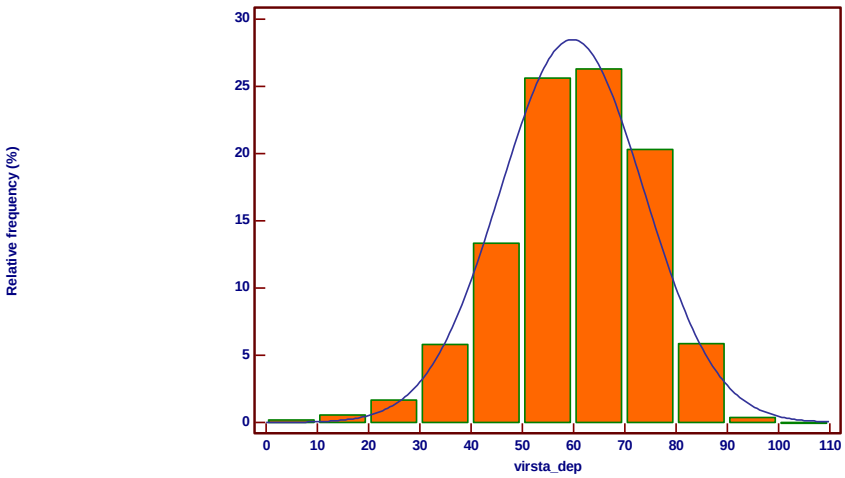
Grafic 1. Histogram for annual distribution of cancer

Were analyzed 19,730 cases of cancer recorded between 1960-2013, of which 34.28% were deaths, means6765 cases. After excluding those who did not meet the criteria required by the design of this study (approx. 300),was drawn graph 2 forannual trend of new cases and deaths, which is rising and can not be explained simply by an ageing.



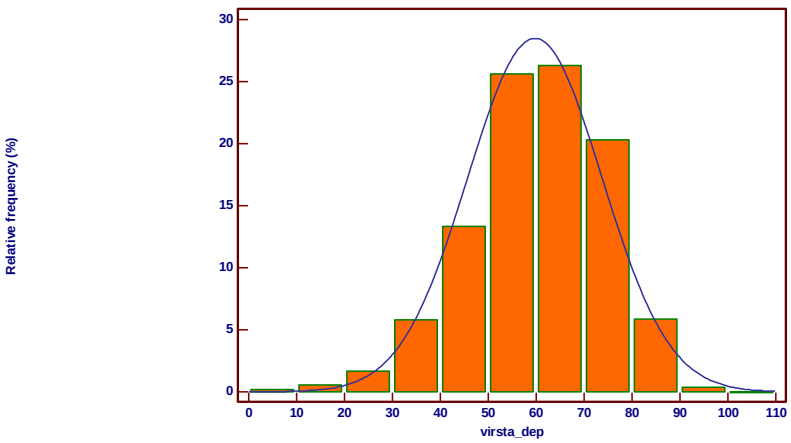
Grafic 2.Annual tendency for new cancer cases and deaths

According to Graphic 3, the average age for all 19,730 new cases is 59.7148 with standard deviation Std. Dev. = 14.0076, which indicates exposure to environmental pollutants or behavioral risks for young adults 30-45 years.



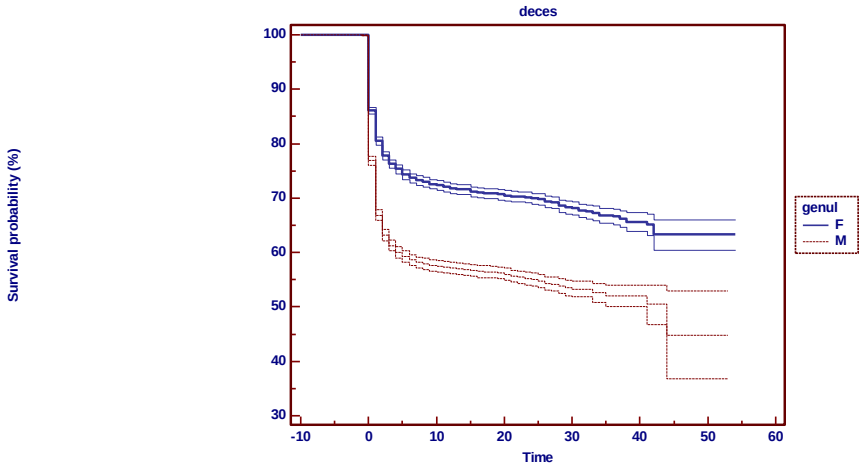
Grafic 3.Histogram for age of new cases

Average age at diagnosis for cases who diedis 64 years, Std. Dev. = 13.7048 (*Graphic*4), which correlated with late detection indicates lack of preventive measures, especially after 40 years.



Graphic 4. ***Histogram for age at diagnosis in deaths***

According to *Graphic* 5, the average survival for all cases is 8 years, with cases curable / survival at 44 years, which confirms that the disease is mostly preventable and curable.



Graphic 5 KAPLAN-MEIER SURVIVAL CURVE/ ALL.

In all cases, the Hazard ratio is slightly higher for men (0.55), indicating that they are at risk before the time of death (Table 2). The relative risk for death in men compared with women is 0.6573 (95% CI 0.6321 to 0.6835, P <0.0001), calculated from data in Table 1.

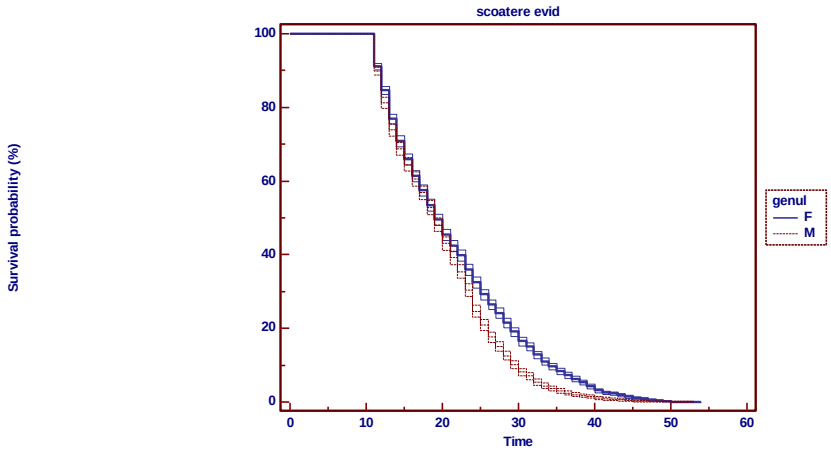
Table 1. *Deaths Relative Risks*

gender	cases	alive	deaths	%alive
F	10629	7691	2938	59.30%
M	9101	5274	3827	40.70%
Total	19370	12605	6765	100.00%

Table 2. Hazard ratio

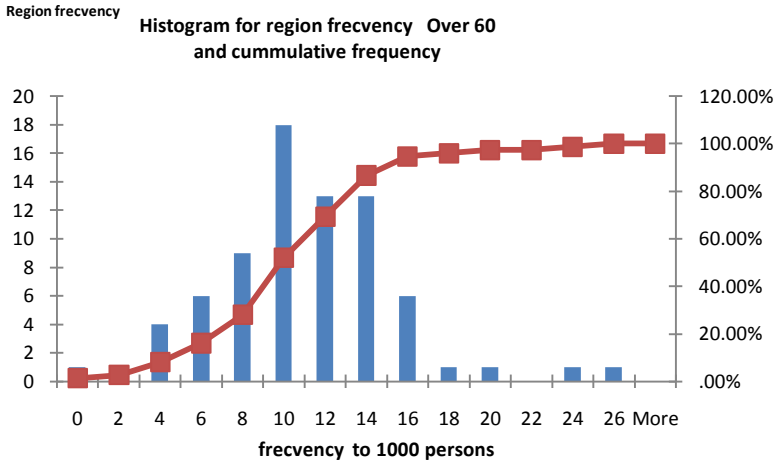
Hazard ratio	**0,5572**
95% CI	0,5293 to 0,5866

Graphic 6 shows that the average survival of fatal cases is equal in terms of gender, 1 year (P <0.0001 Chi-square 84.6552, DF 1), which indicates especially late detection, in noncurable stages.

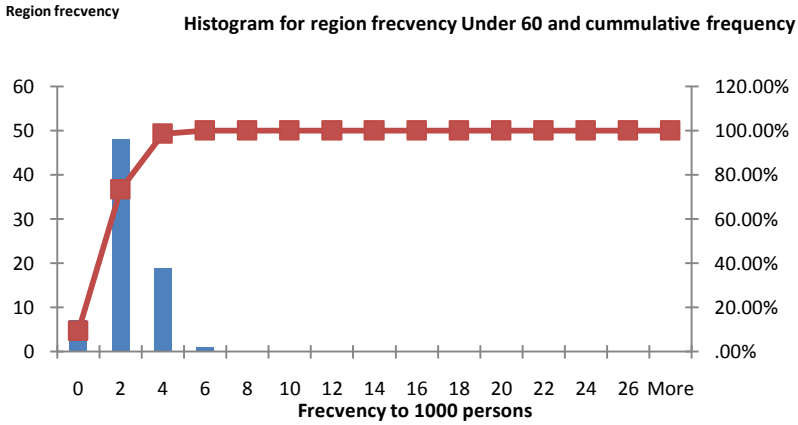


Graphic 6. KAPLAN-MEIER SURVIVAL CURVE/ DEATHS

Cumulative frequencies on regions for two categories of age, under 60 and more than 60 years are shown in Graphic 7 and Graphic 8. Correlation between population ratio under 60 / more than 60 and cancer prevalence is weakly positive (0.222333), which means notable insults under 60 years.



Graphic 7. Frecvency and cummulative frecvency over 60 years



Graphic 8. Frequency and cummulative frequency under 60 years

Newell's analysis Besag-R, ClusterSeer® Method at a cut-off = 45... 47 for all cancers lead to specific maps for cases. Map 1, Map 2 and Map 3 shows that Felnac and Fântînele are local clusters of alltumor disease in both age groups under and over 60.

Map 1 Felnac_k45_under60_total

Map 2 Felnac_Fântânele _k47_under60_total

Map 3 Felnac_Fântânele _k60_over60_total

The maximum / minimum prevalence ratio of cancer is variable. Considering two types of endemic locations - colorectal and cervical ratio is 10.48 (colorectal) and 10.93 (cervical cancer), requiring the analysis of the determinants of health at least inareas with maximum prevalence. The same is true for region with positive prevalence versus those with zero prevalence for all types of cancer. South West region of Arad county records an increased prevalence.

CONCLUSIONS

Spatial Cancer Cluster Analysis Method allows the identification of areas with high prevalence for all cancers, including rare ones, and has to be followed by identification of the hazards which can be modified. Statistical methods enable are valuable, researchers can use geospatial, temporal and temporo-spatial methods in their public health strategies. For this reason, the database will continue to be used to identify temporal and spatio-temporal clusters.

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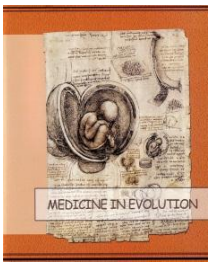
THE OXIDATIVE STRESS IN PATIENTS WITH AND WITHOUT ANTIVIRAL TREATMENT



PETRISOR DIANA, LADISLAU SZEGEDI, OVIDIU BORUGA, CIPRIAN IOVAN

University of Oradea, Faculty of Medicine and Pharmacology Oradea

ABSTRACT

AIM: the paper tries to emphasize the oxidative stress existent within the chronic viral hepatitis B and C

OBJECTIVES: to comparatively evaluate the variation of the oxidative stress on patients treated with antiviral therapy as compared with the group treated with conventional therapy

MATERIAL AND METHOD: two croups were formed; the first of patients with chronic viral hepatitis B and C treated with antiviral treatment and the second one of patients with the same pathology, who were only treated with conventional treatment. Both groups were subjected to an initial clinic, biologic and imagistic evaluation, as well as at the end of the treatment with antiviral treatment of 48 weeks.

RESULTS: the improvement of the clinical state, the normalization of aminotransferases and the negativization viremia after the therapy with antiviral treatment on patients from the first group.

CONCLUSIONS: the antiviral therapy considerably reduces oxidative stress

Key words: *oxidative stress, chronic viral hepatitis B, chronic viral hepatitis C*

Correspondence to:

Petrişor Diana- Corina
Assistant Lecturer
Address: University Of Oradea, Faculty Of Medicine And Pharmacology, no. 10, Piaţa 1 Decembrie st., Oradea, Romania
Phone: +40259412834; +4 0728765432
E-mail address: petrisordiana@yahoo.com

INTRODUCTION

The oxidative stress is a physiological process, damaging for the organism in most of the cases, caused by an imbalance between different reacting substances, like"the reactive species of oxygen"(oxidative activity) and antioxidants (1). The imbalance between the level of the oxidation products and the antioxidant capacity of the organism is called „oxidative stress"and is the source of some diverse pathology, with a great prevalence in modern medicine (2). The reactive species of oxygen (ROS) are naturally formed during the development of the general metabolic processes in the organism at cellular level, and simultaneously the cells develop several protective mechanisms to prevent the forming of ROS and in the same time detoxification of ROS, using a certain type of molecules, called antioxidants. Under certain circumstances, like acute or chronic exposure at certain aggressive effects, the production of ROS is unequally enhanced, and the level of the antioxidant activity is reduced (comparatively). The resulted state, which is characterized by a disturbance of the balance between the production of ROS on one hand and the removal of ROS on the other hand, together with the recovery of the deteriorated complex molecules, is called"Oxidative Stress"(Halliwell) (3). To counter-balance the damaging effect of the oxidative stress, the body uses enzymes of the antioxidant protection, like: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-P_x), proteins which link the metals, vitamins etc. The reactive oxygen damages the nucleic acids and the proteins of the hepatic cell, initiating in the same time the process of lipid peroxidation. The lipid peroxidation is one of the major causes of hepatocytes damaging, initiating a marked increase in the level of malondialdehyde (MDA), which represents the specific biomarker of the oxidative stress (4, 5).

In the recent years, a great number of studies about the oxidative stress on patients with chronic viral hepatitis B and C (6) appeared, among which De Maria et. al. (7) which emphasises that malondialdehyde, the product of fat unsaturated acids peroxidation and in the same time specific marker of the oxidative stress, increases its level in the liver and sanguine serum.

In the present study we will try to analyze the evolution of the oxidative stress on patients with chronic viral hepatitis B and C, and the effect of combined therapy with Pegylated interferon alfa 2-a and possibly Ribavirine on top of this, as compared with a witness group of patients, also with chronic viral hepatitis B and C, who didn't beneficiate of antiviral therapy. Except for the antiviral therapy, the medication therapy was equal for all the members of the group.

MATERIAL AND METHODS

Subjects: we compared a group of patients with chronic viral hepatitis subjected to antiviral treatment with a group of 7 patients with the same pathology, who could only take conventional therapy.

The first group included 4 cases of chronic viral hepatitis C managed with Pegylated interferon alfa 2-a 180 µg/week and Ribavirine 1 000 mg/day for 12 months, and a case of chronic viral hepatitis B managed with Pegylated interferon alfa 2-a 180 µg/week.

In the witness group 5 patients with chronic viral hepatitis and 2

patients with chronic viral hepatitis B were found. The group was managed in the same manner during the same period of time of 12 months as the first group.

The criteria for admittance were: age, between 41 and 65 and an increased level of GPT. In what concerns the patients from the first group, 4 were with chronic viral hepatitis C, with Ac anti-VHC positive, detectible ARN-VHC and the value of Fibromax between A_1 F_1 and A_2 F_3. In the first group, the patient with chronic viral hepatitis B presented Ag HB_s positive, Ag HB_e positive, ADN-VHB of 72 143UI/ml and Fibromax of A_2 F_3.

The criteria for elimination were: normal GPT, small values of the viremia and age over 65. Upon the inclusion in the study, the patients were clinically examined and were performed an abdominal MRI. The Fibromax test was performed and several tests were sampled, among which even markers of the oxidative stress: malondialdehyde, superoxide dismutase and glutathione peroxidase.

The dose of malondialdehyde was decided from venous blood sampled à jeun, which was then processed with HPLC with fluorescent detection method. In order to appreciate the level of the antioxidants, respectively of the superoxide dismutase and of the glutathione peroxidase, venous blood à jeun was sampled, which was then analyzed by photometry, the enzymatic method (8).

RESULTS AND DISCUSSIONS

Table 1. The bioumoral results of the two groups upon the inclusion in the study

The examined marker and the normal interval	Group1		Group 2	
	Average Value	No. ofpatients	Average Value	No. ofpatients
Malondialdehyde (0,36 - 1,24 µmol/L)	9,27 µmol/L	5	10,33 µmol/L	7
Superoxide dismutase (1 200 - 1 800 U/gHg)	1 443,60 U/gHg	5	1 166,76 U/gHg	7
Glutathione peroxidase (1 471 - 10 881 U/L)	3 966 U/L	5	3 778,24 U/L	7
GPT (19 - 23 UI/L)	89,16 UI/L	5	93,40 UI/L	7
GOT (15 - 19 UI/L)	118,04 UI/L	5	115,66 UI/L	7
ARN - HCV	positive	4	positive	5
Anti - HCV	positive	4	positive	5
AgHBs	positive	1	positive	2
ADN-HBV	positive	1	positive	2
Protein C-reactive (< 1 mg/dl)	8,27 mg/dl	5	10,94 mg/dl	7
Leucocytes 4 000 - 8 000/mm^3	11 660/mm^3	5	13 400/mm^3	7
Alkaline Phosphatase 70-170 UI/L	283,16 U/L	5	261,14 UI/L	7
Serum Cholinesterase 8-18 U/L	8,39 U/L	5	6,78 U/L	7
Alpha-fetaprotein <40 ng/ml	37,9 ng/ml	5	41,26 ng/ml	7

The obtained results show that the oxidative stress is present in the pathogenesis of the chronic viral hepatitis B and C, the expression being the increased serum value of the malondialdehyde in the two groups, before the antiviral and conventional treatment managed to both groups

(9,27 µmol/L and respectively 10,33 µmol/L).

In the same time it was noticed the powerless response of the body under the influence of the viral infection, with a weak reaction of antioxidant protection, just under the normal values:

- superoxide dismutase: 1 443,60 U/gHg in Group 1 and 1 166,76 U/gHgin Group 2
- glutathione peroxidase: 3 966 U/L in Group 1 and 3 778,24 U/L in Group 2

The patients in Group 1, as they fulfilled the criteria for inclusion in the etiopathogenic treatment stated by the actual law, received Pegylated interferon alfa 2-a 180 µg/week and Ribavirine 1 000 mg/day (those with chronic viral hepatitis C) for 48 weeks, respectively Pegylated interferon alfa 2-a 180 µg/week for the patients with chronic viral hepatitis B.

During the 12 months under surveillance, both groups received conventional treatment consisting of:

- limited physical activity for those with intense cytolysis (GOT, GPT) and influenced clinical state
- complete, balanced feeding, adapted for each case, in what concerns the level of proteins and the balance between the animal and vegetal proteins
- cytoprotector treatmentand treatment for the limitation of hepatocyte injury and implicitly of the hepatic fibrosis, by managing ursodeoxycholic acid, 250 mg capsules, 15 mg/kg body/day
- to fight the hepatocytolitic syndrome, as a membrane stabilizer, with antioxidant effects, we used Silymarin 3x150 mg
- in the wide category of hepato-protectors we used stimulating substances for the antitoxic function of the liver LIV 52, de 3x1 cpr/day
- 10 days every month, the patients received a treatment with Arginine, 1 oral ampoule/day substance which takes part in the synthesis of the proteins and in the same time in the tying up of the exceeding ammonium

phospholipids with the structural role of a membrane and in the activation of the enzymatic systems at this level were managed as Essentiale Forte N 3 x1 cps/day.

Table 2. The bioumoral results of the two groups after 48 weeks of antiviral treatment

The examined marker and the normal interval	**Group1**		**Group 2**	
	Average Value	**No. ofpatients**	**Average Value**	**No. ofpatients**
Malondialdehyde (0,36-1,24µmol/L)	1,31µmol/L	5	6,14µmol/L	7
Superoxide dismutase (1200-1800 U/gHg)	2 527,50U/gHg	5	1 986,14U/gHg	7
Glutathione peroxidase (1471-10881 U/L)	10 300 U/L	5	4 416,2 U/L	7
GPT (19-23 UI/L)	22,91 UI/L	5	93,4 UI/L	7
GOT (15-19 UI/L)	21,08 UI/L	5	115,66 UI/L	7
ARN-HCV	negative	4	positive	5
Anti- HCV	positive	4	positive	5
AgHBs	negative	1	positive	2
ADN-HBV	negative	1	positive	2
Anti HBs	positive	1	negative	2
Protein C-reactive (< 1 mg/dl)	2,16 mg/dl	5	8,68 mg/dl	7
Leucocytes	7 748/mm^3	5	9118 /mm^3	7

4 000-8 000/mm^3				
Alkaline Phosphatase 70-170 UI/L	123,18 U/L	5	199,16 UI/L	7
Serum Cholinesterase 8-18 U/L	18,44 U/L	5	15,12 U/L	7
Alpha-fetaprotein <40 ng/ml	42,16ng/ml	5	44 ng/ml	7

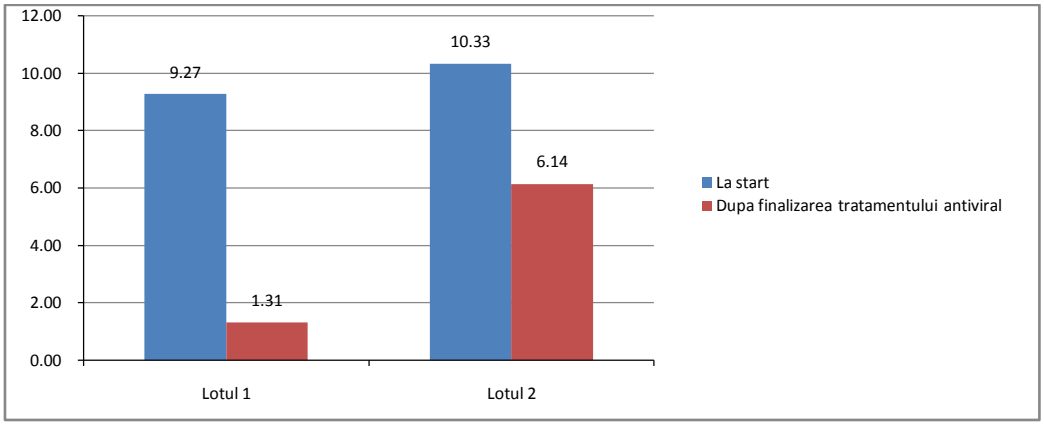


Chart1. The value of the malondialdehyde for the 1st group at the beginning and end of the antiviral treatment: - 9,27µmol/L at the beginning and 1,31µmol/L

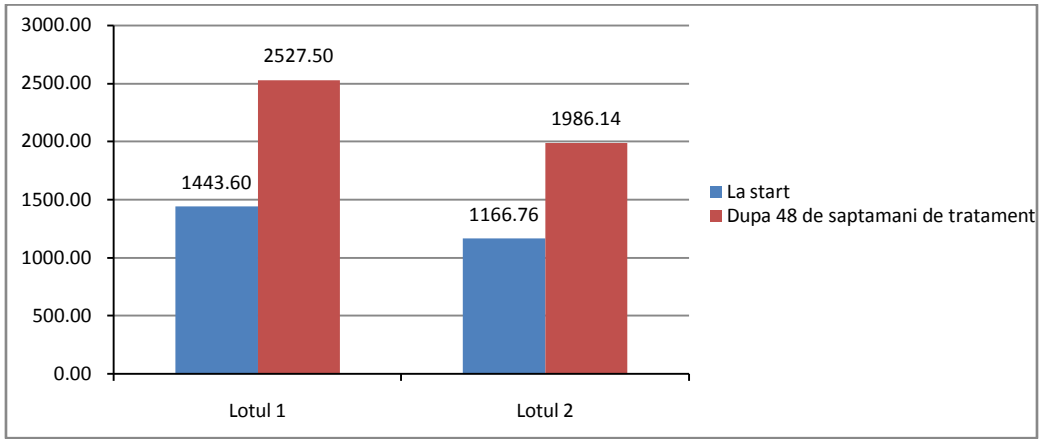


Chart2. The value of the malondialdehyde for the 2nd group at the beginning and after 48 weeks of treatment: - 10,33µmol/L at the beginning and 6,14µmol/L

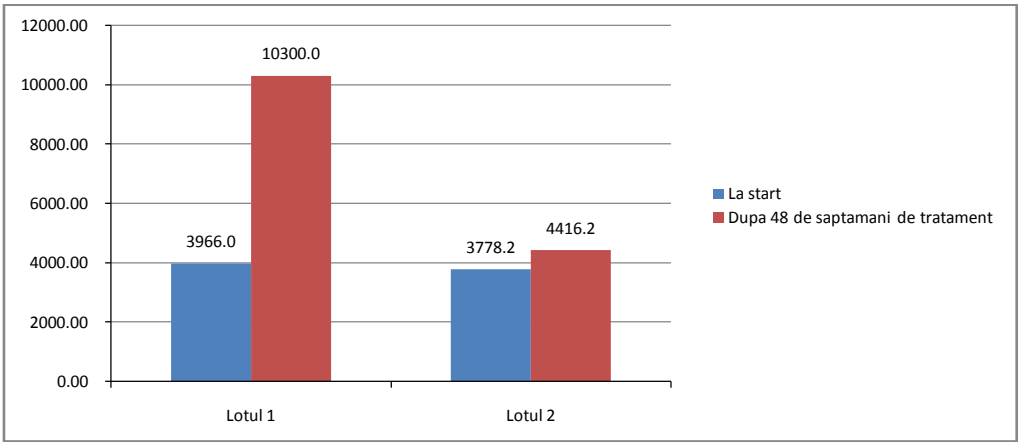


Chart3. ntioxidant enzymes at the beginning:
- superoxide dismutase
- 1 443,60U/gHg (Group 1); - 1 166,76U/gHg (Group 2)
- glutathione peroxidase
- 3 966 U/L (Group 1); - 3 778,24 U/L (Group 2)

Despite de above mentioned treatment, in chronic viral hepatitis B and C, the oxidative stress with the cellular metabolic disorders that it implies, favours the slow evolution towards the hepatic fibrosis, the proof being the bioumoral results at the end of the 12 months of treatment followed (GOT, GPT, MDA, SOD, and GPx, leukocyte, C-reactive protein, etc).

Fighting the infection with the help of the antiviral treatment leads to a decrease in the effect of the oxidative stress, while stimulating and increasing the antioxidant protection (SOD, GPx). After the treatment we can notice a decrease of the general nonspecific inflammatory basis at tissular level which favours the decrease of thecytolytic syndrome, the stimulation of thehepatic antitoxic capacity, with the rehabilitation of the membranar balance and negativization of the viremia (ARN-VHC and respectively of the ADN-VHB).

The clinical state and the reactivation of these patients came to normal almost totally.

The inflammatory character which accompanies the oxidative stress, expressed by the value of the C-reactive protein and of the leucocytes, shows the relationship between the viral infectious background, the general infectious background and the biochemical changes determined by the oxidative stress, reflected also by the hepatocytolytic process concordant in both senses, after 12 months.

The slightly increased presence (2, 16 mg/dl) of the C-reactive protein by the end of the antiviral treatment may represent the inflammatory activity of the hepatic parenchyma under restructuring which evolves in time. Comparatively, in Group 2, we can notice a much increased value of the C-reactive protein (6, 14 mg/dl) and of the leucocytes (9 118 /mm^3) which means an inflammatory activity in evolution.

The hepatocytolytic syndrome (GPT and GOT), together with the alkaline phosphatase under etiopathogenic treatmentbecame normal as compared to the values of the control group, in which, these values remained over the superior limit of the normal.

The favourable answer to antiviral therapy shows the determining role of the infection in the development of the inflammatory reaction with all the molecular and tissular stages, which form together the oxidative stress. As an answer to the treatment, the marker of the oxidative stress - the malondialdehyde becomes se normal, and the antioxidant enzymes (SOD and GPx) from negative progressively become more and more visible at plasmatic level.

CONCLUSIONS

1. The oxidative stress represents an active biochemical manifestation, with the direct implication in the pathogenesis of many diseases, including the hepatic ones;

2. The cells are protected against the oxidative processes by the natural antioxidant products, especially glutathione, but also by superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) [1]. The oxidative stress develops when a disturbance in the balance between the reactive forms of oxygen produced in excess and the factors of protection against their harmful effect occurs.

3. The oxidative stress favours, by destabilizing certain cellular balances, the weakening of the self protection and the development of the viral infection, of the hepatic tissular inflammation, as well as of the process of hepatocytolysis.

4. The inflammation linked to the viral infection increases the oxidative stress, which is proved by the increased serum levels of the malondialdehyde and the decreased

levels of the endogenous antioxidants, together with the increased levels of the C-reactive protein and leucocytes.

5. In chronic viral hepatitis B and C, antiviral treatment, for well selected cases, may produce healing.

6. The hepatitis C virus (HCV) is one of the main agents responsible for chronic viral hepatitis. HCV may cause oxidative stress in infected cells. The smaller capacity of the antioxidants in chronic hepatitis C may emphasize the increased degree of aggression of the oxidative stress in the infection with this hepatic virus, proved by the increased degree of lesion of the hepatocytes in viral hepatitis C. (9)

7. If the results obtained in Group 1 are due to the elimination of the infection and respectively of the inflammation, in Group 2, even if the results were not the same as those in the 1st Group, we could notice an improvement as compared with the values from the start.

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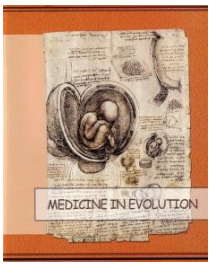
PYOGENICMENINGITIS – CURRENT ASPECTS



RUXANDRA LAZA[1], ALEXANDRU CRISAN[1], RUXANDRA JURAC[3], LUMINITA BADITOIU[2], EMILIA NICOARA[1], NARCISA NICOLESCU[1], VOICHITA LAZUREANU[1]

[1]"Victor Babes"University of Medicine and Pharmacy, 2nd Clinic of Infectious Diseases, Timisoara, România
[2]"Victor Babes"University of Medicine and Pharmacy, Discipline of Epidemiology
[3]Emergency Children's Hospital"L. Turcanu"Timisoara

ABSTRACT

***Objectives**: Acute bacterial meningitis have a high fatality rate, and in the case of favorable outcomes the possibility to determine neuropsychiatric sequels which sometimes are debilitating.*

***Material and methods:** In retrospective, cross-sectional, observational study, conducted on a group of 40 patients, children with age between 3 months and 16 years, hospitalized between January 2011 and December 2013 at"Victor Babeş"Hospital for Infectious Diseases and Pneumophtisiology, the authors sought: the etiological structure of pyogenic bacterial meningitis; CSF analysis; knowledge of antibiotic susceptibility and resistance of isolated germs.*

***Results and discussions:** In the analyzed group, there was encountered the classic etiological triad represented by the meningococcus, pneumococcus and H. influenzae. Multidrug resistance was observed in most identified strains. Favorable outcome was recorded in 85%.*

***Conclusions:** Unfavorable outcome is put in direct relation to the timing of diagnosis. The use of broad-spectrum antibiotics, has led to a selection of multi-drug resistant strains. Antimicrobial therapy should be monitored to prevent the emergence and spread of new resistances.*

***Key words:** etiology, clinical forms, pediatric patients*

Correspondence to:

Dr. Laza Ruxandra
Address: Timişoara, Str. Gheorghe Adam, nr. 13, Hospital for InfectiousDiseases and Pneumophtisiology
Phone: +40745170868
E-mail address: ruxi_martincu@yahoo.com

INTRODUCTION

Subarachnoid space retains the attribute of protected place, of a"sanctuary", as long as the anatomical integrity and functionality of the brain barrier is maintained, as long asvascular endothelial, cell membranes, mesothelial layer of arachnoid, respectively the endothelial, epithelial and mesothelial cells of these membranes are not subject to aggression.

In terms of microbial aggression, once overcome the immunological barrier (non-specific humoral and cellular defense), under the action of components related to microbial cell walls, of certain inflammatory mediators (interleukin 1, tumor necrosis factor α) occurs the hyperpermeability of the blood-brain barrier[1].

At the level of the subarachnoid space, this hyperpermeability leads to inflammatory edema, high-tension of cerebrospinal fluid (CSF), fibrin excess, loculating conditions, disturbance of CSF circulation, brain suffering.The unitary concept of infections development in the central nervous system, synthetically expressed cannot be omitted:"Each meningitis has its own encephalitis and each encephalitis has its own meningitis"[2].

If, until 7-8 decades ago, lethality was over 90%,both in the case of the pyogenic meningitis and tuberculosis meningitis, currently, meningitis therapy showed an obvious progress, however it can't be stated thatwe have full control over the outcome of these diseases.

The area of dissatisfaction is often given by the immediate result of the treatment ("ad vitam quo"), which still records a mortality of 5-10% in the case of meningococcal meningitis and a percentage of 20 and 22% for pneumococcal meningitis, respectively, for those with coliforms in infants[3].

Sometimes, the feeling of dissatisfaction appears with the evaluation of the distant result of antimicrobial therapy. Detectable neurological sequels are found in 20% of patients; they have as a substrate the pathophysiologic alterations that affect the brain or increase the permeability of the blood-brain barrier, cerebral edema (vasogenic and cytotoxic), intracranial hypertension, cerebral ischemia, by reducing cerebral circulation. In the case of a very intense inflammatory response there may occur subarachnoid space jam, arachnoiditis, hydrocephalus and / or cranial nerve lesions.

Dealing with these severe and unpredictablediseases, regular analysis of the conduct of the next few sequences, the decisive role in the disease,is welcomed [4]:

- ✓ sequence at the level of *primary health care,* that requires early recognition of the clinical classification defining meningeal syndrome,, respectivelyknowledge ofclinical manifestations which in the newborn, infant or toddler can be asimilatedas overlapping meningeal syndrome;
- ✓ sequence at the level of *secondary or tertiary healthcare*, which involves the correct use of the data provided by the CSF, respectivelythe possibility of transforming the syndromic classification into specific disease, etiology, the pathogenic mechanism (primary or secondary disease);
- ✓ to whichextent the sequence of specialized network can cover the diversity of clinical casework, which, in addition, to performing bacteriological investigation, requires minimal immunological examination (latex agglutination, co-agglutination, counter-immunoelectrophoresis, ELISA) and imaging (classic radiology, computer tomography, magnetic resonance);

early establishment etiotropic therapy, adapted to microbial resistance, repeatedly signaled in the territory, ofa homeostasis maintenance therapy, of resuscitation if necessary.

MATERIAL AND METHODS

In retrospective, cross-sectional,observationalstudy, conducted on a group of 40 patients, children with age between 3 months and 16 years, hospitalized between January 2011 - December 2013 at"Victor Babes"Hospital for Infectious and Lung Diseases**,** the authors sought: the etiological structure of pyogenic bacterial meningitis; Antimicrobial medications administered during pre-hospital; number of sick days from symptoms onset until admission; the distribution of bacterial meningitis by age; CSF analysis; knowledge of antibiotic susceptibility and resistance of isolated germs; classification of the clinical forms related to the recovery dynamic,analysis of unfavorable outcomes

Observational nature of the study included both descriptive side, as well as the analytical side of theanalyzed phenomena.

RESULTS

The descriptive part of the paper, did not omit the reportof the disease to a few general variables: age, gender, urban/ rural (U / R) environment, risk factors, comorbidities. The highest incidence of bacterial meningitis is present in the age group of 0-6 years (57% - 23 patients). 0-1 age group: 7 patients. In the case of the studied group approximately equal gender distribution (F / B 21/19) was obtained.

The ability to limit the severity of the disease, to improve the prognosis, is in directly dependent relationship with the shorter time betweenclinical onset of the disease and initiation of treatment (Fig. 1).

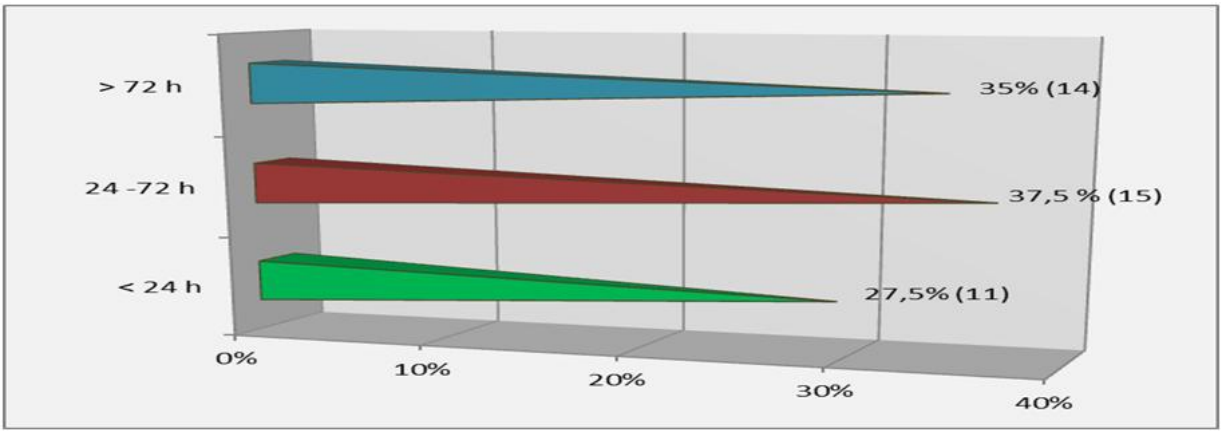


Figure 1. ***Time between clinical onset of the disease and initiation of treatment***

Most commonly, at the onset of bacterial meningitis, the symptomatic triad was found: fever, headache and vomiting of central type. The encephalitis component (sleepiness, psychomotor agitation, seizures) was present in 45% of patients (18). The data regarding bacteriological examination shows, on one hand, a significant mismatch between obtained data concerning bacteriological examination of the CSF sediment data and the CSF culture, on the other hand, a better match between the data regarding the culture and latex agglutination immunoassay – (Fig.2)

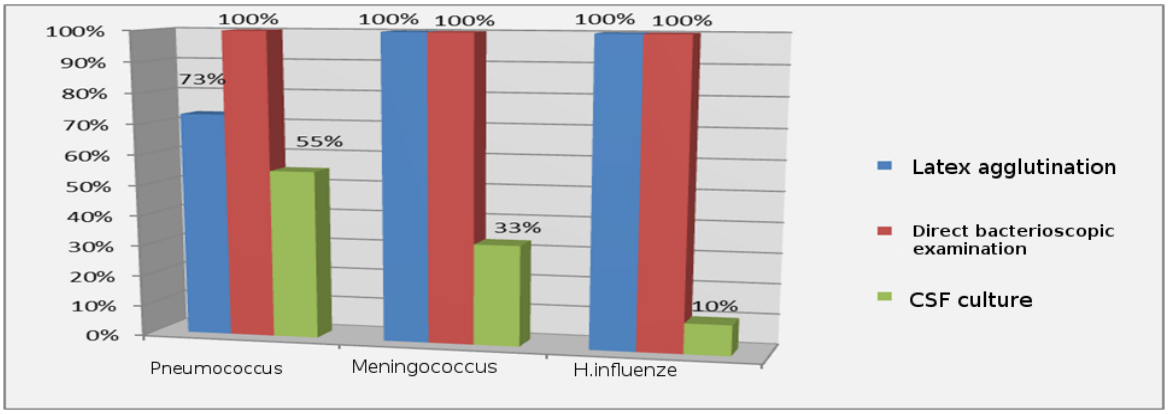


Figure 2.Symmetry and asymmetry of bacteriological samples

Etiological structure of the group analyzed keeps the classic etiological triad, represented by S. pneumoniae, N. meningitidis, H. influenzae, pneumococcus occupying the first position.A rare germ was isolated: Streptococcus salivarius. In addition, there were three cases of dual etiology: H. influenzae and Koch bacillus.In a significant percentage of purulent meningitis the etiology remained undetermined (15 cases / 37%)(Fig. 3).

Determination of resistance to first-line antibiotics for pneumococcus is illustrated in fig. 4.

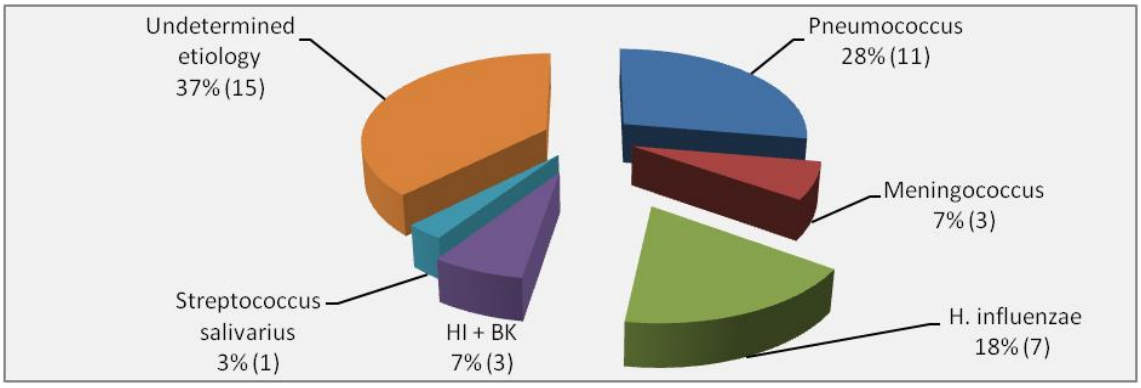


Figure 3.Etiological structure

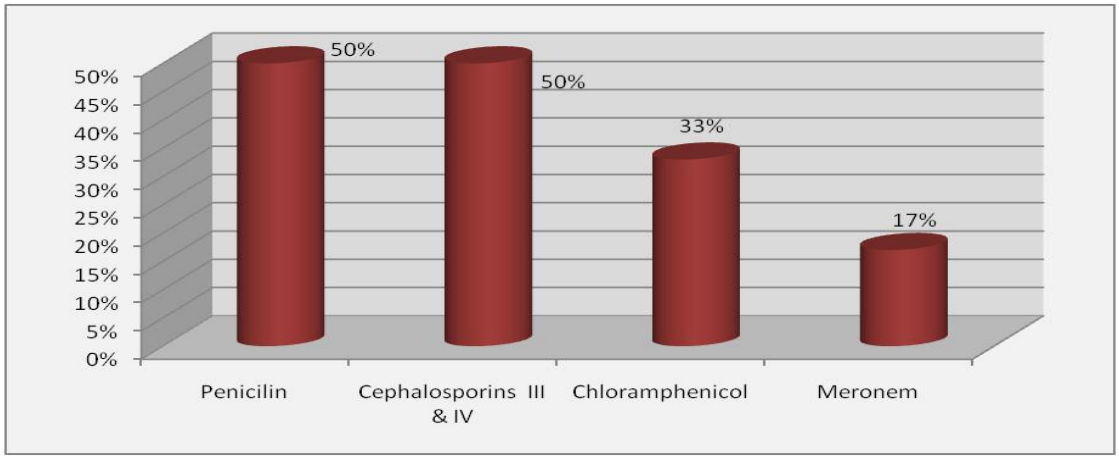


*Figure 4**Resistance to first-line antibiotics for pneumococcus***

Relationship between the pathogen involved and age can be presented as follows - fig. 5; we emphasize that the infection with H. Influenzae interested only age group of 0-6 years.

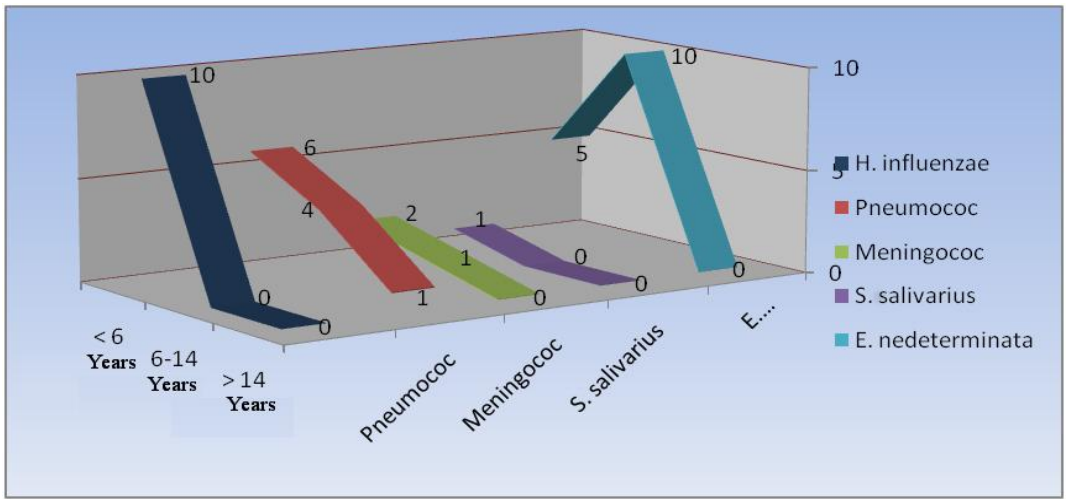


Figure 5Relationship between the pathogen involved and patient's age

The clinical picturesobtained,were enrolled in the group of common forms, of quickly curableor slightly prolonged, except five unfavorable outcomes and one relapse. 68% of patients were hospitalized less then 14 days.

The presence of a high percentage of secondary meningitis determinations undertakes to correct surveillance ofthe primary suppurative foci: lung, ear, ventriculo-peritoneal shunts, head.

DISCUSSIONS

The onset of the disease has been dominated by fever in a proportion of 93%, vomiting 73%, 68% diffuse headache; noisy onset was noted in 3 patients (clinical picture dominated by fever and tonic-clonic seizures). Encephalitic component(seizures, sleepiness, psychomotor agitation) was present in 45% of patients.

Antimicrobial medication was administered to 50% of patients.

Admission within 24 hours of symptom onset was recorded in 27.5% of patients. Ability to limit the severity of the disease, to improve the prognosis, is in a directly dependent relationship with curtailment of the time between clinical onset and the start of appropriate treatment. The time unit of the diagnostic delay is the hour (or overlapping hours),it has been found a relative delay in the addressability and diagnostic orientation of the primary care network.

On admission the CSF had a cloudy appearance in 60%, clear in 35% and hemorrhagic in 5% of patients. Clear macroscopic appearance of CSF, regardless of the germ involved, coincided with antibiotics administration prior to hospitalization, making the appearance of decapitatedbacterial meningitis. Also with clear liquid was recorded a superacute form of pneumococcal meningitis with few cellular elements and with rare germs at direct examination (meningitis paucicellular). In addition, three cases of dual etiology (H. influenzae and BK) produced CSF characteristic appearance of TB meningitis (clear liquid). Hemorrhagic cerebrospinal fluid was found in two cases; in one case the etiology was pneumococcal, the second one remained with undetermined etiology.

Etiological structure of bacterial meningitis recognizes a great variability depending on age and condition of terrain (neoplastic terrain, HIV infection).

In the analyzed group there was encountered the classic etiological triad

represented by the meningococcus, pneumococcus, H. influenzae; Pneumococcus and H. influenzae were found exclusively in the age group 0-6 years.

A total of 15 cases remained with unidentified etiology; a possible interpretation of these cases could be the administration of antibiotics prior to hospitalization.

It was isolated an unusual germ in the etiology of meningitis, Streptococcus salivarius. In addition, three cases were reported with mixed etiology: H. influenzae and Mycobacterium tuberculosis, cases recorded as being rare in the literature.

No Gram negative etiology was present, commonly involved in the production of purulent meningitis in young age group (<2 years) or in case of immuno-suppressed background.

Well expressed inflammatory fluid syndrome was present in relatively equal percentage, both in H. influenzae infection and in meningococcal or pneumococcal infection. Glycorrhachia reduction correlated with the decrease of the dynamics of the CSF chloride values raised the suspicion of tuberculous meningitis in three cases with double etiology (HI and BK).

So, we highlighted an undesirable dissociation between direct bacterioscopy and a relatively small number of positivity of CSF cultures. A good correlation was made between direct bacteriological examination and latex agglutination (recorded 100% for meningococcus, H. influenzae and 73% for pneumococcus). A possible interpretation of the reported inconsistency, especially regarding the results of CSF cultures, could be the initiation ofantibiotic therapy prior to admittance.

The percentage of strains susceptible to all tested antibiotics was small, it stood out the increased incidence of multiple resistance to drugs (76%). The study results confirm the high level of resistance of Pneumococcus to penicillin. Susceptibility to quinolones is kept still good, and very good to vancomycin and rifampicin. Development of a 33% resistance to cephalosporins is a warning sign.

Localization was primary meningeal in 62% of the cases. Secondary meningeal localization was registered in 38% of cases. It was in the context of primary septic foci (10- ENT, 3-lung), head trauma (1 case), ventriculoperitoneal shunt (1 case).

Blood culture tested positive in three cases: two with pneumococcal etiology and one with Streptococcus parasanguinus, all had favorable conditions (pultaceous acute tonsillitis, otitis media, pneumonia), aspects that confirm the secondary meningeal seeding, in the context of bacteraemia.

The investigated meningitis were of sporadic occurrence, without obvious seasonality, they have not been caused by an epidemic micro-foci, from hospitals or maternities, able to invokeinterpersonal transmission of the disease, involving of regular meningococcus, of a gram-negative or H. influenza.

High resistance of the pneumococcal strains to penicilin, means that this molecule can no longer be used as first-line therapy. Development of a 50% resistance to cephalosporinsis a warning sign. Resistance to cephalosporins is frequently associated with multidrug-resistance to other antibacterial agents. The pneumococcal strainsisolated mantaine a great sensitivityto vancomycin and rifampicin.

CONCLUSIONS

Purulent bacterial meningitis remais a major public health problem. Detection of rarelyinvolved bacteria in the etiology of bacterial meningitis,

commensal bacteria of different areas of the body, indicates the need for further testing to detect an immune deficiency.

The use of broad-spectrum antibiotics has led to selection of multi-drug resistant strains.

Antimicrobial therapy should be monitored, to prevent the emergence and spread of new resistances. It is necessary to develop practical guidelines for antibiotic treatment to reach a unified attitude. In case of meningitis with mixed etiology additional tests are required to detect an immune deficiency.

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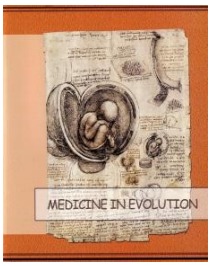
CRITICAL CARE PATIENT WITH CANCER IN INTENSIVE CARE UNIT



TEODORA OLARIU[1], DANA NEGRU[2], ANGELICA CHIOREAN[3], AMALIA NICULESCU[1], IUSTIN OLARIU[1]

[1]Arad "Vasile Goldis" West University
[2]Arad Public Health Department
[3]Cluj-Napoca"Iuliu Hatieganu" Medicine and Farmacy University

ABSTRACT

Introduction.*Critical care patientis that with unstable vital signs or conditions that may have irreversible complications requiring investigations, interventions and / or special care. Clinical assessment of their admission to ICU/Intensive Care Unit is based on methods that determine disease severity and prognosis.Biologically critical patient with cancer´prognosis is generally good. Resuscitation measures are important and allow the patient to survive the initial crisis.*

Aims. *Because elderly patients and one with cancer occurs more frequently in ICU services, we follow two groups based on age at diagnosis categories, under 65 and over 65 years, assisted in ICU on the assumption that mortality rates for cancer free patients are higher than those of patients with cancer, regardless of the underlying disease diagnosis.*

Material and methods*.Were followed 114 cancer patients for survival at 30 days, in order to determine therapeutic approach and survival rates compared with those of patients without cancer. The data were processed SPSS 14.0 for Windows, MedCalc andExcel using descriptive analysis, and measuring the effect of statistical tests.*

Results. *Patients were heterogeneous population as age, gender, cancer staging ;average age was less than 62 years, more frequently in women for breast, ovary, cervix, colorectal and skin cancer, with presence of rare cancers (bladder, biliary, breast in man). Survival at 30 days is better for them by comparison with non cancer patients, P = 0.0003,but there is a massive presence of other morbid conditions, likeobesity, diabetes, emphysema,hypertension, chronic ischemic heart disease in women and anemia in man. Complications were acute respiratory insufficiency, woundsiteinfections; double hydration needs was quantitative in elderly patients and the same for protein infusion requirements / amino acids ;increased pain therapy was usedfor elderly patientsmore often than for younger ones. Mortality in ICU is higher in cancer free patients with acute vital organs impairementsand major comorbidities compared with cancer patients.*

Key words: *intensive care, cancer, survival rates*

Correspondence to:

Olariu Teodora
Address: Arad,"Vasile Goldiş" West University, Bulevardul Revoluţiei 94
Phone: +40257280335
E-mail address: olariu_teodora@yahoo.com

INTRODUCTION

Despite an increasing number of patients with cancer disease admittedin ICU for complications of their underlying disease or to relieve the side effects of specific therapy, they do not benefit of many epidemiological studies regarding therapy and prognosis [1].

Critical care patientis that with unstable vital signs or conditions that may have irreversible complications requiring investigations, interventions and / or special care. Clinical assessment of their admission to ICU is based on methods that determine disease severity and prognosis. Triage (screening) of the patients in order to determine priorities intreatmentinvolves decisions depending on aranking thepatients in low-risk patients or with no chance of recovery. ICUstaffmust perform extensive evaluation and monitoring of patients, the main indication for hospitalization being unstable vital signs [2].

From the point of view of the patient with cancer, the treatment ishighly dependent on disease stage. The most appropriate treatment depends on biological perspectives of the patient and his personal and social circumstances. Biological prognosis is generally good. Resuscitation measures are important and allow the patient to survive the initial crisis [5]. Recovery is aided by the natural forces of healing, rehabilitation is completed by the patient without / or ongoing medical support. Acute and terminal diseases are pathophysiological distinct entities [6]. Many treatments fills the whole spectrum, eg radiotherapy, chemotherapy and surgery. Modern medicine offers combined and complex therapy regimens [7]: surgical approach associated with drug therapy, radiotherapy, chemotherapy which offers chance to the patient with cancer, if discovered in early stages and associated with a suitable lifestyle.

Scientific approach of treatment and symptoms may have result but still needs the methods of early detection through screening, in order to offer the opportunity to discover the disease at an early stage and stop progress.

The method which offers the bestopportunities for successful therapy is early detection of the first symptoms, followed by individualized, customized treatment, and proper communication with the patient, continuousreview of the impact of the disease and treatment by specialized monitoring withoutearly assumptions [8]. The correct diagnosis is followed by complex therapy, controlling pain relief, digestive,respiratory, cardiac, haematologic, neurologic, urinary symptoms, without forgetting the psychological support. In many cases a patient with cancer becomes often an emergency case when surgery and intensive care is required. The costs involved in this type of care are extremely high, regardless of the underlying disease status [3].

AIMS

Because elderly patients and those with cancer occurs more frequently in ICU, we follow two categories groups based on age at diagnosis, under 65 and over 65 years, type of cancer, other morbid conditions, complications, nutritional support, mechanical ventilation, dialysis, blood products, antibiotics and antiviral therapy, assuming that their mortality rates are lower than ICUcancer free patients, regardless of the underlying disease status.

MATERIAL AND METHODS

In study were 114 cancer patients under 65 years and over 65 years, assisted during their ICU admission, for a period of 26 days and after, till 30 days, from the point of wiev of their treatment and survival rate, in comparison withcancer free ICU patient. Data were processed *SPSS 14.0 for Windows*, *MedCalc* and*Excel* using descriptive analysis tools and statistical tests for measuring the effect.

RESULTS

Of1262 ICU patients admitted in2013, 114 have had cancer /9.033% with solid tumors 113 / 99.12% cases, one with anhaematological malignancy.

The average age of the cases is 62.61 years, std.Dev.14.61, extremes 15-89 years, gender distribution in favor of women 79 / 69.3%.

The most common malignancies were breast, colorectal, stomach, kidneys and bladder tumors, the last two being assigned to rare tumors. Recorded deaths were caused by bladder, ovary, cervix and lung cancer.

Cancer patients under 65 years / 61 cases were 4.83% and those aged 65 and over,58 cases / 4,199% of cases ICU assisted in 2013.

The distribution of these age categories according to underlying disease show a new profile for cancer patients in Arad, some morbid entitiesbeing generally different from the age of elective cases in the analysis: thus, breast cancer occurs more frequently after 65 years but to 1.5 for women under 65 years in our study and the ovary cancer as occurring exclusively in women under 65 years, which is discordant with the literature; about colorectal cancer, 4.6 ratio women / men assisted in ICU is discordant with relatively equal frequency presence of such tumors in both genders, both cases indicating no effective screening methods and no interest for the specific regional conditions. Tabel 1

Table 1. Cancer type frequency in ICU patients

tumoră	N	%	death	%death	m	f	under 65 years	Over 65 years
Bladder	6	5.26	2	1.8	5	1	2	4
Retroperitoneum	4	3.50			2	2	2	2
Kidney	8	7.01			7	1	4	4
Mediastinum	1	0.87			0	1	1	0
Biliary tract	2	1.75			2	0	0	2
Bone	3	2.63			2	1	0	3
Pancreas	1	0.87			1	0	0	1
Pharynx	3	2.63			2	1	2	1
Breast	45	39.47			2	43	27	18
Cervical	2	1.75	1	0.9	0	2	2	0
Skin	5	4.38			0	5	3	2
Lung	2	1.75	1	0.9	2	0	1	1
Hodgkin Disease	1	0.877			1	0	1	0
Colorectal	17	14.91			3	14	9	8
Ovary	4	3.50	1	0.9	0	4	4	0
Prostate	1	0.87			1	0	0	1
Stomach	9	7.89			5	4	3	6
total	114	100	5	4.5	35	79	61	53

Tumor staging of disease: 22 patients in stage I-II (20%), 77 in stage II-III(55%) and 21 stage III-IV (25%). Monthly average of deaths in the ICU for 2013 is double for cancer free patients, the relative risk of death for cancer patientsbeing 2.59 times smaller than ICU cancer free patients(95% CI 1.0823 to 6.1982, P = 0.0326) statistical significance [4].Tabel 2

Table 2. Monthly incidence for death in two groups

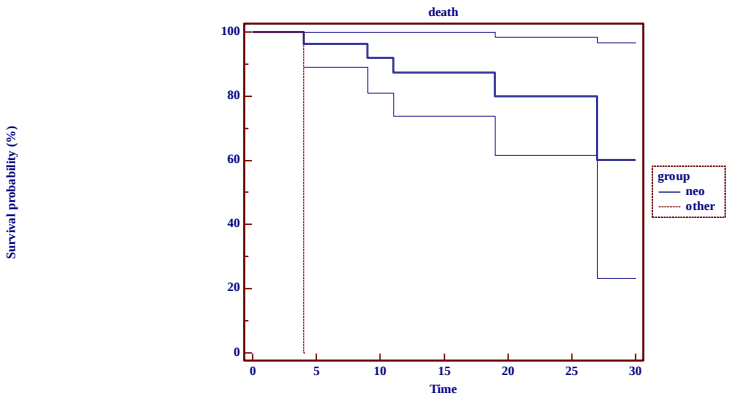
month 2013	admisission cancer free	Death cancer free	% death cancer free	admisission cancer	Death cancer	% death cancer
ian	104	9	8.65	7	0	0.00
feb	99	7	7.07	11	0	0.00
mr	113	10	8.85	10	0	0.00
apr	106	8	7.55	8	1	12.50
mai	92	13	14.13	7	0	0.00
iun	89	13	14.61	8	0	0.00
iul	76	14	18.42	6	0	0.00
aug	83	7	8.43	11	0	0.00
sep	77	7	9.09	13	2	15.38
oct	88	14	15.91	8	0	0.00
noi	106	9	8.49	19	2	10.53
dec	85	16	18.82	5	0	0.00
total	1118	127	11.36	114	5	4.39

Only for 104 patients there were recent surgery / 91.22% with complications for 45 patients / 43.26%, most of which were acute respiratory failure / 35.55%, the most serious being cardiac arrest with deathin 5patientsof 45 / 11.11%. Death rate for cancer patients was 4.38% compared with death rate in cancer free patients/ 10.76%, without statistically significant differences in risk table 3.

Comparison of survival curves (Logrank test) after 30 days in two groups, with and without cancer, shows averagesurvival at 30 days for patients with cancer and five days for the others [4]. graph 1,P = 0.0003.

Table 3. Cancer patients with surgical procedures andICU complications

Cancer patients	Eventration	Digestive Bleeding	Death	Acute Respiratory Impaired	Fistulas	Sepsis	Wound site infection
Surgical procedures	2	2	2	11	3	1	12
No surgical procedures	0	2	3	5	0	2	0



Graphic 1. Comparison of survival curves (Logrank test) after 30 days

Association of other morbid condition indicatesthat17.72% of women are obese and has type 2 diabetes mellitus, 31.64% have emphysema, 83.54% have chronic ischemic heart disease, 51.84% had hypertension, 12.65% have anemia and chronic obstructivepulmonary disease 8.86%. For men the situation is as follows: 14.28% presents benign prostatic hypertrophy, 11.42% are cachectic and has chronic obstructivepulmonary disease, 21.05% have emphysema, 71.42% have chronic ischemic heart disease and 57.14% havehypertension, type 2 diabetes in 14.28%. table 4.

Other morbid conditions are present in 109 patients / 95.61%, the amount of them being0 = no comorbidity, and7 = seven morbid association, is statistically significant,p=0.000, for patients under 65 years regardless of gender. table 5.

Of complications occurring during admission, the most common were acute respiratory failure and wound site infections, table 6.

Complications occurring during hospitalization, 0 = no complications, 5 = five complications have significance in relation to gender F, regardless of age, p = 0.036, Table 7.

Table 4. Type and percent for another morbid condition in cancerpatients

Other morbid conditions	m	%m	f	%f	under 65 years	Over 65 years
Benign prostatic hypertrophy	5	14,28	0	0	2	3
Myocardial infarction	1	2,85	0	0	1	0
Atrial fibrillation	2	5,71	1	1,26	1	2
Cachexia	4	11,42	3	3,79	3	4
Cerebrovascular accident	0	0	4	5,06	2	2
Chronic obstructive pulmonary disease	4	11,42	7	8,86	6	5
Atherosclerosis	2	5,71	5	6,32	1	6
Obesity	5	14,28	14	17,72	11	8
Heart failure	2	5,71	2	2,53	1	3
Chronic kidney disease	4	11,42	4	5,06	2	6
Emphysema	8	22,85	25	31,64	7	26
Chronic Ischemic cardiomiopathy	25	71,42	66	83,54	46	45
Diabeters mellitus	5	14,28	14	17,72	4	15
Hypertension	20	57,14	41	51,89	23	38
Anemia	12	34,28	10	12,65	11	11
T***hrombocytopenia***	1	2,85	3	3,797	2	2

Table 5. Sum for other morbid conditions, in age, gender and its significance for cancer

p=0.000									Total
Sumother morbid conditions –age -gender	0	1	2	3	4	5	6	7	
under65 years	5	17	22	12	2	1	1	1	61
Over 65 years	0	2	14	12	15	10	0	0	53
total	5	19	36	24	17	11	1	1	114
m	0	5	11	8	6	5	0	0	35
f	5	14	25	16	11	6	1	1	79
total	5	19	36	24	17	11	1	1	114

Table 6. Complications during admission for cancer patients

complications during admission	N	%	m	f
Acute Respiratory Failure	16	35.56	11	5
Wound infection	12	26.67	3	9
Cardiorespiratory arrest	5	11.11	3	2
Digestive Bleeding	4	8.89	0	4
Fistulas	3	6.67	2	1
Sepsis	3	6.67	1	2
Eventration	2	4.44	1	1

Table 7. Sum forcomplications occurring during hospitalization, for cancer patients, and its significance for cancer

P=0.036						Total
Sum forcomplications	0	1	2	3	5	
under 65 years	42	12	4	2	1	61
Over 65 years	39	10	3	1	0	53
Total	81	22	7	3	1	114
m	19	10	4	2	0	35
f	62	12	3	1	1	79
Total	81	22	7	3	1	114

Of 114 oncology patients, those under 65 years were 53.5%.Management of cancer patients is listed in Table 8.

Blood transfusion was given at the rate of 28.1% of cases, 32.5% for plasma, no significant differences for the two age groups. Antibiotics were used in 80 cases, no significant differences in the two types of ages.All patients were hydrated with saline solution, the double doses in elderly patients, with statistical significance for Pearson's correlation R p = 0.03. Except for one case, 113 patients received glucose,dosesbeing slightly higher for elderly patients but without statistical significance.

Amino acids were used in 30 patients, significantly different for the two age groups for Pearson's correlation R p = 0.022, according to proteinogram function deficit.

Potassium chloride was used in 36 patients, in amounts not significantly different for the two age groups according to blood ionogram, keeping in mind the effect of potassium deprivation and because were administered diuretics during the anesthesia.

Pain therapy consisted in administration: Ketonal in 114 cases in amounts non significantly different for the two age groups; Mialgin in 20 cases, doses beingraised with statistical significance p = 0.002 for patients under 65 years; Algocalminin 114 casesdoses beingraised with statistical significance p = 0.006 for patients over 65 years; Tramadol in 114 casesdoses beingraised with statistical significance p = 0.020 for patients over 65 years; Fentanyl in 23 cases in amounts non significantly different for the two age groups.

Vit C was used in 34 patients, 30 patients received Diazepam, Phenobarbitalin28 cases in amounts non significantly different for the two age groups.Spontaneous breathing was recorded in all patients except one under 65 years. Endotracheal intubation IOT was used for 6 patients and oxygen in 99 patients, with no significant difference.

Nutrition was orally administered to 110 patients, 106 patients benefited of parenteral nutrition, mixed nutrition in 103 patients, not significantly different for the two age groups.

Antiviral medication was administered in 5 cases, monoclonal antibody was used for 27 patients, not significantly different for the two age groups. Radioherapy was delivered to 12 patients and renal dialysis targeted 8 patients, not significantly different for the two age groups.

Table 8.Therapeutic approach for cancer patients in ICU

therapy	Patients no	%	under 65 years	Over 65 years
blood	32	28.1	14	18
plasma	37	32.5	18	19
antibiotic	91	79.82	46	45
saline solution	114	100	263	456

therapy	Patients no	%	under 65 years	Over 65 years
glucosis	113	99.12	256	388
Amino acids	30	26.3	25	92
KCl	36	31.57	23	28
Ketonal/dose	114	100	147	148
Mialgin/dose	20	17.54	20	3
Algocalmin/doze	114	100	372	602
tramadol	114	100	231	312
fentanyl	23	20.17	22	14
vitC	34	29.82	41	40
diazepam	30	26.31	33	23
fenobarbital	28	24.56	24	18
Spontaneous breathing	113	99.12	60	53
Endotracheal intubation	6	5.26	2	4
oxygen	99	86.84	51	48
Oral nutrition	110	96.49	58	52
Parenteral nutrition	106	92.96	56	50
Mixed nutrition	103	90.3554	49	
medicaţieantivirală	5	4.38	1	4
monoclonal antibody	27	23.68	16	11
Rx therapie	12	10.52	8	4
Dialysis	8	7.01	2	6

DISCUSSIONS

Critical Care Cancer Patients in ICU characteristics in Arad in 2013 are:heterogeneous cases in age, gender, underlying disease and cancer staging ; the average age is under 62 years, which raises the question if screening for cancer should be initiated at 40 years generally ; in particular are women withbreast, ovary, cervix, colonand skin cancer ; the presence of rare cancers (bladder, biliary tract, breast cancer in men); the survival rate at 30 days isbetter than those for ICU cancer freepatients; presence of other morbid conditionslike obesity, diabetes mellitus, emphysema, hypertension, chronic ischemic heart disease in women and anemia in male; acute respiratory failure and wound siteinfections, with statistically significant differences for women; double quantitative hydration and amino acids mainly for elderly patient ; increased requirements forpain therapy inelderly patients; survival by cancer through fair treatment and more complex therapy in elderly patients over 65 years compared to those under this age; the mortality rate is higher in ICU for cancer free patients with acute vital organsimpairements by comparison with cancer patients.

CONCLUSIONS

Cancer patients in critical conditionare not refused in ICUs, although they cover onlyhalf percentof Europe ICUs admissions rates. The prognosis of cancer patients in ICU for 30 days is better than those cancer free. Unlike other authors who have shown that the main complications are sepsis and respiratory failure in our cases the most common complications were acute respiratory failure and wound site infections.

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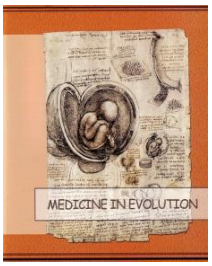
SEVERE ACUTE PANCREATITIS. ANATOMO-CLINICAL CORELATIONS



VÂLCEANU ANDREI PAUL[1], CHIRIAC SORIN[2], DEMA ALIS[3], LUCACIU DAMARIS[4], NICA CRISTIAN[1], GROSU SERGIU[4]

[1]Discipline of Emergency Surgery, University of Medicine and Pharmacy "Victor Babeș", Timișoara, România
[2]II[nd] Departament of Surgery, CFR Clinic, University of Medicine and Pharmacy "Victor Babeș", Timișoara, România
[3]Discipline of Morfopathology, University of Medicine and Pharmacy "Victor Babeș", Timișoara, România
[4]III[rd] Surgical Clinic, Emergency County Hospital of Timișoara

ABSTRACT

The aim of this study is to establish anatomo-clinical correlations in acute pancreatitis (AcP) in order to find a possible means of predicting which cases may benefit later on of a pancreatic transplant.

A 5-year (2009-2013) follow-up was done for all the patients admitted either in a clinic or the intensive care unit and the study refers especially to the cases with severe AcP, comparing the findings with data from literature based on 9 different criteria. The diagnostic was established based on clinical and biological data. Imaging data (the revised Atlanta classification) was mainly used to assert whether there was a case of mild or severe AcP.

Ultrasonography and/or computer tomography was used for all patients with severe AcP with the exception of 2 of them which had a fulminating evolution leading to death within the first 24 hours.

The indication for invasive interventions (whether endoscopic, minim invasive or open surgery) is put in the case of uncertain diagnostic, gallstones or when dealing with complications; such procedures were performed in 22 of these patients.

Local complications occurred in 83% of the severe cases. Global mortality was between 10-25%.

Key words: *acute pancreatitis, pancreatic necrosis*

Correspondence to:

Vâlceanu Andrei Paul
Address: str. IntrareaPlantelor, nr.1, sc. C, ap. 5
Phone: +40723545367
E-mail address: apvalceanu@yahoo.com

INTRODUCTION

Acute pancreatitis (AcP) is defined as the acute inflammation of the parenchyma leading up to its necrosis, all due to the activation of the pancreatic enzymes[1]. The lack of a distinctive capsule[2]is responsible for the spreading of the inflammation and necrosis in the surrounding tissues. The lipase activation leads to peripancreatic and fat interstitial tissue necrosis, and vascular lesions with hemorrhaging and thrombosis[1].

Upper abdominal pain is the main symptom, and in correlation with elevated amylase and especially lipase blood levels, can confirm the diagnostic[3]. Other imagistic and laboratory tests can be performed to determine the etiology, prognosis and complications[1, 4, 3]. The treatment includes pain management, hydric and electrolytic balancing and nutritional support. The indication for invasive interventions (whether endoscopic, minim invasive or open surgery) is put in the case of uncertain diagnostic, allstones or when dealing with complications[1, 4].

The prognosis estimation is based on different scores and is in relation with the disease's severity. The global mortality is initially caused by multiple organ failure (MOF), and later by infection and MOF and is around 10-15%[4], but can reach values of 24.5%[5].

Aim and objectives

The follow-up of patients who were diagnosed with acute pancreatitis over a period of 5 years.

The comparative study of the patients, especially those with severe AcP, in correlation with literature data and based on 9 different criteria.

The histopathological study of the inflammatory, hemorrhagic and pancreatic necrosis modifications.

The monitoring of cases with endo- and exocrine pancreatic insufficiency in order to determine the percentage of cases witch develop severe AcP and are potential candidates for pancreatic transplant.

MATERIAL AND METHODS

The study was done in the 3rd Surgical Clinic of The Emergency County Clinic Hospital of Timisoara (SCJUT) and included all patients diagnosed with AcP admitted over a period of 5 years: 01.01.2009 – 31.12.2013.

A total of 50 patients were included in the study, out of which 34 living in cities (68%) and 16 living in villages (32%). The following 9 criteria were used: sex, age, living area, ethiology (gallstones, ethanolic or idiopathic), investigations that the patient underwent, complications, invasive interventions (edoscopic sfincterectomy, surgical intervention), histopathologic exam and case evolution.

As source materials the following were used: the patients' medical chart, the operatory protocol, imaging data, histopathologic exam from the excision tissues, whether from The 3rd Surgical Clinic or the Anatomo-pathology Laboratory of the SCJUT.

The statistics were analyzed using the SPSS-17 program, the Fischer test, and the results were estimated using the statistic tests' decision criteria:

- $p > 0,05$ – insignificant difference (IS) with a significance tresholdof $\alpha=0,05$
- $p < 0,05$ – significant difference (S) with a significance tresholdof $\alpha=0,05$

- $p < 0,01$ – very significant difference (VS) with a significance tresholdof $\alpha=0,01$

- $p < 0,001$ – extremly significant difference (ES) with a significance tresholdof$\alpha=0,001$

RESULTS

Out of the total of 50 cases, 28 were male (56%) and 22 female (44%). Age varied from 27 to 81 years, the average age being 61.06 (with a standard deviation of +/- 13.99). The maximum incidence was recorded in the 61-70 decade, followed closely by the 71-80 one (tab 1).

Table 1. Distribution of patients according to age

Decade	**Number of cases**
21-30 years	1
31-40 years	4
41-50 years	8
51-60 years	5
61-70 years	17
71-80 years	14
> 81 years	2

From an ethiological point of view, the following were found: 25 cases of acute biliary pancreatitis (50%), 9 cases of AcP due to alcohol abuse (18%) and 16 cases of acute idiopathic pancreatitis (32%).

Table 2 shows the imagistic investigations patients underwent.

Complications occurred only in the severe forms of AcP (22 cases – 44%); a total of 33 invasive interventions were required for these cases, as shown in table 3.

Table 2. Imagistic investigations

	Number of cases (%)
Abdominal Ultrasonography	40 (80%)
CEUS	1
Abdominal CT	22 (44%)
MRI	2
Cholangio MRI	1
Barium swallow	1

Table 3. Invasive interventions

	Nr. cazuri
ERCP + sfincterotomy	1
Operations:	
- open cholecystectomy	7
- laparoscopic cholecystectomy	6
- cholecystoduodenostomy	6
- pancreaticojejunostomy	1
- posterior gastroenteroanastomosis	3
- necrectomy, abces drainage	9

Other polymorphism found were abnorThe patients' discharge status were as follows: cured – 18 cases (36%), ameliorated – 18 cases (36%), stationary – 2 cases, aggravated – 1 case, deceased – 10 cases (20%), transferred – 1 case.

Out of the total of 50 cases, 23 suffered from severe AcP (10 male, 13 female). Their distribution according to

age was as follows: 1 case (21-30 years), 2 cases (31-40 years), 3 cases (41-50 years), 8 cases (61-70 years), 7 cases (71-80 years), and 2 cases (81 years). The patients' age varied between 27 and 81 years, with an average age of 62.69 years.

Etiologically, these 23 severe AcP cases were: 13 cases of acute biliary pancreatitis (56.52%), 6 cases of AcP due to alcohol abuse (26.08%) and 4 cases of acute idiopathic pancreatitis (17.40%).

The following imagistic investigations were done: abdominal ultrasonography – 17 cases (74%), CEUS – 1 case, abdominal CT – 12 cases (52.2%), MRI – 2 cases, Cholangio-MRI – 1 case, Barium swallow – 1 case.

Figure 1 shows a nearly-total organ necrosis in acute pancreatitis on a CT image with contrast.

Figure 1.Nerotic pancreas on a CT image with contrast

Complications were found in 19 of the severe cases (82.69%) and consisted of pancreatic and peripancreatic collections (16 cases), pseudocysts (3 cases), biliary fistula (2 cases), pleural collections (5 cases), and persistent MOF (4 cases – 17.40%).

A total of 20 invasive interventions were performed on 13 patients as follows: ERCP and sphincterectomy (1 case), open cholecystectomy (3 cases), laparoscopic cholecystectomy (1 case), necrectomy and drainage (9 cases), posterior gastroenteroanastomosis (2 cases) and biliodigestive anastomosis (4 cases).

A histopathological exam was performed in 3 of the cases with severe AcP that underwent necrectomy (fig. 2, 3, 4, 5).

Figure 2. Necrectomy with quasi-total excision of necrotic pancreas (Prof. Dr. D. Vâlceanu, Dr. Grosu)

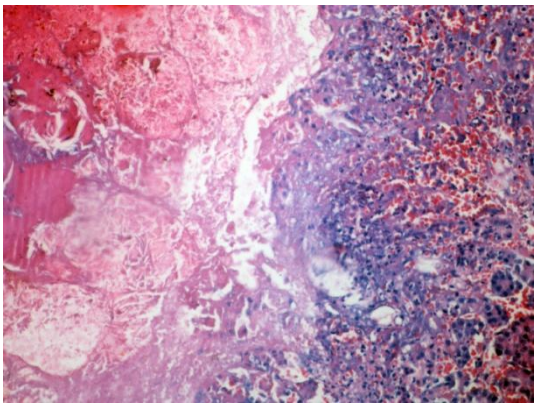


Figure 3. Acute hemorrhagic necrosis of the pancreas: pancreatic and fat tissue with necrotic and hemorrhagic focuses, rare viable pancreatic acins (lower right). Hex200 – Prof. Dr. A. Dema

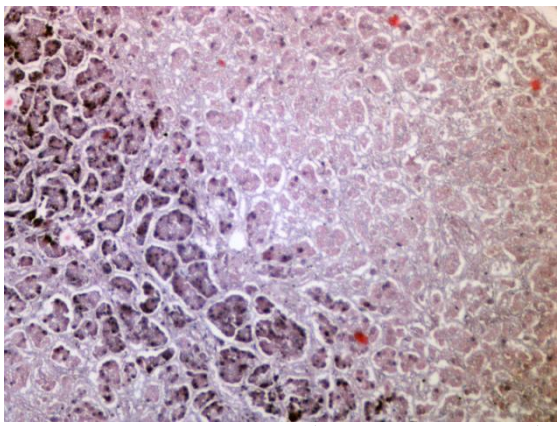


Figure 4.Pancreatic tissue (exocrine component) with extensive necrosis Hex200 - Prof. Dr. A. Dema

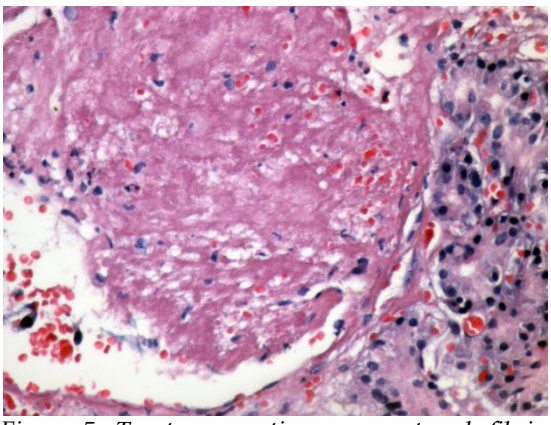


Figure 5. Țesut pancreatic: vena cu tromb fibrinos în lumen. HEx400 - Prof. Dr. A. Dema

The patients' discharge status was as follows: cured – 7 cases (30.43%), ameliorated – 5 cases (21.74%), stationary – 0 cases, aggravated – 1 case, deceased – 10 cases (43.48%).

DISCUSSIONS

This disease has a relative low occurrence worldwide: 5-80 cases out of 100.000 in the USA[4] and12.4-15.9 cases out of 100.000 in Europe[1]; on the other hand it has a grave evolution with a high mortality rate of 10-15%[4] or 24%[6], or even as high as 42% early mortality within the first 2 weeks[7]. The risk of developing AcP grows with age and the average age of the patients is 55.6 years[7] and 49.7 years[3].

Our study included 50 cases, which represent 0.65% of the total number of admitted patients. Mortality was 20%.

Regarding sex distribution, a little over half of the cases were male (56%), which constitutes an insignificant statistical difference p=0.23 (IS). This result is similar to that found in literature[3, 4, 8]: 56% male / 44% female[2].

Within the studied lot the average age was higher: 61.12 years.

Most of the patients lived in urban areas: 34 (68%), whereas only 16 came from villages (32%); statistic p=0.0005 (ES).

Regarding the disease's etiology, literature data varies, showing a predominance of gallstones, followed by alcohol consumption, metabolic (toxic), autoimmune, vascular, genetic and idiopathic form (gallstones – 68.4%, alcohol consumption – 26.8%, other etiology – 4.8%)[4, 10, 11]. Gallstone etiology is more frequent in women, while alcohol consumption more frequent in men[3, 11]. The idiopathic form does not favor women or men[4].

In our statistic we found gallstone etiology in 25 cases (50%), idiopathic in 16 cases (32%) and alcohol consumption in only 9 cases (18%). A special note goes to the high percentage of idiopathic cases and their inverted ratio to cases due to alcohol consumption compared to most of the data from literature. By comparing the number of cases with gallstones to that of the cases with alcohol consumption, a p=0.0011 is obtained, a difference which is extremely significant statistically (ES); the comparison between gallstones and idiopathic causes – p=0.07 a statistic insignificant difference (IS). The subsequent question is raised: is this real or is it due to lack of accuracy when collecting data or other investigations? We aim to compare our results with those of other medical and surgical clinics in our region in a future study.

In literature, severe AcP occurs in 10-20% of the cases[6, 12, 17]. Based on the

revised Atlanta classification criteria, we had a number of 23 cases classified as severe AcP (46%). The difference between these findings is probably due to the fact that the mild cases of AcP are mostly admitted to medical clinics (gastroenterology).

In the USA, imagistic investigations provide a sensibility of 95-98% and a specificity of 100%[16].

In the studied lot, each patient with severe AcP underwent at least one imagistic investigation (ultrasonography, CT or MRI); an exception to the above statement is noted and consists of 2 patients with fulminating evolution where death occurred within the first 24 hours.

Excluding the experimental studies, the number of articles with histo-pathological studies of AcP is rare. This is probably due to the fact that advanced necrosis deters examination. Despite the necrosis surrounding the lesions, we were able to present the 3 examined samples with severe inflammatory modifications (hemorrhage, necrosis and thrombosis) because of existing fragments that maintained tissular structure.

The necrotic form of AcP affects both exocrine and endocrine functions of the pancreas in more of half of the cases[14]. Even in the moderate form, endocrine insufficiency is present in 39.5% of the cases[13, 15]. If we also take into account the milder cases admitted in the gastroenterology clinic, we can consider 46% of the severe cases as comparable to the data in literature. In theory, all severe cases with favorable evolution, whether with a high or low functional deficiency, are possible candidates for substitute medical or surgical therapy (transplant). The selected cases will be dictated by the severity of the functional deficiency.

CONCLUSIONS

1. Acute pancreatitis is a relative rare disease that affects both sexes, with men being more affected then women.
2. Imagistic investigations are not only necessary, but also very useful in establishing severity (Atlanta classification) and the suitability for surgery (emergency or delayed).
3. The moderate forms of AcP have a favorable evolution.
4. Severe forms of AcP have a very high mortality (43.5%).
5. Cases that show favorable evolution, whether severe or moderate, require follow-up even after full remission for the assertion or endo- and exocrine pancreatic function
6. Severe forms of AcP are accompanied by functional deficiency and represent candidates for pancreatic transplant.

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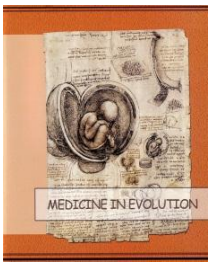
OVARIAN CANCER, A PUBLIC HEALTH ISSUE



ANCULIA RAMONA- CAMELIA[1], JEBEREAN ADRIAN[2], POPOVICI RAMONA- AMINA[3]

[1]"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania, Department of Social Medicine
[2]"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania, Department of Surgery Semiology II,
[3]"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania, Department of Preventive, Community Dentistry and Oral Health

ABSTRACT

Worldwide, nearly 239,000 women were estimated to have been diagnosed with ovarian cancer in 2012, with incidence rates varying across the world. In Europe, around 65,600 new cases of ovarian cancer were estimated to have been diagnosed in 2012. Ovarian cancer has a natural evolution unknown, debuting the often insidiously, without specific symptoms, diagnosis occurring during a routine exam. Although the association tried precursor lesions results were not conclusive, cellular changes can be criminalized and other non-tumor pathologies. Later symptoms may include: bloating, pelvic pain, and abdominal swelling among others. Common areas of spread include the lining of the abdomen, lungs, liver or lymph nodes. Ovarian cancer occurs more frequently in women who ovulate more, thus those who never have children are at increased risk. Other risk factors include hormone therapy after menopause, fertility medication, smoking and obesity. Factors that decrease the risk include hormonal birth control, tubal ligation, and breast feeding.

Key words: *Ovarian Cancer, Incidence of Ovarian Cancer, Survival 5 yr rate, Prevention*

Correspondence to:

ANCULIA RAMONA- CAMELIA
Address:"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania, Department of Social Medicine, 2 Eftimie Murgu Square, 300041 Timisoara, Romania

INTRODUCTION

Worldwide, nearly 239,000 women were estimated to have been diagnosed with ovarian cancer in 2012, with incidence rates varying across the world. In Europe, around 65,600 new cases of ovarian cancer were estimated to have been diagnosed in 2012. At European level highest incidence is found in Lithuania, Estonia, Ireland and the opposite we find countries like Portugal, Cyprus, Spain. Our country is located in the middle firing rate was 12.8 per 100,000 women in Europe and the world average for the white race. This percentage may not correspond to reality, in the absence of national programs for monitoring the incidence of ovarian cancer, but the proportion of cases detected and reported by the Ministry of Health is similar to those in Bulgaria, Poland and the Czech Republic. Ovarian cancer is misleading symptoms: abdominal or pelvic pain, changes in bowel habits, bleeding suspicious, painful intercourse, fatigue etc. Predictive factors for unfavorable evolution of CO are: age> 50 years at diagnosis, impaired performance status (ECOG ≥ 2), stage IC disease (with ovarian capsule rupture) or more advanced at diagnosis, tumor volume increased before and after debulking surgery, the presence of dense adhesions tumor ascites in large quantities with clear cell histological types / mucinous tumors differentiation grade G34, mutations in the BRCA1 gene, over expression of HER2 / neu [1,2].

Known risk factors for ovarian cancer are the following [3]: Caucasian (white), age> 40 years, late first pregnancy (after 30 years), late menopause, anovulatory cycles/ nulliparous / infertility / use fertilization medication, chronic exposure to talc (perineal applications), residing in industrialized urban areas, family history of cancer (ovarian, endometrial, breast, colon), mutațiiBRCA1 / BRCA2

Currently, there is no reliable screening test for ovarian cancer. However, there are a number of things that may help prevent ovarian cancer. There is no known way to prevent ovarian cancer. But are some things which may lower a woman's chance of getting ovarian cancer, like: having used birth control pills, having had a tubal ligation (getting your tubes tied), Prophylactic oophorectomy, or a hysterectomy (an operation in which the uterus, and sometimes the cervix, is removed), having given birth and breastfeeding. Some studies suggest that women who breastfeed for a year or more may have a modestly reduced risk of ovarian cancer. While these things may help reduce the chance of getting ovarian cancer. Risks and benefits are associated with each.

MOLECULAR CHARACTERISTICS OF OVARIAN CANCER

Ovarian cancer is heterogeneous, like other cancers, comprising a collection of subtypes with different histological and molecular characteristics that in turn inform prognosis [4]. Accumulating evidence suggests that there are two general pathways in the molecular pathogenesis of what is known as ovarian cancer [5, 6]. The first (Type I) pathway leads to borderline tumors, which can develop into low-grade serous, mucinous, endometriosis, and clear cell carcinomas. These are for the most part low-grade tumors that are characterized by a high frequency of mutations of KRAS, BRAF, ERBB2, CTNNB1 (the gene encoding beta catenin), and PIK3CA, low proliferation, and a 5-year survival of approximately 55% [4]. A stepwise model of progression from

cystadenomasto low-grade carcinomas has been proposed for these neoplasms.

In contrast to the Type I tumors, the Type II tumors are high-grade and highly aggressive, spreading rapidly throughout the pelvis. Type II tumors include high-grade serous carcinoma, malignant mixed mesoderm tumors, and undifferentiated carcinomas. They are characterized by a high frequency of mutations in TP53, a tumor suppressor gene, and a high proliferative index. It is estimated that 60% of sporadic ovarian carcinomas and the majority of those diagnosed in BRCA1 mutation carriers are of the high-grade serous type [3, 4]. Preliminary data suggests that these TP53 mutations may develop early in the carcinogenic process. I in fact this is confirmed, new approaches to early detection and prevention can be developed.

Staging of ovarian cancer (see table below) is classified according to the International Federation of Gynecological Oncologists (FIGO) guidelines[2] with approximately 75% of women presenting with advanced stage 3C and 4 diseases.

Table 1. FIGO Classification of Ovarian Cancer

	Stage	Disease
Stage 1 Tumour confined to the ovaries	1A	Limited to one ovary with capsule intact, no ascites
	1B	Limited to both ovaries with capsules intact, no ascites
	1C	Stage 1A or 1B with disease on surface on one or both ovaries, or capsule rupture, or malignant cells in ascites of peritoneal washing
Stage 2 Tumour confined to the pelvis	2A	Extension or metastastasis to the uterus or fallopian tubes
	2B	Extension or metastasis to the other pelvic organs
	2C	Stage 1A or 2B with disease on the or both ovaries, or capsule rupture, or malignant cells in ascites or peritoneal washing
Stage 3 Tumour confined to the abdomen	3A	Microscopic seeding of tumour on the abdominal peritoneal surfaces or mentum
	3B	Macroscopic metastasis on the abdominal peritoneal surfaces or mentum < 2 cm diameter
	3C	Macroscopic metastasis on the abdominal peritoneal surfaces or mentum < 2 cm diameter, or positive retroperitoneal or inguinal lymph nodes.
Stage 4 Distant spread outside of the abdomen	4	Positive cytology on pleural effusion, parenchymal liver metastasis or Sister Mary- Joseph nodules (umbilical metastasis) or other extra abdominal site.

RESULTS

The word 'prevalence' of Ovarian Cancer usually means the estimated population of people who are managing Ovarian Cancer at any given time (i.e. people with Ovarian Cancer). The term 'incidence' of Ovarian Cancer means the annual diagnosis rate, or the number of new cases of Ovarian Cancer diagnosed each year (i.e. getting Ovarian Cancer) [10]. Hence, these two statistics types can differ: a short disease like flu can have high annual incidence but low prevalence, but a life-long disease like diabetes has a low annual incidence but high prevalence. The statistics used for prevalence/incidence (from figure 1.) of Ovarian Cancer are typically based on US, UK, Canadian or Australian prevalence or incidence statistics,

which are then extrapolated using only the population of the other country. This extrapolation calculation is automated and does not take into account any genetic, cultural, environmental, social, and racial or other differences across the various countries and regions for which the extrapolated Ovarian Cancer statistics below refer to. The extrapolation does not use data sources or statistics about any country other than its population. In Europe the highest incidence of Ovarian Cancer is in Russia, Italy, Germany and UK. Romania is at the middle with the incidence of Ovarian Cancer, but this is in raise.

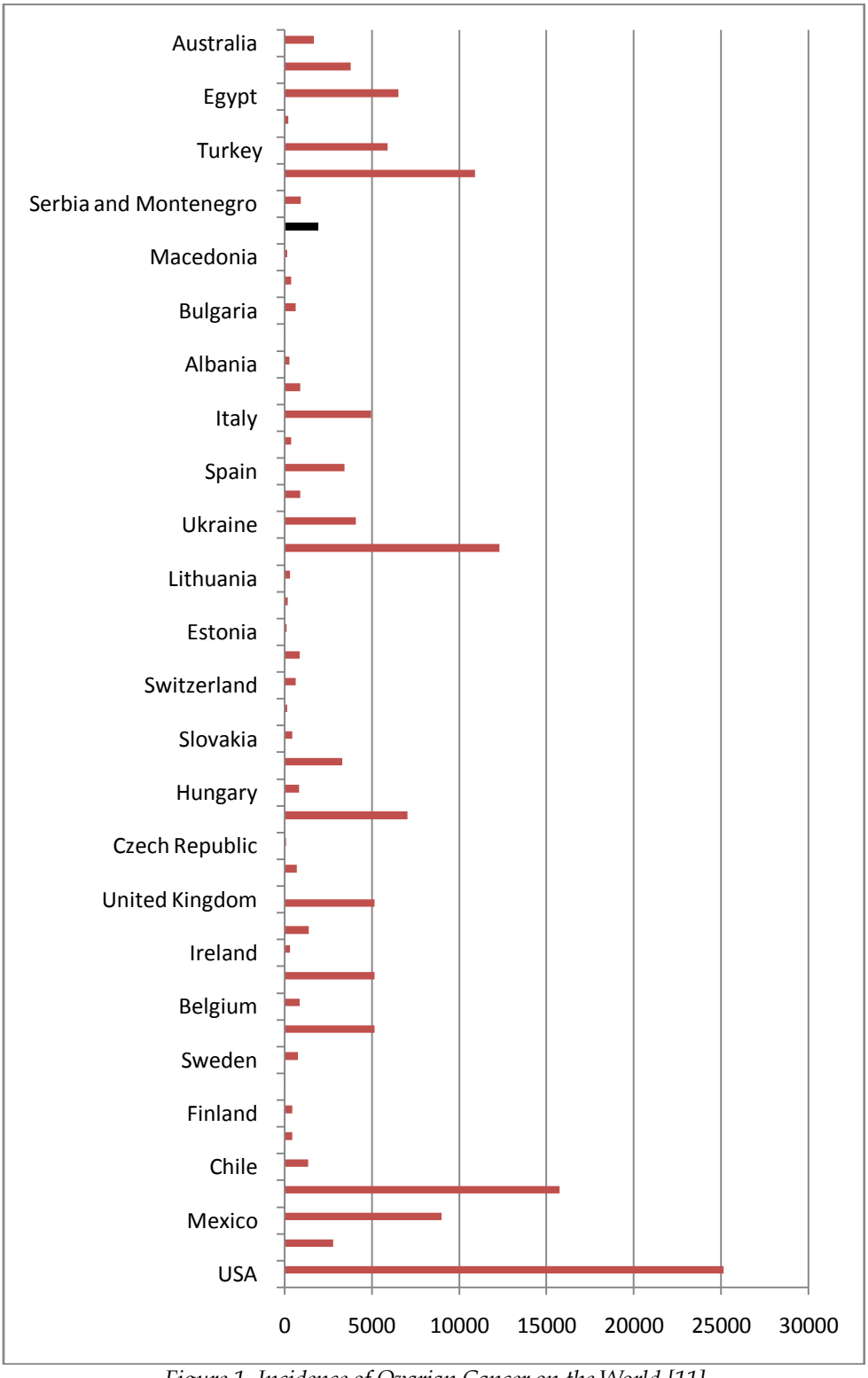


Figure 1. Incidence of Ovarian Cancer on the World [11]

Globally, as of 2010, approximately 160,000 people died from ovarian cancer, up from 113,000 in 1990. The disease is more common in industrialized nations, with the exception of Japan. In the United States, females have a 1.4% to 2.5% (1 out of 40-60 women) lifetime chance of developing ovarian cancer. Older women are at highest risk. More than half of the deaths from ovarian cancer occur in women between 55 and 74 years of age and approximately one quarter of ovarian cancer deaths occur in women between 35 and 54 years of age [11].

From 2004–2008, the median age at diagnosis for cancer of the ovary was 63 years of age. Approximately 1.2% was diagnosed under age 20; 3.5% between 20 and 34; 7.3% between 35 and 44; 19.1% between 45 and 54; 23.1% between 55 and 64; 19.7% between 65 and 74; 18.2% between 75 and 84; and 8.0% 85+ years of age. 10-year relative survival ranges from 84.1% in stage IA to 10.4% in stage IIIC. [13,12]

The age-adjusted incidence rate was 12.8 per 100,000 women per year. These rates are based on cases diagnosed in 2004–2008 from 17 SEER geographic areas (see Figure 2.).

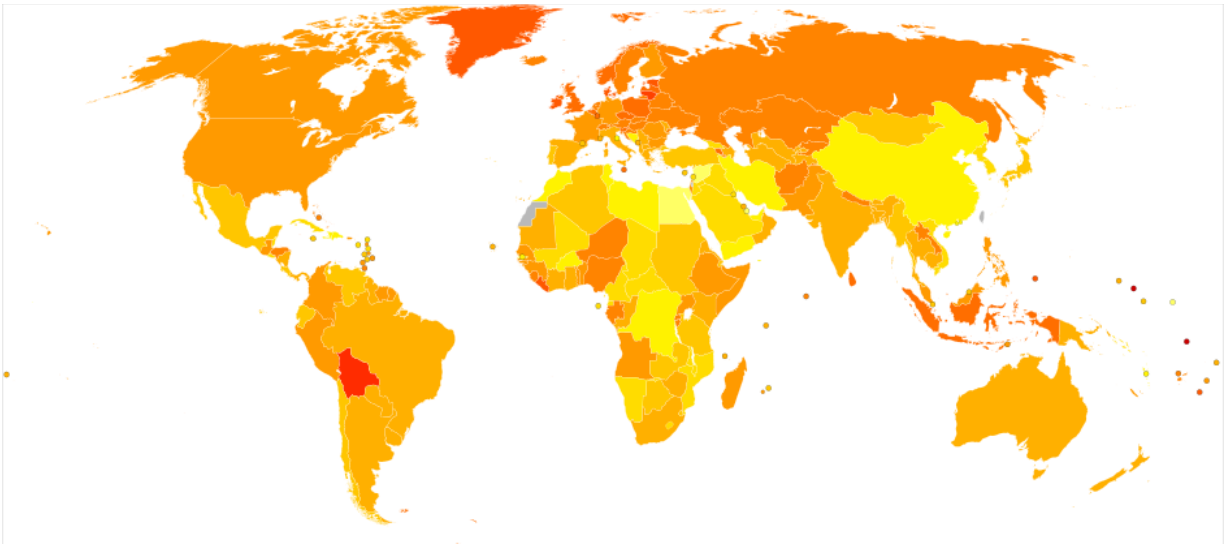


Figure 2.Age-standardized death from ovarian cancer per 100,000 inhabitants in 2004(no data,less than 0.6,0.6-1.2,1.2-1.8,1.8-2.4,2.4-3,3-3.6,3.6-4.2,4.2-4.8,4.8-5.4,5.4-6,6-7,more than 7) [13]

Survival at 5 years in the early stages is good, but 75 to 80% of patients present with advanced disease, with a life expectancy of 5 years only 20%, see Figure 3. [8] Intraperitoneally disseminated ovarian carcinoma (mainly), lymphatic, retroperitoneal and diaphragmatic, marrow and contiguity. At necropsy examinations metastases are most commonly peritoneal (90%). Bone metastases are found in the brain and 1% of the cases, the lung and the liver parenchymal 5% 5 10% cases [9]. Most of the women are diagnosed once the cancer has already spread which makes treatment more challenging. Diagnosed in the earliest stage of ovarian cancer, women have a very good chance of surviving, with five year survival rates of above 90%. When diagnosed at the latest stage, five year survival rates are below 10%[3]. Research has shown that just 3% of women in the UK are very confident about recognizing a symptom of ovarian cancer[4]. Delays in diagnosing ovarian cancer are not uncommon.

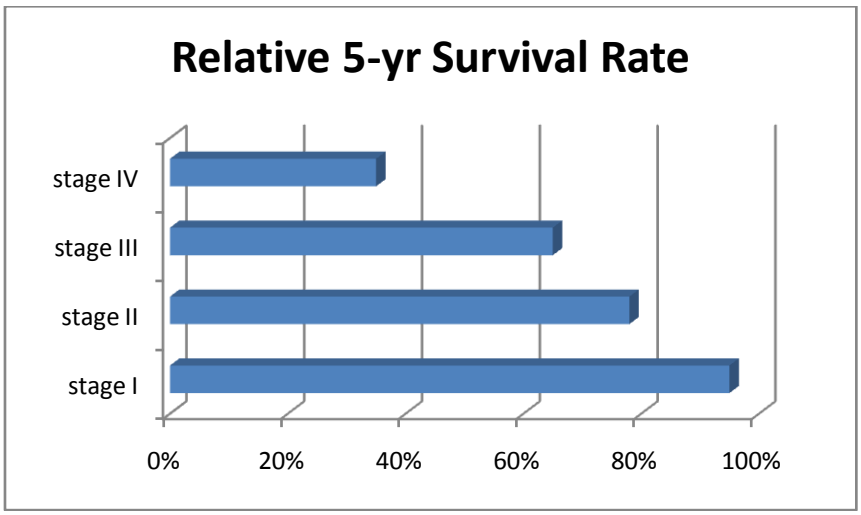


Figure 3.5 Yar Survival Rate from the Ovarian Cancer Diagnosis. [14]

CONCLUSIONS

Ovarian Cancer is a Public Health issue because: all women are at risk for ovarian cancer- annually dies 140,000 women on the globe, Awareness of the symptoms of ovarian cancer may enable women to receive an earlier diagnosis, when the disease is more easily treatable. Diagnosis at an early stage vastly improves a woman's chance of survival- when ovarian cancer is detected at an early stage, when the cancer remains confined to the ovary, up to 90% of women are likely to survive for more than five years. Ovarian cancer is often diagnosed at a late stage and many women mistakenly believe a cervical smear test (or Pap test) will detect ovarian cancer.

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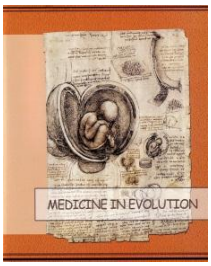

BENEFICIAL EFFECT OF LONG-TERM SIMVASTATIN THERAPY ON GALLSTONE DISSOLUTION. OUTCOMES IN A TRIAL OF HYPERLIPIDEMIC PATIENTS FROM SOUTHWESTERN ROMANIA

ELENA CIURARIU[1], V. DUMITRASCU[2,3]

[1]Department of Allergy and Clinical Immunology,"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania
[2]Pharmacology Department,"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania
[3]Timisoara County Emergency Clinical Hospital, Romania

ABSTRACT

Aims *To investigate the specific changes which occur in gallstones chemical composition in order to evaluate the role of simvastatin as a gallstone-dissolving agent.*

Material and Methods *Gallstones were collected from 125 hyperlipidemic patients, aged 28 to 78 years. The fragmented stones were quantitatively analyzed by Fourier transform infrared spectroscopy for cholesterol, bilirubin, carbonate and phosphate and the results were correlated with stone type and patient age. Scanning electron microscopy was used in order to highlight the different crystalline composition of gallstones. 75 patients (60%) enrolled in the study were previously treated with 40 mg/day simvastatin for 8-years.*

Results *82 patients had cholesterol stones (65.6%) and only 43 (34.4%) were pigment gallstones.Gallstones proceeding from simvastatin patients were radiolucent, homogenous and monocomponent, morphologically formed by large needle-shaped crystals and soluble cholesterol.*

Conclusion *Long-term simvastatin therapy is effective in gallstone dissolution.*

Key words: *simvastatin, Fourier transform infrared spectroscopy, gallstone dissolution*

Correspondence to:

Elena Ciurariu
Resident physician, trainer for a doctor's degree in pharmacology
Address: Department of Allergy and Clinical Immunology,"Victor Babes"University of Medicine and Pharmacy, 2 Eftimie Murgu Square, 300041 Timisoara, Romania
Phone: +40723081655
E-mail address:ciurariu.elena@gmail.com

INTRODUCTION

Simvastatin, as an inhibitor of 3-hydroxy,3-methylglutaryl coenzyme A (HMG-CoA), has been reported in previous studies to prevent formation of gallstones in animal studies (1), and in humans (2),and to decrease the cholesterol saturation index in humans as well (3),(4).

Gallstone disease occurs in patients with obesity and impaired lipid profile, requiring long-term statin therapy. Therefore, it is very important for the practitioner to understand the pleiotropic effect of statins and to evaluate their association with gallstone formation.

In the cholesterol-suprasaturated bile of hyperlipidemic patients in southwestern Romania, over 75% of gallstones are cholesterol gallstones (figure 1).

The aim of our study was to investigate the specific changes which occur in gallstones chemical composition in order to evaluate the role of simvastatin as a gallstone-dissolving agent.

Figure 1. Multiple radiolucent cholesterol gallstones removed by cholecystectomy in patient M.A., 45 years

MATERIAL AND METHODS

Patient design and study randomization

In a randomized, prospective and comparative study, including 125 hiperlypidemic patients, aged 28 to 78 years, diagnosed with biliary stone disease and hospitalized in the surgical clinics from the Timisoara County Emergency Clinical Hospital, gallstones were surgically removed and analyzed. The participants included in the study were similar as body mass index and plasma lipid profile. Among the randomized patients, 75 patients (60%) enrolled in the study were previously treated with 40 mg/day simvastatin for 8-years. Patient with diabetes, different metabolic diseases or drug-induced calculi were excluded.

The fragmented stones were quantitatively analyzed by Fourier

transform infrared spectroscopy for cholesterol, bilirubin, carbonate and phosphate and the results were correlated with stone type and patient age. Scanning electron microscopy was used in order to highlight the different crystalline composition of gallstones core and shell.

Plasma lipid levels were assessed and ultrasonographic examination of the gallbladder was performed yearly in order to follow-up the gallstone formation rate.

In order to participate in the study, patients filled out a medical form including written consent, in accordance with current medical ethics.

Study method

Infrared absorption spectra were plotted with a JASCO unit - FT/IR (automatic reading of absorption bands), the existing unit at the Timisoara Institute of Chemistry of the Romanian Academy.

The measuring range was set to 600-4000 cm $^{-1}$.Spectra were taken at normal temperature and pressure existing in the laboratory.

Features JASCO unit - FT / IR - 4200 used for experimental measurements are presented below:

- Measuring range: 7.800 - 350 cm^{-1}
- Precision of wavelength: ± 0,01cm^{-1}
- Optical system: Single beam
  Interferometer: Michelson 450

RESULTS AND DISCUSSIONS

The Fourier transform infrared spectroscopy indicated that 82 patients had cholesterol stones (65.6%) and only 43 (34.4%) were pigment gallstones (figure 2). No patient had both types.

Figure 2. Multiple pigmentary gallstones removed by cholecystectomy in patient S.P., 52 years

We revealed that the mean content of bilirubin was only 25% before age 30 but increased at 68% at the age of 70, while the content of bilirubin, phosphate and carbonate gradually increased (8% at age 30 to 58% at age 70).

The gallstones proceeding from simvastatin patients were homogenous and monocomponent, morphological formed by large and needle-shaped crystals (figures 3,4):

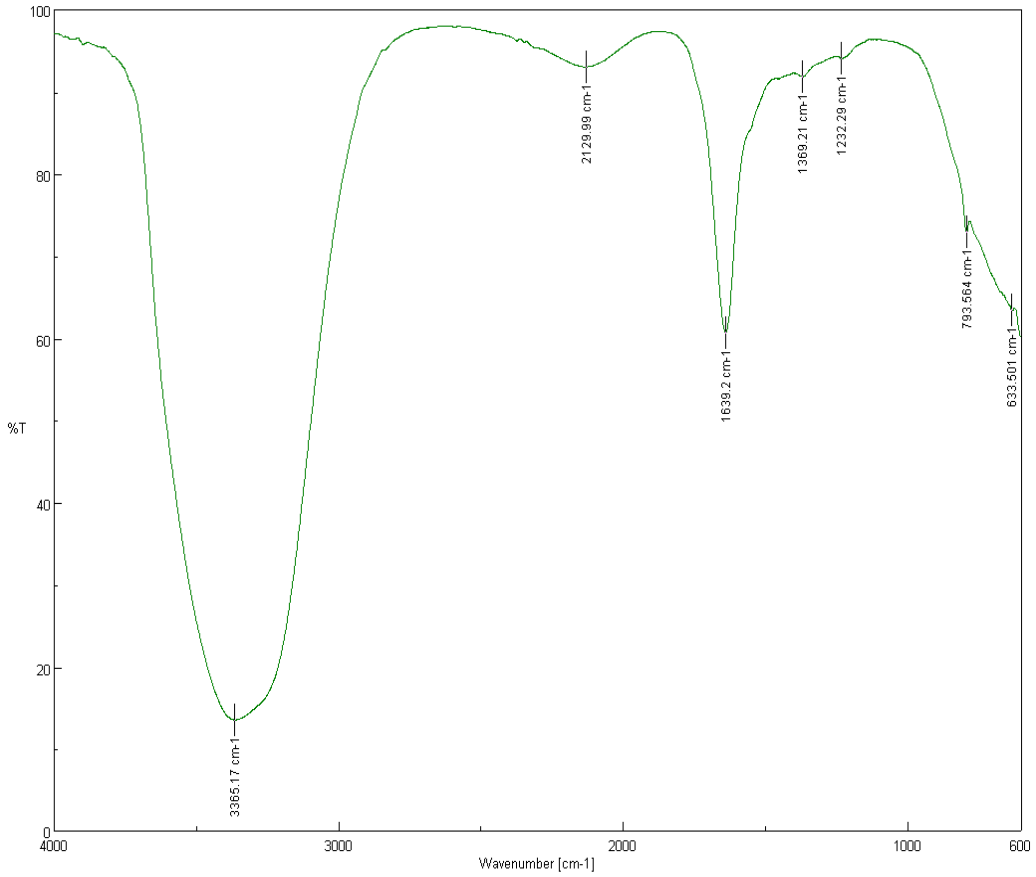

Figure 3.IR spectrum of one of the gallstone nucleus removed from patient M.A, 45 years on therapy with simvastatin for 8 years

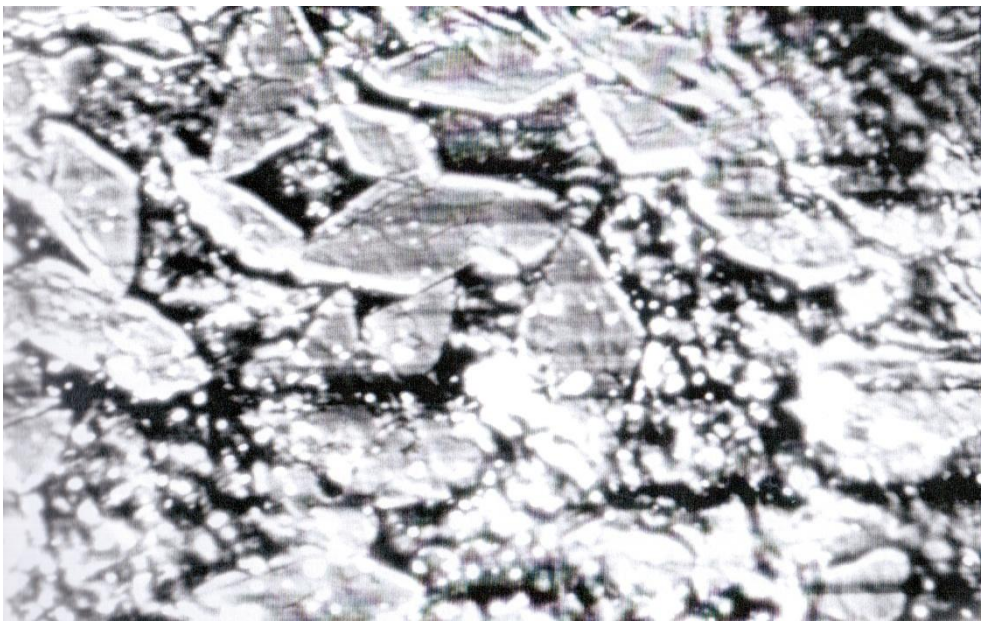

Figure 4. Scanning electron microscopy of one of the gallstones removed from patient M.A, 45 years on therapy with simvastatin for 8 years

Gallbladder stones removed from the other hyperlipidemic patients without statin therapy were heterogeneous and with a complex and multicomponent structure, revealed by Fourier transform infrared spectroscopy and scanning electron microscopy (figures 5,6).

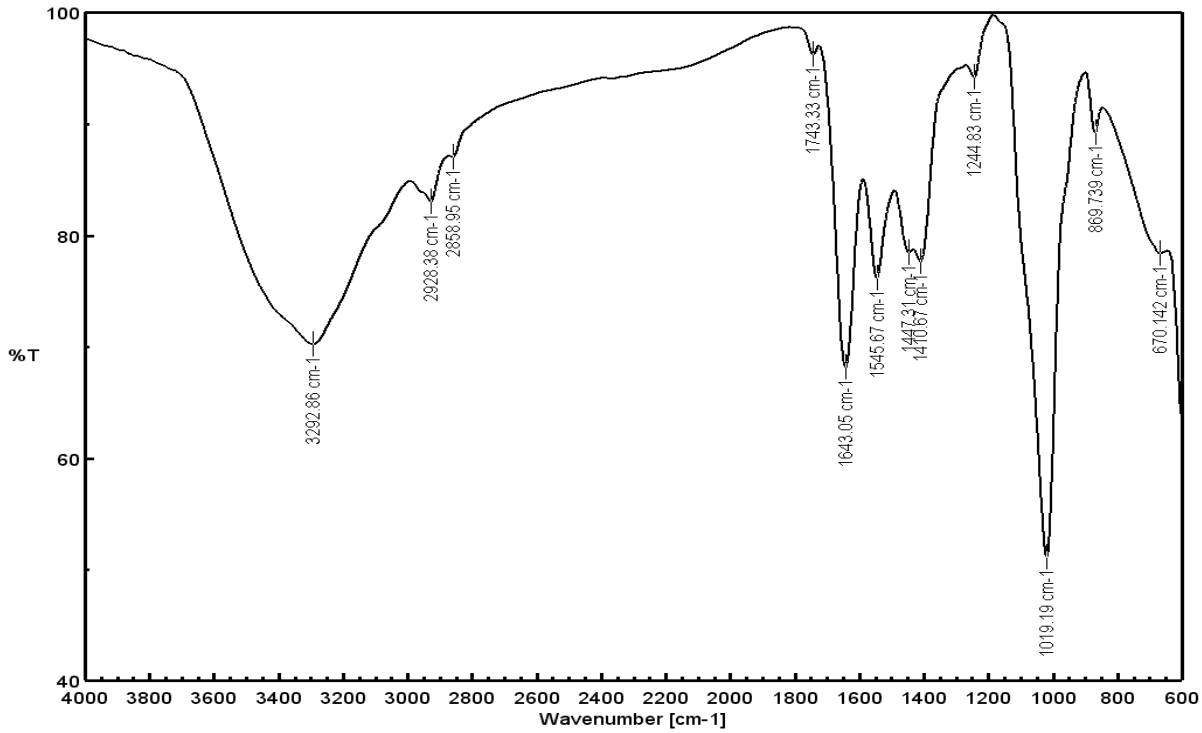

Figure 5.ComplexIR spectrum of one of the gallstones removed from patient S.P, 52 years, with chronic dyslipidemia

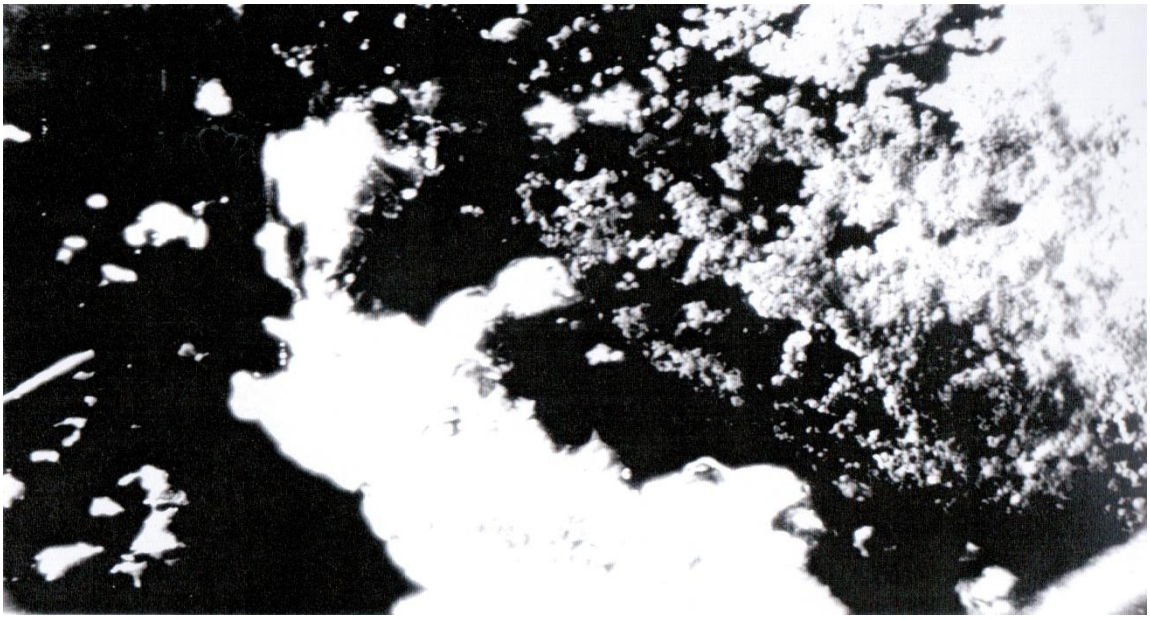

Figure6. Scanning electron microscopy of one of the gallstones removed from patient S.P, 52 years, with chronic dyslipidemia

The complexity of the chemical composition of gallstones and the changes due to simvastatin therapy are very important for the practitioner, but they are still poorly understood.

In accordance with previous studies, our research highlight the pharmacological pleiotropic properties of simvastatin therapy beyond LDL-lowering (5),(6),(7).

Gallstones became smaller because statins have a beneficial effect – acting on the main mechanisms of crystallization, respectively - nucleation, fixation and epitaxy, and lipophilicity, revealed by using modern spectral analysis, such as Fourier transform infrared spectroscopy and scanning electron microscopy. Our study suggests that, during long-term simvastatin therapy, cholesterol becomes more soluble, with high possibilities of dissolution (8).

Pigment gallstones rate increases directly with age, becomes prevalent in the hyperlipidemic elderly and therefore these cases need a special clinical survey because soluble cholesterol is replaced by calcium salts of carbonate, phosphate or bilirubinate (9),(10). Based on these findings, we revealed that this kind of gallstones, usually occurred in geriatric population, are structurally harder and are much more difficult to destroy than those of patients who received long-term simvastatin therapy.

CONCLUSIONS

Our study indicates that long-term simvastatin treatment is effective in gallstone dissolution and statin users have a lower risk of gallbladder disease.

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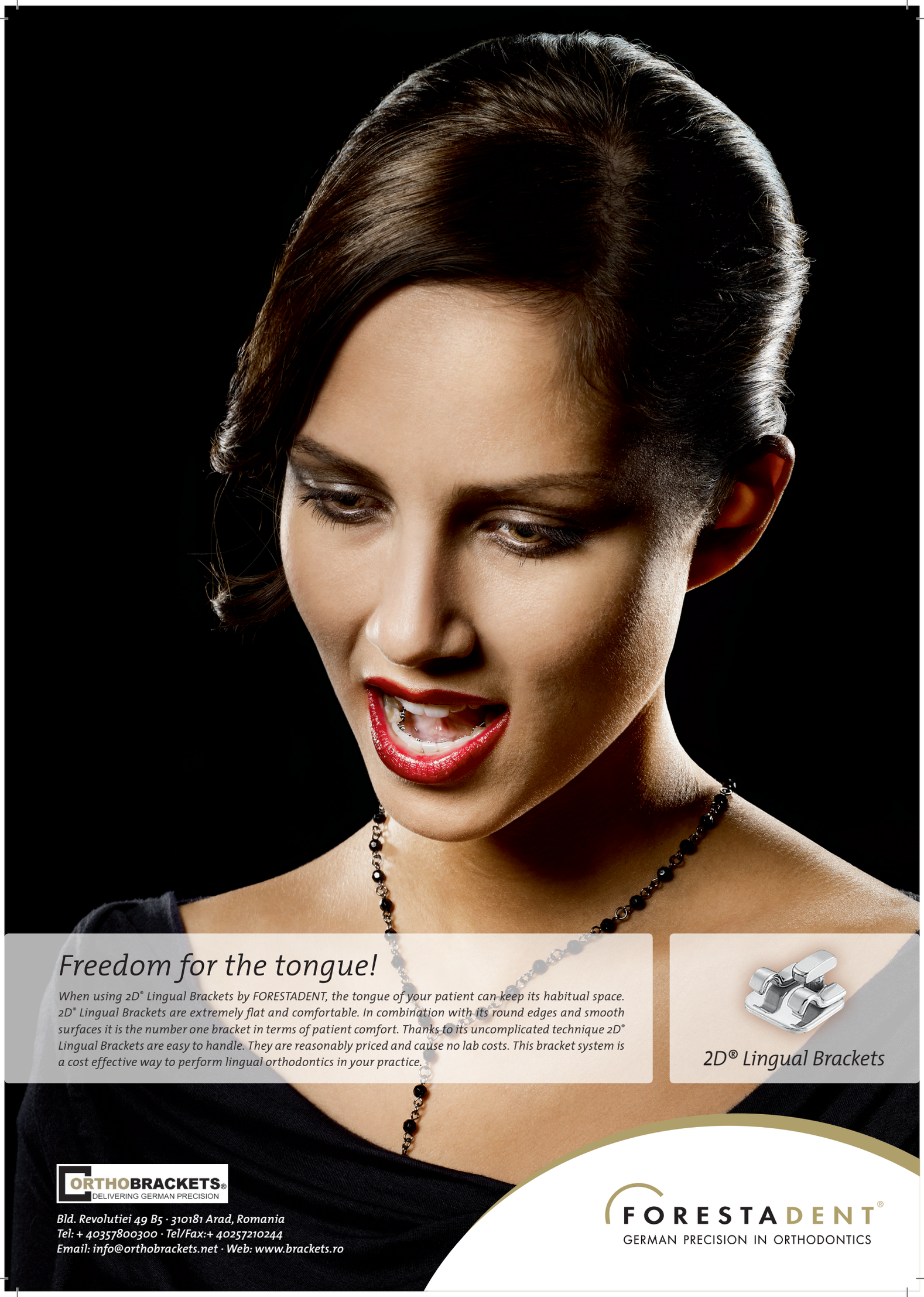
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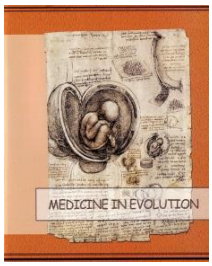

THE INCLINATION OF THE UPPER AND LOWER INCISORS AFTER TREATMENT WITH A FULLY CUSTOMIZED LINGUAL APPLIANCE IN COMBINATION WITH HERBST APPLIANCE ON PATIENTS WITH AN ANGLE CLASS II/1

PASARIN TEODORA ADINA[1], MODJAHEDPOUR ESFANDIAR[2], TALPOS CRISTINA[3], BRATU ELISABETA[4]

[1]University of Medicine and Pharmacy"Victor Babes"Timisoara, Departement of Pedodontics and Orthodontics,Phd Student, Fellowship POSDRU 107/1.5/S/ID 78702
[2]Orthodontist, MSC, Private Practice Krefeld, Germany
[3]University of Medicine and Pharmacy"Victor Babes"Timisoara, Departement of Ergonomics
[4]University of Medicine and Pharmacy"Victor Babes"Timisoara, Departement of Pedodontics and Orthodontics

ABSTRACT

Aim: The purpose of this study is to determine the final position of the upper and lower incisors inclination after using a fully customized lingual appliance in combination with the Herbst Appliance (2).

Materials and Methods: 8 consecutively debonded cases with an initial malocclusion class II division 1 patients were examined. The final position ofthe upper incisors and lower incisors (5) were determined using lateral cephalograms.

Results: After debonding all cases showed a final position of the upper incisorsinclination between 100,7° and 103,7 ° in reference to 1_-N-S (7).

The inclination of the lower incisors using the mandibulare plane as a reference varied between 86° and 94° (8).

Conclusion: Correction of class II devision 1 patients with a fully custumized lingual and herbst appliance delivers reliable treatment results and stabile position of the incisors.

Key words: *Incognito lingual appliance, class II divison 1, invisible orthodontic treatment, Herbst Appliance*

Correspondence to:

Teodora Adina Pasarin
MD, PhD Student
Address: Departement of Pedodontics and Orthodontics, University of Medicine and Pharmacy"Victor Babes"

INTRODUCTION

The class II division 1 is a malocclusion which can be treated using different techniques in order to achievea dental class 1. Depending on the age of the patient the treatment effect can be a dentoalveolar effect or a scelettal effect or a combination of both. Functional appliances may work well on childreen and adolscents pending on their compliance during treatment. This is also true for the use intermaxillary elastics.

Various techniques for distalisation oft he upper dentition are being used in orthodontics.

A headgear appliance (11) may distalize the molars andin combination with a functional applianceit is used as theTeuscher Activator. Headgears in combination with an lingual appliance have restrictions due to patients acceptance and visabilty of the headgear.

Distalizing the upper molars can also be achieved succesfully using miniscrews. Two coupled miniscrews in combination with heavy wires can distalize the upper dentition (3). Distaljet can also be used in ordert o distalize (10).

In addition the extraction of the first upper bicuspids and „en masse „retraction can reduce the overjet. On adults the combination of orthodontic treatment and class two surgery (4,9) is also a frequently performed treatment strategy. This treament approach results in higher costs and higher treatment risks.

PATRIENTS AND METHODS

8 consecutively debonded cases with an initial malocclusion class II division 1 patients were examined. The final position ofthe upper incisors and lower incisors (5) were determined using lateral cephalograms.

The patients presented in this article were treated with a fully customized lingual appliance (Incognito-3M Bad Essen) designedby using CAD/CAM manufacturing technologies. In order to connect the Herbst Appliance to the lingual appliance two fully customized bands were bonded on the upper molars and lower canines. The bands on the upper molars were bonded seperatly from the bonding tray in a direct bonding procedure using dual cure bonding agent wherase the lower canine bands were bondedonly after levelling and aligning the frontal teeth, giving the patients an extended time with an invisable treatment appliance.

The Herbst appliance consists of several parts. The two telescopes have a tube, the two plungers are connected to the bands with screws. The tubes and plungers are pre adjusted lab side and angulation in the head oft he plungers prevents a precontact tot he lower first pre molars during mouth openening and closing.

Activation rings in different sizes can be placed on the plungers in order to activate the amount of mandibulareadvancement. Connecting the Herbst Appliance treatment to the lingual bracket system iscompared to traditional labial bracket systems time saving, because no interruption of the multibracket treatment occurs. With Incognito appliance the only replacement that occurs is as discribed the exchange of the lower canine brackets to bands during Herbst therapy. This exchange typically occurs during an archwire change. It is recommended to place the bands on the lower canines one the 0,016”x 0,022”NiTi wire is replaced by the 0,018 x 0,025 NiTi as a preparation fort he fullsize stainless steel wire 0,018 x 0,025. This fullsize archwire povides a

full anchorage on the lower incisors during Herbst treatment with the clinical achivement of a reverse torque effect on the lower canines. After the Herbst Phase which lasts from depending on the age oft he patient and on the sceletall patern 6-8 month the final archwire is engaged. For the final detailing of the torque a 0,0182"x 0,0182"Beta III TMA wire required.

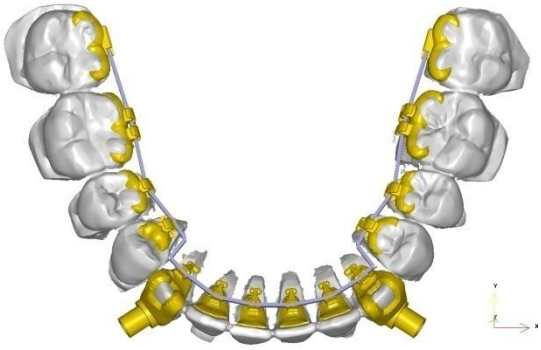

Figure 1. showing the digital design of the lower appliance

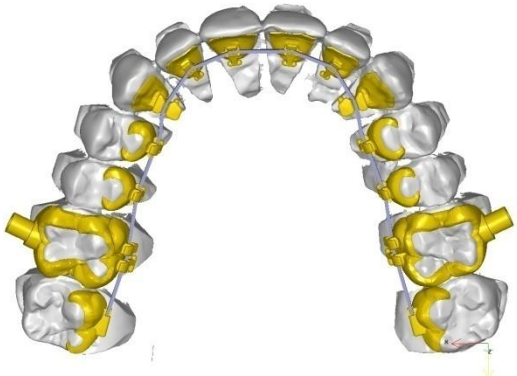

Figure 2. showing the digital design of the upper appliance

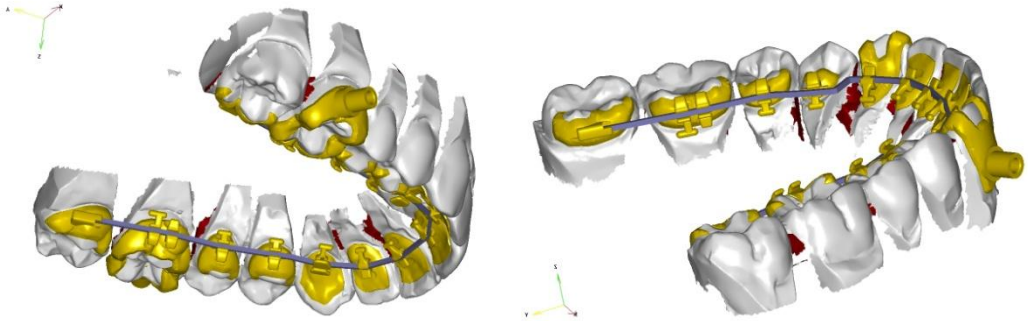

Figure 3 and 4. show the buccal / labial attachments of the bands

CASE REPORT

Figure 5, 6, 7. Angle class II/1 malocclusion

Figure 8. Herbst Phase

Figure 9. Final Occlusion

Figure 10. Herbst Phase

Figure 11. Final Occlusion

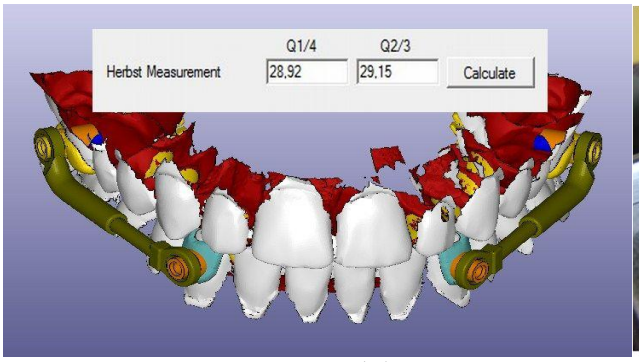

Figure 12. Digital design

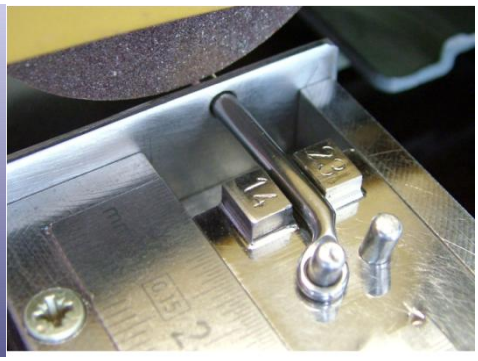

Figure 13. Lab side preperation

The combination of lingual appliances and herbst appliances is being used also in patients with an Angle class II division 2 malocclusion. For this study we excluded those patients.

For this study we included patients with minimum half a premolar unit class two on both sides. For all patients a target set up was planned and the fully customized lingual appliance and the herbst appliance were produced based on that set up.

Out oft he 8 patients were 5 females and 3 were male. All patients were between 31,2 and 36,8 old.

RESULTS

After debonding all cases showed a final position of the upper incisorsinclination between 100,7° and 103,7 ° in reference to 1_-N-S (7).

The inclination of the lower incisors using the mandibulare plane as a reference varied between 86° and 94° (8).

The longest treatment was 20,3 month, the shortest treatment time 19,1 month.

1. patient inclination of the upper incisor before / after treament 100,5 / 102,2°
2. patient inclination of the upper incisor before / after treament 100,1°/ 103,7
3. patient inclination of the upper incisor before / after treament 102,3/ 103,1
4. patient inclination of the upper incisor before / after treament 102,1°/ 103,6°
5. patient inclination of the upper incisor before / after treament 102,8°/ 103,1°
6. patient inclination of the upper incisor before / after treament 100,3 °/ 103,2°
7. patient inclination of the upper incisor before / after treament 103,1°/ 102,9°
8. patient inclination of the upper incisor before / after treament 102,9 °/ 103,6°

1 patient inclination of the lower incisor before / after treament 86°/ 90,1°
2 patient inclination of the lower incisor before / after treament 93°/ 91,4°
3 patient inclination of the lower incisor before / after treament 89°/ 91,1°
4 patient inclination of the lower incisor before / after treament 94°/ 92,1°
5 patient inclination of the lower incisor before / after treament 88,6°/ 93°
6 patient inclination of the lower incisor before / after treament 88,8 °/ 91,6°
7 patient inclination of the lower incisor before / after treament 92,4°/ 91,8°
8 patient inclination of the lower incisor before / after treament 89,4 °/ 90°

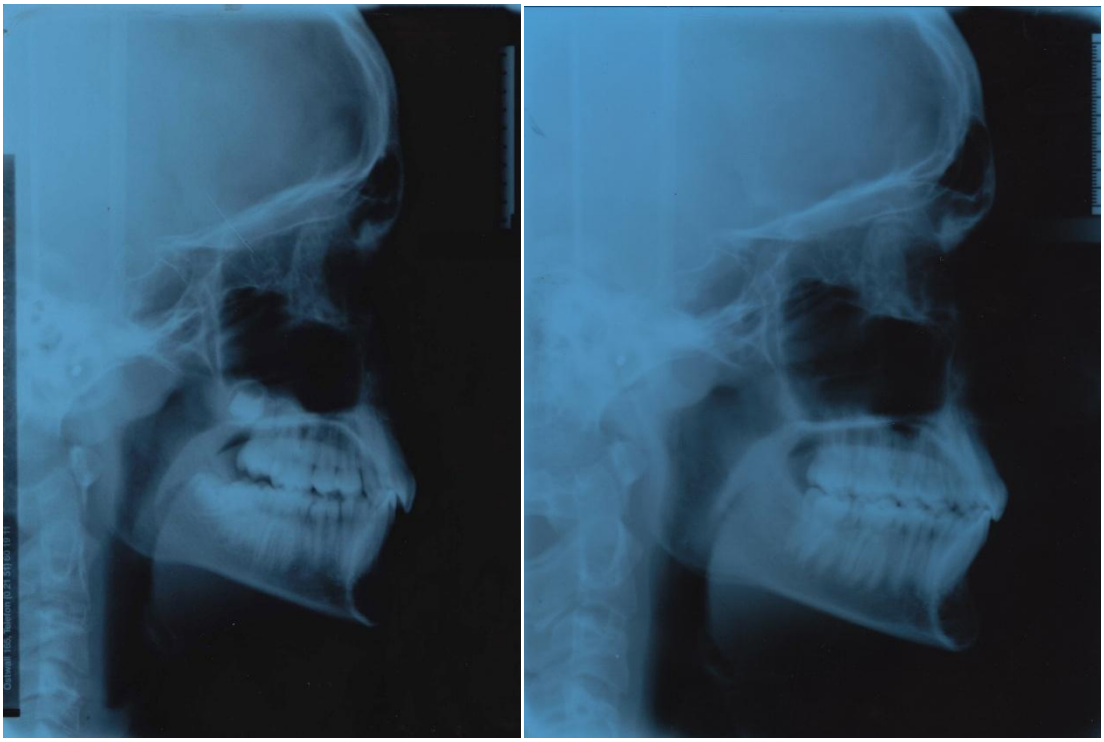

Figure 14 and 15. Showing lateral cephs before / after treatment with corrected inclinations oft the incisors

DISCUSSIONS

Using bite jumping devices in orthodontics can be used to correct Angle class II/1. Two different types of bite jumping devices can be considerd. Flexible bite jumping devices allow somerotational movements around the axis of the telescopes.

In contrast to that, the Herbst Appliance is a very rigid bite corrector. The design of the appliance allowsa saggital mandibular advancement. Using lingual appliances combined with Herbst Appliance delivers reliable treatment outcomes based on the target set up (1). Due to the position of the lingual wire engaged posterior to the center of resistance of the incisors a reverse torque effects occurs which stabilzies the incisors. Using the 0,018 x 0,025 ss wire during Herbst treatment phase allows full anchorage control on the incisors (6). In order to avoid space opening the wire should be vertically bend back. Powerchains should be placed from molar to molar in order to preventspacing and proclination.

CONCLUSIONS

Correction of class II devision 1 patients with a fully custumized lingual and herbstappliance delivers reliable treatment results and stabile position of the incisors.

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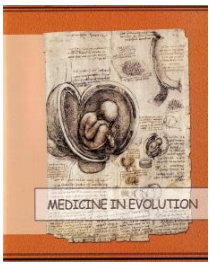
STRESS DISTRIBUTION IN AUGMENTATION OF THE MAXILLARY SINUS FLOOR: A FINITE ELEMENT STUDY



HOSAM EL TAWIL[1], OCTAVIAN DINCA[2], MIHAI BOGDAN BUCUR[3], FLORIN URTILA[4], CRISTIAN VLADAN[2], ALEXANDRU BUCUR[2], BITA ROMINA GEORGIANA[4]

[1]Ajman Univesity of Science and Technology, Faculty of Dentistry
[2]University of Medicine and Pharmacy „C.Davila"Bucureşti
[3]University of Medicine and Pharmacy „C.Davila"Bucureşti, Dent-Implant Bucureşti
[4]"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania

ABSTRACT

The use of dental implants is limited by the subantral bone reserve, which tends to diminish with the loss of teeth. Sinus lifting procedures were widely used to obtain adequate bony support at the atrophic maxillae. A number of augmentation methods have been developed, whith the use of various bone graft types. Although the autologous grafts are the most biological materials, many patients refuses this treatment and alloplastic sinus grafts are much more easily accepted by the patient. This study aims to perform a multidisciplinary analysis of alloplastic bone grafting materials.

Key words: *finite element analysis, alloplastic bone graft, implant*

Correspondence to:

Octavian Dincă
Address: Bucureşti, Calea Plevnei 17-21, sector 1, Bucureşti
E-mail address: O-dinca@yahoo.com

INTRODUCTION

Over the past years, the reconstruction of edentulous posterior maxilla with dental

implants has been increasingly used because this is the most biological method, with good results.

Immediate functional loading of dental implants has been advocated by several authors in order to minimize the delay between surgical and prosthetic phases.

Numerous bone graft technologies that have been used to regenerate bone. Although useful for the widest spectrum of clinical applications, limitations of autologous grafts has prompted the development of new materials. Alloplastic materials are today being used with greater frequency. These materials have demonstrated their usefulness in sinus lift procedure in conjunction with implant placement in atrophic partially edentulous posterior maxilla.

The purpose of this article is to analyse the stresses and displacements of alloplastic bone graft in immediate loading.

MATERIAL AND METHODS

Two three-dimensional models were released to simulate sinus lift procedure in conjunction with implant placement in atrophic partially edentulous posterior maxilla. 3D models were meshed using tetrahedral and octahedral elements and modeled by identifying the exact location of nodes after mathematical calculation. The discretization used a small element size and slow size transitions in order to provide better accuracy of the results.

An eight-nodded brick isoparametric element was used for the mesh, resulting a model incorporated 53370 nodes and 30157 elements (Figure 1).

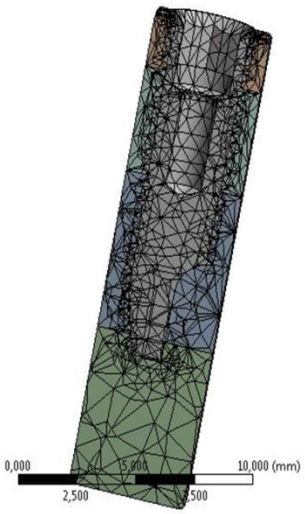


Figure 1. View of the volume mesh of the sinus augmentation with the bone graft inside the augmentation with the implants

Each implant design consisted of fixture of 13-mm length, incorporating V threads with a thickness of 0.2 mm, and having a constant pitch length and height. The model was presumed to represent ideal osseointegration.

The bone consisted in the first case of 2 mm alveolar cortical bone and the rest cancellous bone; in the second case consisted of 2 mm cortical bone and the rest alloplastic and cancellous bone. Cortical and cancellous

anisotropic properties were applied to the bone. Given the large range of the alloplastic bone mechanical properties, we have chosen those corresponding to β-tri-Calcium phosphate (Table 1).

Table 1. The mechanical properties of the materials used in the analysis

Material	Young's modulus (MPa)	Poisson's ratio
Titanium alloy	105000	0.33
Compact bone	10500	0.4
Cancellous bone	800	0.3
b-tri-Calcium phosphate	11000	0.41

Each model was analyzed with 300 N force applied 25° oblique to the vertical axes. The boundary conditions were defined by restraining all nodes at the base ofthree-dimensional models. The modeling analyses were performed using ANSYS software program.

RESULTS

The detection of susceptibility for implant displacement is the endpoint often pursued in clinical studies. In order to asses susceptibility for these types of failure, we monitored the the directional deformation (Figure 2).

The results obtained in this study are shown in Table 2

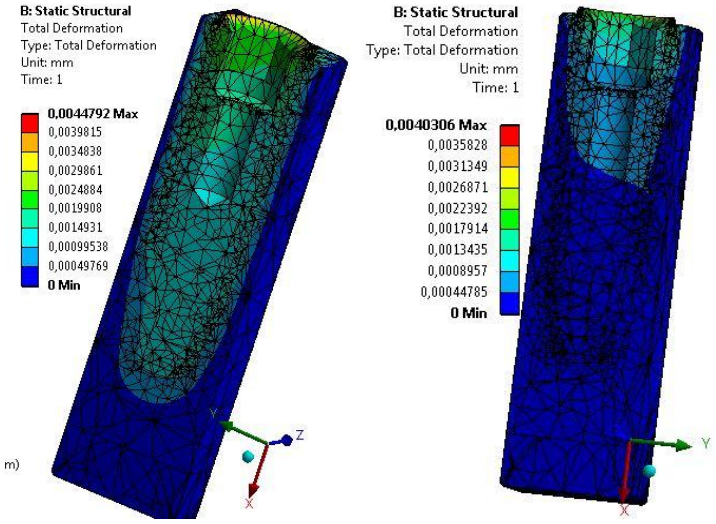


Figure 2.Models oftotal directional deformation

Table 2. Maximal directional deformation

Model	Laterotrusion (mm)	Protrusion	Masticatory strength
Implant with cancellous bone graft only	0.0035948	0.0026651	0.00081541
Implant with alloplastic graft and cancellousbone	0.0028205	0.0028811	0.00098971

DISCUSSIONS

Autografts are considered the"gold standard"for bone reconstruction, but they also have disadvantages such as: deficient

vascularization, complications at the donor site and insufficient size of the bone graft.

Researchers has focused on the discovery of augmentation materials that can successfully replace autologous bone grafts. Multiple types of grafts have been proposed, from lyophilized human bone, bovine bone to alloplastic grafts. The alloplastic materials remain among the most accessible augmentation materials. The histopathological analysis of the alloplastic graft applied to the maxillary sinus has shown newly formed bone content. Autogenous bone in combination ofalloplasts yielded similar results.

Under delayed loading, the finite element analysis models bonded the implants perfectly to alloplastic graft and cancellous bones.However, the conditions are different under immediate loading method. Minor displacements at the bone-implant contact surface are present. These micromovements need accurate evaluation, as they are of more concern in preclinical and clinical conditions.

The Young's modulus of β-tri-Calcium phosphate appears to possess high stiffness, while cancellous bone is marked by low stiffness. Embedment of cancellous bone graft in alloplastic augmentation material reduces the difference in the Young's modulus and stabilizes the augmented area. Therefore, the qualityof the graft is of great concern when the quantity of existing cancellous maxillary bone is limited.

CONCLUSIONS

This study achieved its aim of demonstrating that sinus lift with alloplastic materials followed by the placement of endosseous implants in the grafted site is an alternative for the patients with edentulous maxillary areas.

This study will be followed by computer and clinical studies, comparing the behavior of allopastic grafting sinus lifting procedure.

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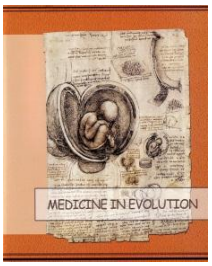
IMMEDIATE REHABILITATION OF THE EDENTULOUS JAW WITH FULL FIXED PROSTHESES SUPPORTED BY FOUR IMPLANTS: A REVIEW



TANER CHEMAL, RUSU MIHAELA, BOBESI COSMIN

Implantodent, Bucharest

ABSTRACT

The"All-on-four"treatment concept was developed by Paulo Malo and encompasses an immediately loaded full arch fixed prosthesis anchored with four implants in either the maxilla or mandible. The purpose of „All-on-four"treatment is to allow with high predictability, immediate esthetical and functional rehabilitation for total edentulous patients, ensuring a better quality of life.

Key words: *dental implant, angulated abutments, complete arch, immediate function*

Correspondence to:

Taner Chema
Address: Implantodent, Banul Antonache nr.51, sector 1, Bucharest, Romania
E-mail address: tanerchemal@implantodent.com

INTRODUCTION

After teeth loss, a considerable decreasing bone level is noticed associated with a low bone density and the only possibility to use fixed rehabilitation is the bone augmentation.

„All-on-four"treatment respects the basic items for the patient's satisfaction; it is total, fix, quick (provisional restoration applied in maximum 24-48 hours), it is no need for horizontal or vertical ridge augmentation or sinus surgical interventions and eliminates the associated comorbidity and offers the ideal costs predictability.

„ALL-ON-FOUR"CONCEPT

The principle is the insertion of four to six implants at the maxillary and four at the mandible. The distal implants are inserted with an increased angulation to avoid compromising important anatomical areas like inferior alveolar nerve or the maxillary sinus.

After 24-48 hours the abutments are covered by provisional restorations as a short-term interim step without using distal extensions and the final fixed prosthesis is applied after 3-5 months. We can use distal extensions according with the anteroposterior distance between the two imaginary lines that connects the anterior and the posterior implants (the extension must be half of the anteroposterior length between the implants).

Choosing the normal path procedure, to obtain the needed volume structure a bone augmentation is needed and in this case the healing tissue period of time would extend with minimum 6 months in the absence of sinus pathology.

According with the implants insertion in the distal mandible region, we must preserve anatomical elements and this is the reason why we often use vertical bone graft or the NAI transposition. Alternative like long extensions, short implants, zygomatic or pterygoidien implants used with a low bone mass have significant advantages and disadvantages, risks and complications and the success rate may not be so predictable. Although vertical and angulated implants are used, they interlock under the fixed prostheses with no impact over the force distribution; in fact, it is similar to the force attributed to axial implants and allows the final prostheses with 12 teeth to sustain short extensions. Further, the angulated axes after the insertion facilitate prophylactic maneuvers; a clean mouth is a mandatory required condition for the implant insertion success.

SURGICAL PROTOCOL

Frequently local anesthesia administered in block and infiltration technique provides excellent work conditions. In some cases intravenous (conscious) sedation or general anesthesia is required according with the preexisting medical patient condition.

Preoperative and after the intervention antibiotherapy administration combined with anti-inflammatory drugs is recommended according with the prescription. Further, special attention is needed for the correct application of the means of the oral hygiene including the instructions regarding the usage of Clorhexidine gluconate mouthwash (oral rinse) in different concentrations.

Occlusal vertical dimension (OVD) is measured based on subjective signs related to esthetics and phonetics and the obtained value is kept is patient's records. It is possible to appear OVD modifications and in this case the new situation is transferred on the occlusal rims and used for a new OVD determination.

Crestal incisions and total flaps are used to expose the bone ridge and the remaining teeth that needs extractions. The role of the follow-up procedure, the osteotomy, is to regulate the osseous ridge and to achieve the desired bone level by using the bone clipper or rotary instruments, drills mounted at phyziodispenser or piezoelectric device.

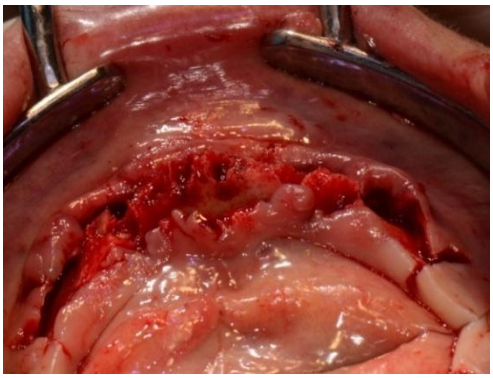


Figure 1. Clinical view with the flap raised

At the maxillary four implants are inserted in the anterior region between the maxillary sinuses and in some cases of poor density bone structure six implants insertion is recommended. The distal implants angulations vary between 30 and 45 degrees meanwhile the anterior implants are axial. Regarding the mandible, the four implants are inserted between the mental foramen and the distal ones are angulated as those inserted at the maxillary. The implants insertion may use a prefabricated surgical guide or the orientation instrument provided by Euroteknika obtained from a flexible material which allows flexion due to ridge position.

PROSTHETIC PROTOCOL

Immediate application of an easy and passive prosthesis without distal extensions is required to connect the implants (it is imperative to avoid overloads and accidental fractures).

After the implants insertion the following prosthetic components are attached:

a. Plural abutments with different angulations (0, 17 and 30 degrees)
b. Cover screw (gingival conformer)

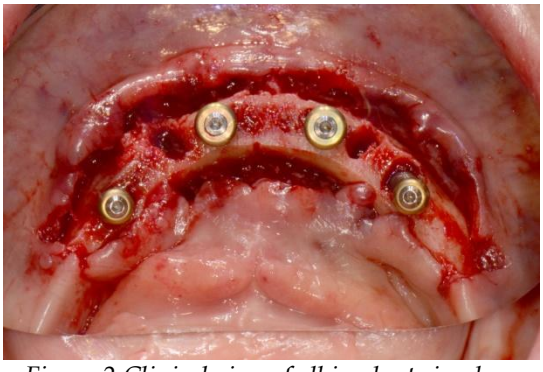


Figure 2.Clinical view of all implants in place

It is recommended the suture with separate threads and nonresorbable thread; after the suture a functional impression is required.

After 24 hours, recall is recommended to control the patient hygiene, to remove the cape screw (gingival conformer) and to screw the only prosthetic abutment available in the prosthesis.

The final rehabilitation depends on the needs, the expectations and the patients budget and we can choose one of the following:

1. Fixed prosthesis

a. with CAD/CAM designed and milled structure (Titanium, Zirconium, BioHPP) and individual crowns with integral ceramic (highly esthetic)

b.With CAD/CAM designed and milled structure (Titanium, BioHPP) and acrylate overlay (including the acrylate teeth)

2. Deployable prosthesis

a. with bar – implants fixed and acrylic prosthesis with rider bar

b. with"locator"-like prosthetic systems and acrylic prosthesis

Figure 3.Provisional prosthesis in place

CONCLUSIONS

„All-on-four"concept offers the patients the possibility for an excellent social life and eliminates the disadvantages of classical prosthesis and the low patient acceptance improving the quality of life.

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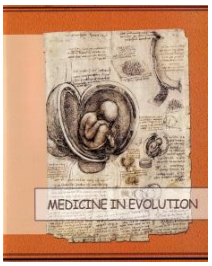
PROTECTIVE EFFECT OF CELECOXIB ON GINGIVAL LEPTIN LEVELS IN PATIENTS WITH CHRONIC PERIODONTAL DISEASE



CRISTIAN VLAD[1,2], DALIBORCA CRISTINA VLAD[2,3], ADINA BUCUR[4], ROXANA POPESCU[3], MARIOARA NICOLETA FILIMON[3], V. DUMITRASCU[2,3]

[1]Dentissimo Care SRL, Timisoara, Romania
[2]Pharmacology Department,"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania
[3]County Emergency Clinical Hospital, Timisoara, Romania
[4]Department of Public Health,"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania

ABSTRACT

Aims *To analyze if the cyclooxigenase 2-specific inhibitor celecoxib has beneficial roles in periodontal disease by increasing the leptin levels in patients with chronic periodontitis.*

Material and Methods *In a prospective study were enrolled forty-seven patients, mean aged 55.33±12.56 years, treated with celecoxib, 100 mg daily, 7 days/month, for a period of 10 month. Inclusion criteria: severe chronic periodontal diseases and alveolar osteitis. Exclusion criteria: blood sedimentation rate > 40 mm/h and chronic inflammatory diseases. Gingival crevicular leptin levels were evaluated at baseline, after 5 month, and after 10 month.*

Results *Leptin concentrations increased significantly from baseline (1085.75pg/mL), were statistically higher after 5 month (1508.78 pg/mL), and doubled at the end of the study (2276.48 pg/mL ($p < 0.001$). One revealed a negative correlation between the severity of alveolar osteitis and the crevicular fluid leptin concentration.*

Conclusion *Celecoxib has a protective role in periodontal health, increasing the gingival crevicular leptin levels and decreasing the severity of alveolar osteitis.*

Key words:*Celecoxib, Chronic Periodontitis, Gingival Crevicular Leptin Concentration*

Correspondence to:

Cristian Vlad
stomatologist and assistant physician, trainer for a doctor's degree in pharmacology
Address: Department of Pharmacology,"Victor Babes"University of Medicine and Pharmacy,2 Eftimie Murgu Square, 300041 Timisoara, Romania
E-mail address: cristivlad32@yahoo.com

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a large group of medicines used for more than four decades in the treatment of periodontal disease, and in particular to combat the effects of fast pain relief. Of all the dozens of existing products, only a few have proven therapeutic clinical utility, with a safety profile effectively.

Gingival crevice fluid (GCF) is composed of substances derived from serum, leukocytes, oral bacteria and cells of the periodontium (1). Leptin is a 16-kDa non-glycosylated peptide hormone belonging to the class I cytokines, present in gingival crevice fluid, in periodontal health and disease (2). Many studies have investigated the relationship between leptin levels and chronic periodontal disease. Thus, one revealed that a high concentration of leptin in GCF is associated with healthy gingival tissue, but the decrease of leptin concentration is a marker of chronic periodontal disease progresses (3).

We previously revealed that several NSAIDs drugs, like celecoxib, are efficient in patients with chronic periodontal disease (4).

Aim of the study

The aim of the present paper was to analyze if the cyclooxigenase 2-specific inhibitor celecoxib has beneficial roles in periodontal disease by increasing the leptin levels in patients with chronic periodontitis.

MATERIAL AND METHODS

In a prospective study were enrolled forty-seven patients, 28-76 years range (mean age 55.33±12.56 years), 27 female and 20 male, as outpatients followed-up at dental private office"Dentissimo Care"

Inclusion criteria: severe chronic periodontal diseases and alveolar osteitis, diagnosed clinically and radiographically.

Exclusion criteria: patients with blood sedimentation rate (VSH) > 40 mm/h and/or chronic inflammatory diseases. Twelve patients were excluded because they presented higher VSH values than 40 mm/h. Therefore only thirty-five patients were included in the study.

They were treated with systemic NSAID therapy, respectively with celecoxib, 100 mg daily, 7 days/month, for a period of 10 month and none of them was withdrawn from the study.

Gingival crevice leptin levels were determined by enzyme-linked immunoabsorbent essay (ELISA) and samples were obtained from maxillary anterior teeth by the technique of Rudin and co.(5). Leptin concentrations were evaluated at baseline (visit 1), after 5 month (visit 2), and after 10 month, at the end of the study (visit 3). The efficiency of the therapy was measured by analyzing the mouth pockets depth (PD).

In order to participate in the study, patients received approval from the Ethics Committee.

RESULTS AND DISCUSSIONS

Leptin concentrations increased significantly from baseline (1085.75pg/mL), were statistically higher after 5 month (1508.78 pg/mL), and doubled at the end of the study (2276.48 pg/mL ($p < 0.001$) (figure 1).

The initial level of the deep periodontal pockets (>5 mm) was 8.5% and decreased to 1.5% after treatment.

The quantity of pockets with moderate depth (3-5 mm) decreased from 55.8 % to 42.3% after celecoxib treatment

One revealed a negative correlation between the severity of alveolar osteitis and the crevicular fluid leptin concentration.

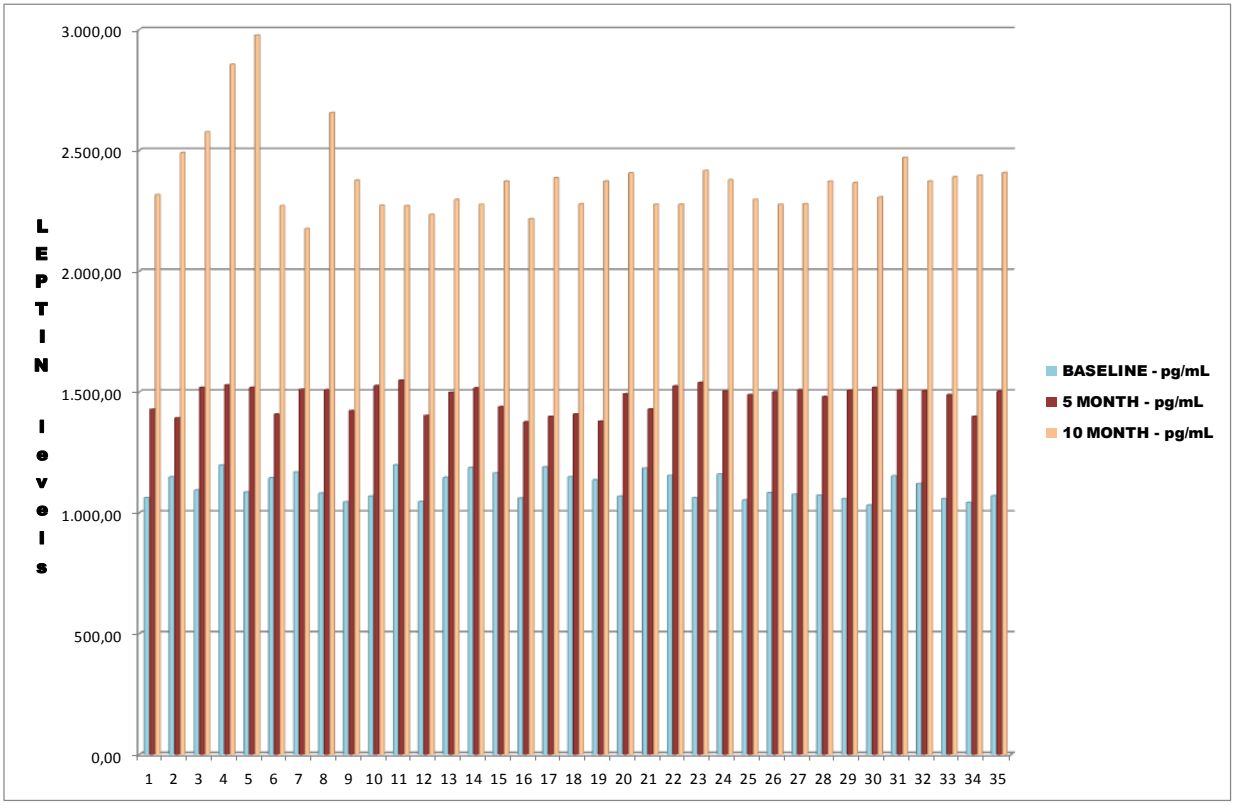


Figure 1. Leptin concentrations in gingival crevice fluid in patients with chronic periodontitis treated with celecoxib

Recent studies revealed that the pathogenesis of periodontitis is complex and the bacterial infection mediates tissue destruction (6), (7). The severity of periodontal disease is guided by the production of pro-inflammatory mediators from gingival tissues. In accordance with previous studies, we revealed in this research the protective role of leptin in periodontal health in the elimination of gingival inflammation with pocket depth reduction under additional NSAID's therapy (celecoxib) (8), (9).Successful reduction of proinflammatory cytokines in gingival crevice fluid is realized during adjunctive NSAID's therapy with celecoxib (10).

CONCLUSIONS

Celecoxib has a protective role in periodontal health, increasing the gingival crevicular leptin levels and decreasing the severity of alveolar osteitis by successfully elimination the gingival inflammation with pocket depth reduction.

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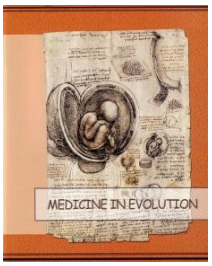
3D AESTHETIC PREVIEW IN PROSTHODONTIC REHABILITATION – GERIATRIC CASE REPORT



GAGIU CATALIN[1], BODNAR CRISTINA[1], IONESCU ECATERINA[2], OANCEA LUMINITA[1], PANTEA MIHAELA[1]

[1]University of Medicine and Pharmacy „Carol Davila"/ Bucharest, Faculty of Dentistry, Department of Fixed Prosthodontics and Occlusology
[2]University of Medicine and Pharmacy „Carol Davila"/ Bucharest, Faculty of Dentistry, Department of Orthodontics and Dento-Facial Orthopedics

ABSTRACT

***Purpose**: The aim of this study is to obtain a **3D computerized personalized** model that allows configuring an **aesthetic preview** in complex prosthetic restorations for elderly patients and to build up a valuable and accurate **temporary fixed restoration,** as an important clinical phase.*

***Materials and method**: An extra - and intraoral set of photographs is taken and edited with available software.A new method is used to collect and process, with special software packages, a second series of standardized photos of the head region of the patient.*

***Results**: The **personalized** 3D computerized model allows to build up a **preview** for aesthetic dental rehabilitations and to obtain a correct temporary prosthetic **restoration,** in accordance with the facial details of each patient.*

***Conclusions**: The method proved to be a useful instrument for aesthetic diagnosis and treatment planning, while increasing elderly patients' perception and acceptance of the treatment plan and results.*

***Key words:**aestheticpreview, 3D personalized computerized models, elderly patients*

Correspondence to:

Dr. Mihaela Pantea
Address: 25A - Rahmaninov Str., apt. 2. Sector 2, 020195, Bucharest, Romania
Phone: +4072387969
E-mail address: mihaela_pantea@yahoo.com

INTRODUCTION

We aim to obtain a personalized 3D model of the head and neck, based on a specific computerized processing of a series of standard photos; this improved possibilities in diagnosis, treatment planning and its implementation and successful application in various clinical situations. Specifically, the method improves the ability of our geriatric patients to better understand and to accept the treatment plan, as well as the aesthetic results of the prosthetic rehabilitation. In order to asses the feasibility of this technique, we performed a clinical study in the Department of Fixed Prosthodontics and Occlusology, Faculty of Dentistry, University of Medicine and Pharmacy „Carol Davila"/ Bucharest, Romania.

CASE REPORT

A new 72 years old patient in our clinic reported masticatory and esthetic problems. After the complete initial extra-oral and intr-oral examination has been made, it was obvious that a complex oral rehabilitation was recommended, in order to obtain a functional and harmonious final result. The patient was informed about the purpose of the study and a written consent was obtained before starting the study.

ANAMNESIS

Our geriatric patient was in a very good state of health, had no chronic diseases, was under no medical treatment and showed no pathological relevant data from personal medical history.

I. Clinical oral examination data

Relevant clinical data: - biterminal edentulous arches, restored with faulty removable partial dentures; tooth 1.3. - incorrect root canal treatment, cast post and core and a root fracture; tooth 3.1 - incomplete root canal treatment, apical chronic granuloma, accentuated mobility; fixed resin-fused-to-metal restoration on teeth 1.4., 1.3., 1.2., 1.1., 2.1., 2.2., 2.3. – with wearing of the resin veneers due to the frontal malocclusion; a fixed resin-fused-to-metal restoration on teeth 3.5., 3.4., 3.3., 3.2., 3.1., 4.1., 4.2., 4.3., 4.4.; chronic gigivitis with moderate gum recession.

II. Paraclinical invetigations:

A complete set of intra-oral radiographs was made, and a panoramic radiograph was taken, to evaluate the actual status of anatomical structures.

III. Additional paraclinical investigations

In order to obtain a better personalized 3D model, we used the following technique: We took an extra - and intraoral set of photographs, from different angles, using the following instruments: (1) a standard camera"Fujifilm Finepix S7000", with a fixed focal length lens and manual focus setting, (2) a tripod, (3) four additional artificial light sources, (4) a retractor for soft perioral tissues.

Only one standard camera was used for the initial set of photographs, as opposed to other systems that made use of two or more cameras, for example the „3D capture systems"of Genex or 3dMD. The 3dMD cranial system, for example, works with five camera viewpoints to obtain a full 360° picture of the head. [1,2,3,4]

The number of photos we took with this system was 60. We performed three shooting sessions (20 photos per each session). The shooting process

involved a continuous moving of the camera around the subject from a distance of 1.2 m. The exposure time: 1/25, manual focus setting, ISO 200, fixed focal length 47 mm, from an approximately 35° angle between the incidences, on two transversal planes: one at the menton level and the other on the bi-pupilar line.

Figure 1. The processed photographs stitched in order to obtain a tridimensional personalized model of the head and neck

Various anatomic points were marked on the skin, in order to obtain a correct stitch of the photos: menton, subnasion, glabella, trichion, gonion, zygion, labial commissures, external angle of the eye, earlobe, back of the neck. The photos were taken in different circumstances: (1) mouth closed and light lip contact; (2) dental arches apart and a slight smile; (3) dental arches kept apart by a flexible retractor for perioral soft tissues.

The processed photographs were stitched in order to obtain a tridimensional personalized model of the head and neck, using software packages such as"Autodesk 123D Catch"(Fig 1).

A digital smile design can be projected on the 3D model, to serve as a useful test tool for an aesthetic rehabilitation and a functional occlusal plane, combined with specific details such as: relationship between the Camper's plane and the occlusal plane, Spee's occlusal curve concavity, dental and facial harmony, the correlation between the width and the height of teeth..

IV. Results

A functional and aesthetic preview of the prosthetic reconstruction is obtained from frontal and lateral perspectives – that were selected from the 3D personalized models of the head. (Fig. 2)

Figure 2.Functional and aesthetic preview of the prosthetic reconstruction from frontal and lateral perspectives

A complete treatment plan - in a logical sequence of procedures - was presented to the patient, in a written form, along with the aesthetic preview of the prosthetic results on specific selected frames belonging to the 3D personalized models of the head; these were discussed in detail.

We noticed a positive reaction of our geriatric patient to these presentations. The communication with the patient, his understanding and perception of details were improved. The patient's needs and preferences were easier and more completly self-evaluated. Finaly, the impact of the method used was positive, considering the acceptance of the suggested treatment plan.

A temporary resin fixed partial denture was made on the upper arch, on teeth 1.4., 1.2., 1.1., 2.1., 2.2., 2.3. The design of the fixed partial denture was based on specific details that we obtained from the frames of the 3D personalized models of the head. The communication with the laboratory was easier and clearer, given the amount of the transffered data.

All the neccessary preprosthetic treatments were done in advance, including the removal of the old resin-fused-to-metal fixed restorations, extractions of teeth 1.3. and 3.1., root canal treatments and core build-ups on remaining teeth.

During the clinical try-in phase of the temporary prosthesis, in accordance with phonetic and aesthetic tests, but also with patient's preference, we adjusted / reduced 0,25-050 mm of the hight of the upper central incisors, compared to the initial crown height planned on the 3D personalized model; a correct frontal occlusion was also obtained.(Fig. 3)

Figure 3.The clinical try-in phase of the temporary prosthesis - the hight of the upper central incisors in accordance with phonetic and aesthetic tests and patient's preference

The presented method has some limitations, consisting in the partial discontinuity between different processed frames selected for the 3D personalized models. We intend to improve the method and to create an intra-office processing system for obtaining a personalized 3D smile-design for the pacient.

DISCUSSIONS

This recent innovation in photography, incorporating the third dimension, offers the possibility to analyze delicate details of the facial surface and soft tissue morphology [5].

The presented method facilitates the design of 3D personalized models of the head and neck directly in the dental office, thus improving the capabilities to elaborate an aesthetic diagnosis, to plan the prosthetic or the surgical treatment and allowing to build-up a correct temporary prosthetic restoration. It also proves to be minimally invasive, easy to use, less expensive and less time consuming than the classical methods.

The next step was to manufacture the final restorations, combining the 3D planning information with data collected from the temporary rehabilitation.

A relevant 3D preview of prosthetic rehabilitations helps the interdisciplinary data transfers, facilitates the follow-ups and offers better communication between physicians and patients - which is an important aspect, especially for elderly patients, considering the advantage in assesing the final aesthetic results of the suggested prosthetic treatment.

Acknowledgement

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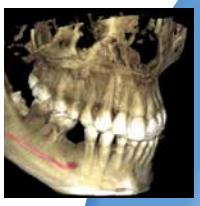

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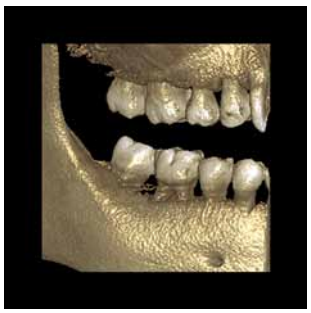

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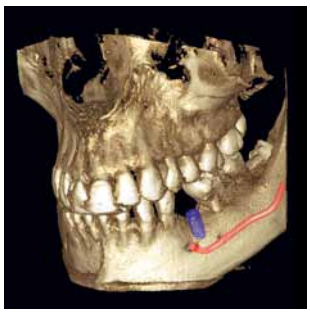

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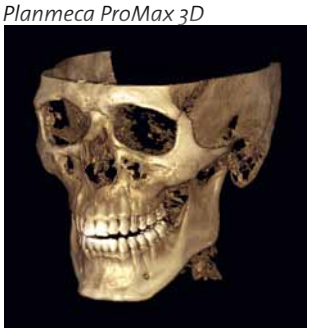

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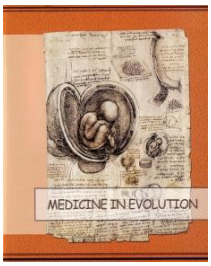

SELENIUM ANTIOXIDANT AND ANTI-INFLAMMATORY BENEFITS IN ADOLESCENTS WITH POST-STREPTOCOCCAL REACTIVE ARTHRITIS

DORIN ANA[1], IOANA ANA[1], ADINA BUCUR[3], V. DUMITRASCU[1,2]

[1]Pharmacology Department,„Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania
[2]Timisoara County Emergency Clinical Hospital, Romania
[3]Department of Public Health,"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania

ABSTRACT

Aims *To analyze whether serum selenium concentrations in adolescents with rheumatic diseases are low, and therefore enhance the inflammation of the joint soft tissues.*

Methods *In a 6 month retrospective study, one evaluated the therapeutical effects of the daily 200 mcg selenium doses, administered as a nutrient supplement, in a trial of 45 patients, aged from 16 to 25 years, followed-up ambulatory for post-streptococcal reactive arthritis. Serum selenium levels, acute-phase reagents as well as significant parameters concerning the pain syndrome were evaluated comparatively before and after the treatment. Serum selenium levels were determined by atomic absorbtion spectrophotometry.*

Results and discussions*The significant clinical antiinflammatory effects due to the selenium action consisted in decrease of joint rest and improvement of physical activity ($p < 0.001$). The favourable evolution was also assessed by the decrease of acute-phase reagents and by reducing the joint inflammatory process.*

Conclusion *Selenium therapy is effective in adolescents with post-streptococcal reactive arthritis.*

Key words: *Selenium, Adolescents, Post-Streptococcal Reactive Arthritis*

Correspondence to:

Dorin Ana, M.D.
trainer for a doctor's degree in pharmacology
Address: Department of Pharmacology, University of Medicine and Pharmacy"Victor Babes", 2 E. Murgu Square, 300041 Timisoara, Romania
Phone: +40724749529
E-mail address: anadorin@yahoo.com

INTRODUCTION

Selenium has proven its effectiveness in patients with rheumatic diseases because it is a trace mineral that acts as an important antioxidant and anti-inflammatory agent (1). In previous studies we reported the beneficial effects of selenium supplementation in adolescent patients with chronic bronchial asthma and impaired thyroid hormone metabolism (2),(3).

Numerous studies have shown that patients with rheumatism and rheumatoid arthritis show low levels of serum selenium, below the therapeutic level of 50 mg/L, associated with periarticular soft tissue inflammation (4).

Poststreptococcal reactive arthritis (PSRA) has an increasing frequency in adolescents;clinical features include additive rather than migratory arthritis that responds relatively poorly to salicylates and non-steroidal anti-inflammatory drugs; persistence for mean of 2 months, elevated acute phase reactants and laboratory (usually serologic) evidence of recent group A streptococcal infection (5).

The aimof our study was to investigate whether serum selenium concentrations in adolescents with poststreptococcal reactive arthritis are low, and therefore enhance the inflammation of the joint soft tissues.

MATERIAL AND METHODS

A longitudinal, randomized, six month retrospective and comparative survey was conducted in a primary care center, during March 1-August 31, 2013.

Incusion criteria: 45 adolescent patients, aged 16 to 25 years, with poststreptococcal reactive arthritis,were included in the study; their distribution by sex is shown in figure 1:

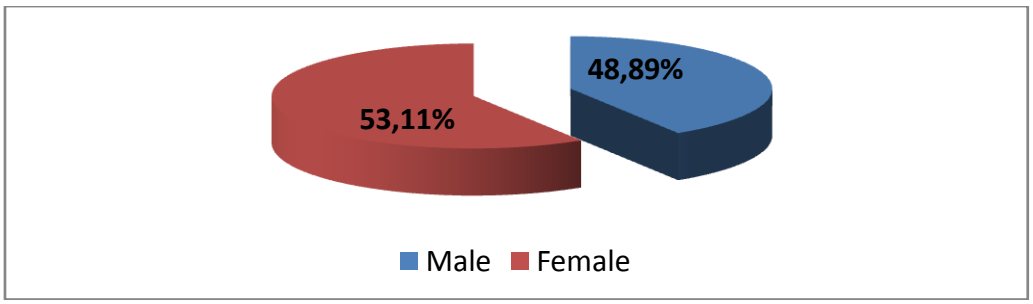

Figure 1. Distribution of patients treated with selenium by sex

Patients with progressive but uncomplicated arthritis, affecting one or more joints, were eligible for the study. All patients in the study group expressed written consent to participate in this survey.

Exclusion criteria: adolescents with heart failure, hypertension, liver cirrhosis, chronic renal disease, hematologic disorders, diabetes, treatment with anticoagulants, history of alcohol or drug abuse.

Serum selenium levels, acute-phase reagents as well as significant parameters concerning the painsyndrome were evaluated comparatively before and after the treatment. Serum selenium levels were determined by atomic absorbtion spectrophotometry (6),(7).

All patients received a daily dose represented by 200 mcg selenium (one tablet after lunch, Walmark-strongly formula), for a period of six months, and were advised not to take any

inflammatory drugs during selenium therapy.:

RESULTS AND DISCUSSIONS

Serum selenium concentrations in the adolescent patients with poststreptococcal reactive arthritis belonging to the study group were significantly lower at baseline thanthose after 6 month selenium supplementation, reference values ranging between 64.36 and 256.26 µg/L (figure 2).

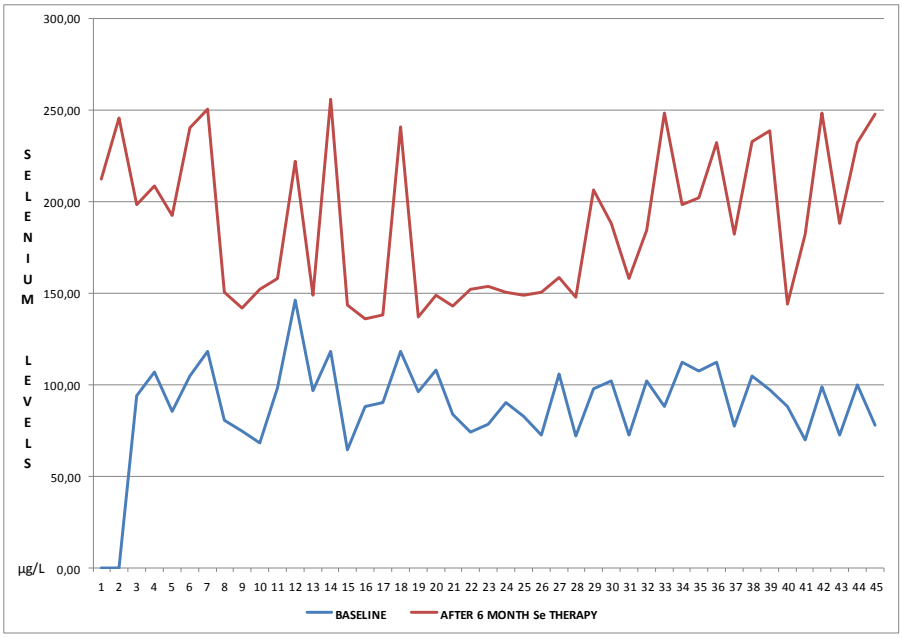

Figure 2. Serum selenium levels at baseline and after 6 month of selenium supplementation in adolescents with poststreptococcal reactive arthritis

Patients in the study group were investigated and were followed-up for stiffness, inflammation of the periarticular soft tissues and limitation of physical activity.

The significant clinical antiinflammatory effects due to the selenium action consisted in decrease of joint inflammatory process and improvement of physical activity ($p < 0.001$) (figure 3):

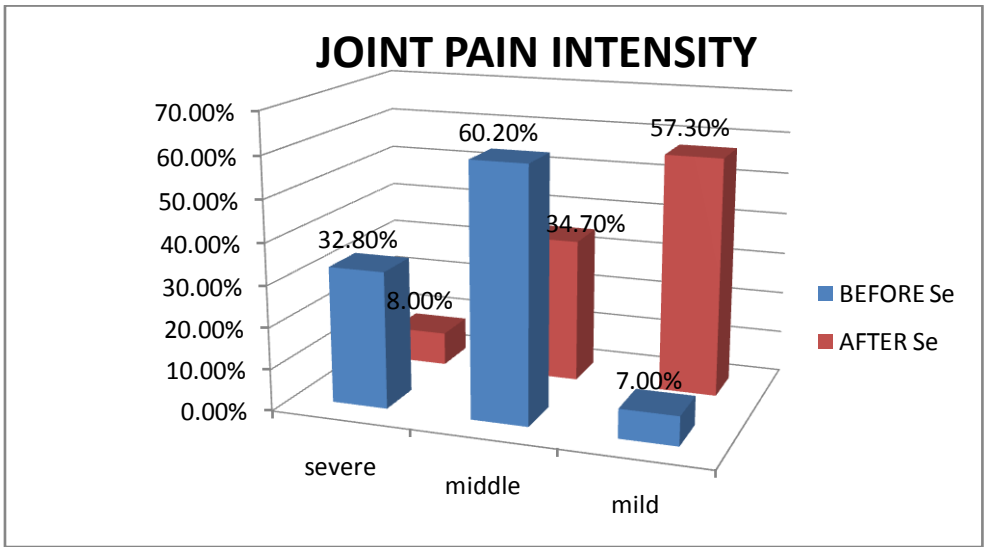

Figure 3.Joint pain intensity at baseline and after 6 month of selenium supplementation in the study group

The favourable evolution was also assessed by the decrease of acute-phase reagents, respectively:

- Erythrocyte sedimentation rate (ESR);
- Fibrinogen;
- The rheumatoid factor (RF) as determined by a qualitative test Latex be noted from 0 to 4;
- C-reactive protein (CRP);
-Antistreptolysin O (ASO) test.

Table I highlights the comparative values of acute phase reactants prior to initiation of selenium therapy at baseline and after it. Overall, it is noted that the values of acute phase reactants were greatly improved under treatment with selenium.

Table 1. Evolution of the acute phase reactants before and after selenium therap

Biological parameter	Baseline	After 6 month selenium therapy
ESR	55,6 ± 1.30 mm/h	35,61.07 mm/h
Fibrinogen	480,5 ±3.30 mg/dL	315,5 ±8.42 mg/dL
RF	3,0 +	2,2 +
CRP	10,6± 0.92 mg/dL	4,8 ± 1.12 mg/dL
ASO	460±5.70 IU	200±2.60 IU

Legend:
ESR = Erythrocyte sedimentation rate; FR = Rheumatoid factor;
CRP = C-reactive protein; ASO =Antistreptolysin Otest
*Values are given as mean ± standard deviations

According to the literature data, we observed low serum selenium levels in patients with post-streptococcal reactive arthritis (8).

Low values of serum selenium in patients in the study group are an important facilitator of joint inflammation. The mechanisms by which selenium exerts favorable effects relate to its role of primary antioxidant, protecting cells against free radicals. It has been shown that free radicals produced by normal cells were identified in excess in patients with rheumatoid arthritis and seems to contribute to joint destruction (9).

Selenium has an important role as mineral cofactor of the enzyme glutathione - peroxidase system. This prevents the production of proinflammatory compounds involved in inflammatory processes in the joints and periarticular soft tissue damage (10).

CONCLUSIONS

Selenium therapy has beneficial pharmacotherapeutic effects in improving clinical and biological parameters in adolescents with post-streptococcal reactive arthritis.

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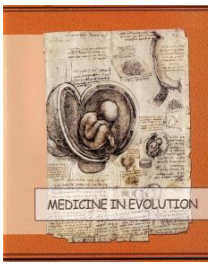

BLOCKERS OF THE RAA SYSTEM: PERINDOPRIL AND CANDESARTAN AND THEIR IMPLICATIONS ON ENDOTHELIAL DYSFUNCTION

VALENTINA BUDA[1], MINODORA ANDOR[2], CARMEN CRISTESCU[1], MIRELA VOICU[1], LIANA SUCIU[1], MARIA SUCIU[1], MIRELA CLEOPATRA TOMESCU[2]

[1]"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania, Faculty of Pharmacy
[2]"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania, Faculty of Medecine

ABSTRACT

In the last two decades, many studies have proved that assessment of endothelial function provides important information regarding patient risk for any atherosclerotic disease.

Several studies have shown that all conditions predisposing to atherosclerosis are associated with endothelial dysfunction. Among these, an impaired function of endothelium has been observed in hypertensive patients.

Angiotensin II, the main substance of the RAA system, plays an important role in the development of the hypertensionwith all complications, having also huge effects on the endothelium and its function, this is the reason why many drugs that treat these pathologies are involving this substance in their mechanism of action.

This review talks about the most used blockers of the RAA system: ACE inihibitors and ARBs,their mechanism of action and their clinical implications on revearsing the endothelial dysfunction.

Key words: *endothelial dysfunction, hypertension, ACE inhibitors, ARBs, perindopril, candesartan, FMD, flow mediated vasodilatation*

Correspondence to:

Buda Valentina Oana
Address: University of Medecine and Pharmacy"Victor Babes"Timisoara, Faculty of Pharmacy, Department of Pharmacology and Clinical Pharmacy
Phone: +40755100408
E-mail address: buda.valentina.oana@gmail.com

INTRODUCTION

In the last two decades, many studies have proved that assessment of endothelial function provides important information regarding patient risk for any atherosclerotic disease. [1-10]

In the development of research in the endothelial field, a crucial discovery was that it synthesizes nitric oxide (NO). This led to a change of perspective regarding the vascular endothelium from a passive interface between blood and the vessel wall to an important organ. The normal endothelium is involved in the balance between molecules with antagonistic effects: vasodilating/vasoconstrictor, antithrombogenic/prothrombotic and antimitogenic/proliferative. Thus, the vascular endothelium is now viewed as an important paracrine, endocrine and autocrine organ, indispensable for regulation of vascular tone and maintenance of vascular homeostasis. The dysfunction of the endothelium is anearly step in the development of atherosclerosis and it is involved in plaque progression and complications. [1]

The first evidence in humans of impaired endothelium dependent vasodilation was observed by constriction of the arteries with proved coronary artery disease. Therefore, endothelial dysfunction is present in atherosclerotic vessels. Subsequently, further studies confirmed that endothelial dysfunction is present also in the preclinical stages of atherosclerosis. [1-10]

MATERIAL AND METHODS

Endothelial dysfunction and the cardiovascular risk

The links between endothelial dysfunction and coronary risk factors in persons with no clinical evidence of coronary disease were studied. The more systemic cardiovascular risk factors are present, the worse epicardial vascular function is. Many studies have shown that all conditions predisposing to atherosclerosis are associated with endothelial dysfunction. Among these, an impaired function of endothelium has been observed in hypertensive patients, normotensive subjects with dyslipidemia, smokers, ageing patients, with diabetes mellitus or patients with inflammatory of infectious disease.

Endothelial dysfunction in hypertension

Endothelial dysfunction has been documented in both peripheral and coronary arteries in patients with arterial hypertension [2]. Hamasaki et al. found that coronary blood flow and the vessel area in patients with hypertension and left ventricular hypertrophy were significantly greater than in patients with uncomplicated hypertension or in normotensive person. Furthermore, the response to both acethylcoline and adenosine (endothelial dependent and independent vasodilating agents) was significantly impaired in patients with left ventricular hypertrophy.

The mechanisms involved in endothelial dysfunction in hypertensive patients are complex:

-In patients with salt-sensitive hypertension it is an impairment of L-arginine - NO pathway [3]

-In renovascular and primary aldosteronism hypertensive patients, the impairment of endothelium-dependent vasodilation is linked with cyclooxygenase-dependent vasoconstrictor mechanism [4]

-Patients with essential hypertension have a defect in endothelium-derived NO system, and this cause an increased vascular resistance under basal conditions and impaired response to endothelium-

dependent vasodilators. Endothelial abnormality in essential hypertension is not restricted to muscarinic receptors [5]

-Endothelial dysfunction should be primary or become irreversible once the hypertensive process has become established. This is suggested by the fact that antihypertensive therapy does not restore completely the impaired endothelium-dependent vasorelaxation in patients with essential hypertension [6]

Angiotensin II and the endothelial dysfunction

The physiological actions of angiotensin II in cardiovascular and renal systems are nearly all mediated by the angiotensin II receptor.Actions include, for example, the regulation of arterial blood pressure, electrolyte and water balance, and renal function.[7]

Angiotensin II is a potent arteriole vasoconstrictor which can increase total peripheral resistance thereby increasing arterial pressure.As the primary agent of the RAA system, angiotensin II also has a central role in endothelial dysfunction (Figure 1) [8]. In addition to increasing blood pressure, angiotensin II acts via the angiotensin II type 1 receptor (AT_1) receptor to increase oxidative stress, causing NO breakdown [9,10].

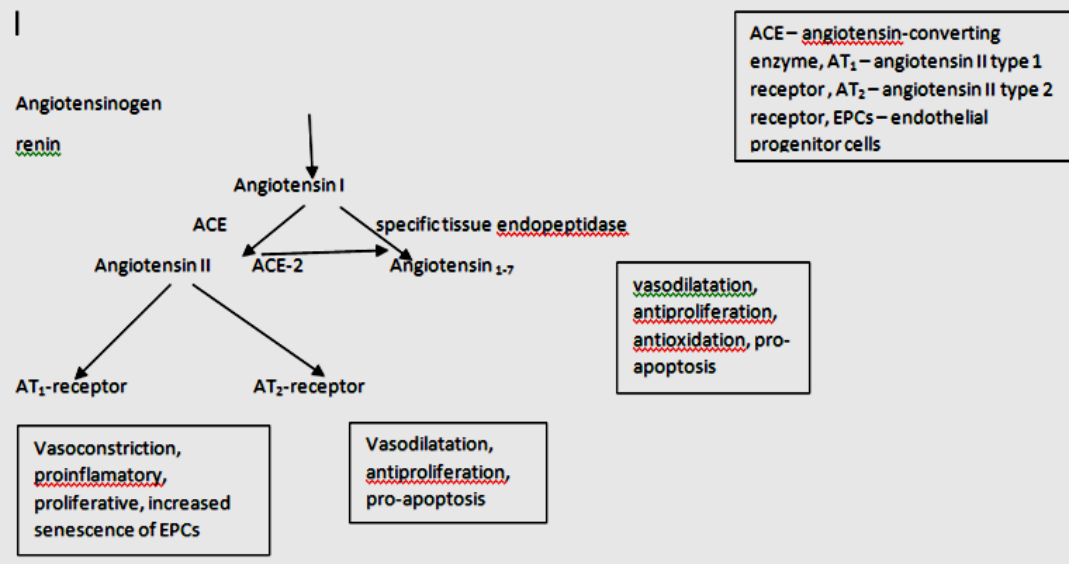

Figure 1. The renin-angiotensin-aldosterone system (RAA system)

Angiotensin II, the main substance of this system, plays an important role in the development of the atherosclerosis, having huge effects on the endothelium and its function. It possesproinflammatory effects, effects that are produced by an increase in oxidative stress. It also increases the levels of"the principal"source of reactive oxygen species: NADPH oxidase. The proliferative effects of angiotensin II are mediated by the stimulation of platelet-derived growth factors and fibroblast growth factors, factors that have proliferative and mitogenic effects on the endothelium and the vascular smooth muscle cells, and they stimulate also the release of the matrix metallo proteinases. By binding to AT_1 receptors (angiotensin $_1$ receptors), angiotensin II induces vasoconstriction. This vasoconstriction is intensified also because angiotensin II stimulates the release of the peripheral adrenaline andbecase it sensibilizates the blood vessels to noradrenaline.Also, the senescence of EPCs (endothelial progenitor cells) is increased by angiotensin II. [11,12,13,14]

Each mechanism that was described above will lead to an important inflammation and to the migration of the macrophages into the

subendothelial space. The macrophages will then increase the oxidation of LDL particles, leading to the formation of the so-called"foam cells"and then to the proliferation of the vascular smooth muscle cells, from the medial layer of the resistance arteries. When the RAA system becomes activated, it will also have an impact on the endothelium regeneration, affecting the plaque stability. [11]

Thus, besides the bad effects of angiotensin II on the pathogenesis of atherosclerosis, this system, the RAA system, produces several substances that counteract these effects of angiotensin II, such as: angiotensin $_{1-7}$. Angiotensin $_{1-7}$is obtained after the hydrolysis of angiotensin I bye ACE-2 (angiotensin-converting enzyme 2). It produces vasodilatator effects, growth inhibitor effects, and diminuates the neointimal proliferation, after vascular injury. [13,15]As a conclusion, in a healthy vascular endothelium, angiotensin II together with angiotensin $_{1-7,}$ are in a perfect balance, in order to maintain the vascular homeostatis.

It has been observed that ACE is involved not only in the transformation of angiotensin I in angiotensin II, but also in the degradation of bradykinin, ACE inhibition leading to increased levels of bradykinin. This substance, bradykinin, poses favorable vascular effects (by binding to bradykinin B_2-receptor) like: vasodilatation and restoration of the endothelial function, due to the stimulation of the production of nitric oxide (NO), prostaglandin I_2 and endothelium derived hyperpolarizing factor.So, high concentrations of tissue bradykinin, tend to restore the vascular smooth cell proliferation and to inhibit platelet adhesion, by the release of tPA (tissue plasminogen activator), processes that can facilitate and reverse the fibrinolytic balance. [11,15]

Drugs were designed to block this system, such as: ACE inhibitors (angiotensin-converting enzyme inhibitors) and ARBs (angiotensin receptors blockers), drugs that proved to have important effects in the reduction of cardiovascular events and in the improvement of the endothelial dysfunction.Based on these considerations, ACE inhibitors block the formation of angiotensin II and also the degradation of bradykinin, thus improving the vasodilatation, endothelial dysfunction and diminishing myocardial and maybe vascular remodeling. Unfortunately, high tissue levels of bradykinin in the posterior pharynx may induce a dry cough that was observed in some patients treated with ACE inhibitors. [11]

The other well known class of drugs that can block the RAA system, the ARBs or sartans, block the stimulation of AT_1-receptors by angiotensin II, thus allowing angiotensin II to activate AT_2-receptors. They also lead to the conversion of angiotensin II in angiotensin $_{1-7}$, by ACE-2. Angiotensin $_{1-7}$ will the manifest its good effects such as: vasodilatation, antiproliferation, antioxidation, pro-apoptosis. ARBs are not associated with high tissue levels of bradykinin, or with cough.[11,16,17]

All these data suggest the huge impact of these drugs in the pathology of endothelial dysfunction.

Clinical implications of ACE inhibitors and ARBs in improving the endothelial dysfunction

Over the last decades, intensive research had investigated the potential clinical benefits of ACE inhibitors and ARBs in reversing the endothelial dysfunction.

Several trails tested the effect of these drugs on endothelial function as measured by brachial FMD in patients with endothelial dysfunction caused by several diseases.

ACE inhibitors are a heterogeneous class of antihypertensive drugs, varying in pharmacologic properties, with

different therapeutic impact on patient profile, including lipophilicity, duration of action, half-life, tissue-ACE binding and increased bradykinin availability. Among this class, the substance perindopril in particular, has pleiotropic effects that are not the same for all the other substances from the class. [18]

Perindopril has been shown to have a longer duration of action, offering a full-24 hour blood pressure control. It has a higher lipophilicity (stronger tissue-ACE binding) and produces local inhibition of RAA system in tissues like: heart, blood vessels, kidneys, brain, adrenal glands. It has also a higher selectivity for bradykinin binding sites when compared with other ACE inhibitors.Also, studies performed on perindopril, showed that it has anti-inflammatory, antiatherosclerotic, antithrombotic, antiapoptotic, antioxidant, antifibrotic, NO-stimulating and profibrinolytic properties that are not the same for the other substances of the class and that the huge pleiotropic effects of perindopril may be because of the strong tissue-ACE binding and high selectivity for bradykinin sites when compared with other ACE inhibitory therapy. [18,19-24]

Table 1. Comparative pharmacokinetics of some ACE inhibitors:[18-24]

	Captopril	**Ramipril**	**Perindopril**
Active metabolite	No	Ramiprilat	Perindoprilat
Bioavailability	70 – 75 %	60 %	75 %
Duration of action	8 – 12 h	24 h	24 h
Elimination	Renal 95 %	Renal 40 – 60% Hepatic 40%	Renal 75 % Hepatic 25 %

Table 2. A summary of the perindopril's advantages versus other ACE inhibitors

- **Higher duration of action (24 h blood pressure control)** [18, 22]
- **Higher tissue and plasma ACE inhibition**[18, 19-22]
- **Higher target organ specificity** [18, 19, 20]
- **Lesser first-dose hypotension** [18]

The following table (table 3) will summarize the effect of perindopril on endothelial dysfunction, measured using FMD (flow mediated vasodilatation):

Table 3.

ACE inhibitor	**Dose/day**	**Participants (number)**	**Control substance**	**Dose/day**	**Participants (number)**	**Results**	**Reference:**
versus placebo							
Perindopril	4 mg	8	Placebo	-	10	No effect on FMD	[25]
Perindopril	8 mg	167	Placebo	-	166	Modest positive effect on FMD	[26]
versus ARBs, CCB (calcium channel blockers), β-blockers							
Perindopril	4 mg	28	Telmisartan	160 mg	29	FMD improvement under ACE inhibitor	[27]

Perindopril	4 mg	28	Nifedipine / Amlodipine	60 mg / 10 mg	56	FMD improvement under ACE inhibitor	[27]
Perindopril	4 mg	28	Atenolol / Nebivolol	100 mg / 10 mg	57	FMD improvement under ACE inhibitor	[27]

As a conclusion, all these studies confirm the effect of perindopril in reversing the endothelial dysfunction.

In what concerns the other class of blockers of the RAA system, the **ARBs**, losartan was the first substance of the class that was approved for clinical use. For the moment, there are several substances on the market: losartan, valsartan, candesartan, telmisartan, irbesartan, olmesartan, eprostan. Studies performed on these substances had shown that except their antihypertensive properties, they offer additional benefits on reducing the cardiovascular events, including here their effect on the endothelium and their improvement of the endothelium dysfunction. Although these substances are from the same class, they vary in some aspects, because of their chemical structure, which leads to important differences in their pharmacokinetic and pharmacodynamics characteristics and also in their pharmacological efficacy. For example: losartan, candesartan cilexitil and olmesartanmedoxomil are pro-dugs, so they become active only after metabolisation, while telmisartan, irbesartan and valsartan are active substance, from the beginning, and they don't require metabolisation to become active. Also the mechanism of antagonism is different between the ARBs: candesartan has aninsurmontable antagonism (long lasting inhibition, irreversible binding, conformational changes, slow dissociation, potentially internalization), while losartan has a surmontable antagonism (short-lasting inhibition, fast reversible binding). Losartan only binds at two angiotensin II type 1 receptor (AT_1) sites, compared with candesartan which binds at four sites, from the same receptor, fact that may account to the long duration of action and for the magnitude of the antihypertensive effect of candesartan. [28-32]

Table 4. Comparative pharmacokinetics and pharmacodynamics of some ARBs[28-32]

	Losartan	**Candesartan cilexitil**
Active metabolite	EXP-3174	Candesartan
Bioavailability	30%	15%
Terminal $t_{1/2}$	6-9 h	5-9h
Elimination	Hepatic (65%) Renal (35%)	Hepatic (60%) Renal (40%)
Mechanism of antagonism	Surmontable (short-lasting inhibition, fast reversible binding)	Insurmontable (long lasting inhibition, irreversible binding, conformational changes, slow dissociation, potentially internalization)
Sites of binding on the AT_1 receptor	Two	Four

Candesartan, a long-acting antihypertensive agent, has been shown to have more potent antihypertensive activity than other

ARBs, such as losartan. A multicenter study, compared the antihypertensive effect, but also tolerability of candesartan cilexitil with those of placebo and losartan, in patients with hypertension. The conclusion was that a single 16 mg dose per day of candesartan cilexitil is significantly more effective than 50 mg of losartan, and that the 8 mg dose of candesartan is as effective as 50 mg losartan. [33, 34]

Several clinical studies showed to be a well tolerated drug, capable to reduce microalbuminuria in type 2 diabetics, to prevent the progression of CIMT (carotid intima media thickness) and to prevent type 2 diabetic retinopathy. [33]

In what concerns its effect on reversing the endothelium dysfunction, the next table (table 5) summarizes some studies performed on candesartan and ramipril and their effect on FMD.

Table 5.

ARB	Dose/day	Participants (number)	Control	Dose/day	Participants (number)	Results	References
Candesartan	16 mg	34	Ramipril	10 mg	34	FMD improved under both substances	[35]
Candesartan	16 mg	31	Ramipril	10 mg	30	FMD improved under both substances	[36]

The table above shows that both ARBs as well as ACE inhibitors can restore the endothelial dysfunction and improve the FMD in hypertensive pacients. Unfortunately, we couldn't find comparative studies with candesartan and perindopril and their effect on FMD, but as we showed before, perindopril is from the same class as ramipril, so there is no doubt that FMD should be also improved under treatment with perindopril and candesartan as it is under treatment with ramipril and candesartan.

CONCLUSIONS

Although at molecular level we have clinical evidences that both ACE inhibitors as well as ARBs have an important effect on the endothelial function, for the moment there aren't studies that can prove an improvement of the function of the endothelium on a long term. Also, it is very important to know which one of the both classes of blockers of RAA system: ACE inhibitors or ARBs have the best benefits in reducing hypertension and restoring the endothelial dysfunction with lesser side effects.

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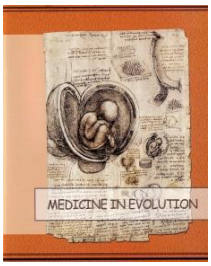

ERRATA - LAPAROSCOPIC TRANS-GASTRIC REMOVAL OF THE INTRA-LUMINAL MIGRATED LAPAROSCOPIC ADJUSTABLE GASTRIC BAND – TECHNICAL NOTE

DOBRESCU AMADEUS[1], DUTA CIPRIAN[1] ,TARTA CRISTI[1], LAZAR FULGER[1]

[1]"Victor Babeş" University of Medicine and Pharmacy Timişoara,

ABSTRACT

One of the most used method in bariatric surgery is lap-adjustable gastric banding(LAGB). We present three cases with intra-gastric migrated LAGB, in which the eroded band was removed by a laparoscopic trans-gastric approach. The start-up symptoms were epigastric pain in 3 out of 3 patients, port site infection in 2 out of 3 cases, and weight regain in 2 out of 3, dysphagia in one. The excess weight loss(EWL) was more than 50 % until the start of the symptoms. We suspended to the anterior abdominal wall the stomach on both sides of the planned gastrotomy, using sutures. This maneuver provides us with a better vision inside the gastric cavity and lowered the risk of the spillage of the gastric content. No post-operative leakage was recorded. The laparoscopic trans-gastric LAGB removal is safe performed by experienced surgeons. Patients with eroded LAGB should be referred to tertiary centers with experience in bariatric surgery.

Key words: *Gastric erosion; Laparoscopic adjustable gastric band; Lap band removal*

Correspondence to:

Dobrescu Amadeus
Address: Timisoara 300585, str. FC Ripensia 34 ap.1
Phone: +4 0740014355
E-mail address: amadeusdobrescu@gmail.com

INTRODUCTION

One of the most used techniques in the world for losing the excess weight is the lap-adjustable gastric-banding (LAGB). This method had a relative high rate of late complications – one of the fearsome is the migration of the ring inside the stomach cavity by eroding the gastric wall occurring in 0.5–11% of cases [1, 2]. Sometimes the removal of migrated LAGB cannot be achieved by trans-oral endoscopy. We propose a technique for migrated LAGB using a modified laparoscopic trans-gastric approach described by Basa [3].

METHODS

LAGB for obese patients had been performed for the first time in our clinic, at the Surgical Clinic 2 of County Emergency Hospital Timisoara in 2002, since then until December 2012, 234 patients underwent this procedure. The technique for placing the LAGB was the same as described by Fielding [4,5]. Out of these 234 patients we had 3 cases of intra-gastric migrated LAGB, in which the removal of the band was performed laparoscopically trans-gastric.

The time between initial surgery and the start of the symptoms of migrated band was 38, 47, and 41 months. The presentations symptoms were epigastric pain in 3 out of 3 patients, port site infection in 2 out of 3 cases, and weight regain in 2 out of 3, dysphagia in one patient. The EWL was more than 50% until the start of the symptoms; only the patient with dysphagia maintained the loss. [Tabel I].

The period from the start of the symptoms until diagnosis of the eroded band was 72, 78 and 38 days, the surgical removal of the band was performed during the first week after upper gastrointestinal endoscopy (UGIE) revealed the intra-gastric migration of LAGB.

UGIE showed the migration of more than 50 % of the band length, including the buckle. The patients were taken to the operating room (OR) and several attempts for endoscopic removal were made in our first patient. The reason for trying to remove the eroded band in the OR was that there are few possible complications of endoscopic maneuvers: bleeding, perforation of gastric wall after removal of the band, and an unsuccessful procedure; all of this might require surgical solutions.

Pre-operative work-up: the health status of the patient was assessed; special attention was addressed to concomitant comorbidities. Deep vein thrombosis prophylaxis was made by low molecular weight heparins 1 mg/kgc/day one night before procedure.

The patient was placed in modified lithotomy position with the hips and the knees slightly flexed and tied up to the operating table to prevent the patient from slipping down, position recommended for all the bariatric procedures. Using an anti-Trendelenburg position we obtained the displacement of the intra-abdominal viscera and the remaining free fatty omentum downward, so the upper part of the abdomen including the stomach was proper exposed. The patient abdomen was cleansed with povidone-iodine solution and draped sterile.

The operating surgeon was placed between the patient legs with straight access to esophageal-gastric junction area. The camera-assistant surgeon was placed on the right side of the patient, sitting on a chair in a manner that he didn't interfere with

the operating surgeon and still was comfortable to provide good image during the entire procedure.

The pneumoperitoneum is obtained through a Veress needle introduced through a supra-umbilical incision; usually there are no adhesions from initial surgery as the site for camera-trocar is inserted between the xiphoid and the umbilicus in the obese patients. The pressure insufflated in obese patients might be higher than regular pressure of 12 mmHg because they have sometimes a higher baseline pressure due to abdominal wall weight; we used 14 mm Hg in our series.

The standard sites for trocar insertions are showed in picture 1. The landmark used for insertion of the trocars is the xiphoid bone, because the umbilical scar is often moved caudally in the obese patients. We used same insertions sites as in the initial surgery. Camera trocar site was placed at 2/3 from the xiphoid lateral left from the xiphoid-umbilical line. Then the abdominal cavity was inspected and the region of esophageal-gastric junction assessed. If laparoscopic procedure was possible the next two trocars were inserted under direct view. 2nd trocar (5mm) was placed 5 cm laterally from the median line on the right side. 3rd trocar (15 mm) was placed 5 cm under the left costal margin on the mid clavicle line.

The LAGB was all hidden by inflammatory dense adhesions between the omentum, the lesser curvature of the stomach and the left liver lobe, as we were able to see only the calibration tube. This whole inflammatory pseudo-tumor was between 10 and 15 cm diameter. As we were unable to see any portion of the band and endoscopy showed that anterior gastric wall was eroded we decided that dissection of the esophageal-gastric junction pose a great risk of perforating the esophagus or the stomach. Also bleeding from the underneath surface of the left liver lobe could occurred. A much more appropriate approach was trans-gastric laparoscopic removal of the eroded LAGB [3].

First we cut the calibration tube near the inflammatory process and remove it together with the port by an incision to the subcutaneous site of implantation of the original surgery.

Then we elevated the anterior gastric wall towards the abdominal wall using two sutures (2-0 PROLENE™ Polypropylene Suture, Ethicon, USA). The sutures are passed through gastric sero-muscularis layers, and then passed through the abdominal wall with the fascia closure device (BERCI Fascial Closure Instrument, Karl Storz, Germany), clamped and anchored with a Kocher grasper.

The gastrotomy was performed along the avascular line of the anterior gastric wall, way below the area of inflammation and had 3 cm in length. First the gastric wall was perforated with the hook, and then LigaSure (LigaSure™Covidien, USA) was used for enlargement of the breach. Traction on the sutures along the breach revealed the gastric cavity; aspiration was performed if needed [Picture 2]. After establishing a good view we found the eroded LAGB which had a greenish color and was migrated through the anterior gastric wall more than 50% of his length. We searched the stomach for other lesions, and then we cut using the laparoscopic scissor the band and removed it from the stomach [Picture 3]. The LAGB was extracted through the 15 mm left trocar, usually it fits inside the trocar lumen and there is no need for trocar removal and then repositioning.

A new evaluation of the stomach cavity was performed searching any bleeding after the extraction of the band. We didn't have any bleeding in our 3 cases series.

The gastrotomy was closed using continuous double layer sutures (2-0 PROLENE™ Polypropylene Suture,

Ethicon, USA), first layer was total, second one sero-serosal. [Picture 4]

A 50 cc methylene-blue test was performed through nasogastric tube under camera vision, while the gastro-duodenal passage was closed using pressure at the level of anterior wall with the left flank laparoscopic instrument. No leak was observed either to the tube site of insertion in the inflammatory area, either to the suture line of the gastrotomy.

Peritoneal lavage was done with 500 cc of saline, the hemostasis was secured. A 24 Fr silicone drainage tube was placed through the right trocar beneath the liver just near to the inflammatory process. Nasogastric tube was placed for 24h.

The site for extraction was closed using fascial closure instrument, and then was heavily washed out with saline solution.

Oral intake was resumed first postoperative day and gastrografin swallow test was performed after 24h and 1 month postoperatively. Discharge was in the POD 2 or 3.

30 days postoperative evolution was without any complications.

Table 1. Clinical features
BMI = body mass index; EWL= excess weight loss; F=female

	Patient 1	Patient 2	Patient 3
Age (years)	34	29	39
Sex	F	F	F
BMI (kg/m^2)	26.8	28.4	27.1
Symptoms starts (months)	38	47	41
EWL %	62%	59%	60%
Epigastric pain	Yes	Yes	Yes
Port site infection	No	Yes	Yes
Weight regain	No	Yes	Yes
Dysphagia	Yes	No	No

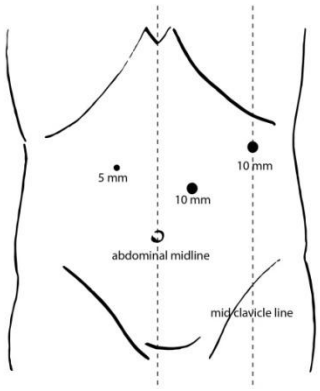

Figure 1. Trocars insertion site

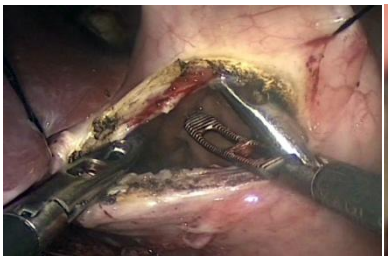

Figure 2. Traction sutures along gastrotomy with ease gastric exploration

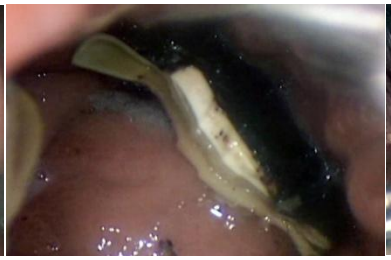

Figure 3. LAGB identification, cutting and extracting through gastric wall

Figure 4. Closing gastric wall with 2 running sutures (Prolene 2-0). On the left side of the image dense inflammatory adhesions

DISCUSSIONS

LAGB has a relatively high reoperation rate compared to other bariatric procedures, mainly related to slippage, pouch dilatation, gastric erosion or ante-gastric positioning of the band[6]. More than 55% of LAGB erosion occurs in the first two years [7] and are related to the surgeons' experience, later erosions are not linked to the surgical technique.

Basa described an adapted trans-gastric laparoscopic technique for removing the LAGB migrated inside the stomach cavity. With increasing laparoscopic skills of our contemporary surgeons this method seems feasible. We added one new feature to this technique – we suspended the gastric anterior wall and so we created more working space for removing the LAGB, without adding significant time to the operating time or any other adverse event.

Why laparoscopy? - these obese patients have a high risk of surgical site infections (SSI) and opening the stomach can increase this risk in a thick fatty abdominal tissue.

Laparoscopic trans-gastric technique was used first for removing the benign gastric tumors [8], than for ERCP at patients with previous Roux-en-Y gastric bypass [9], also to remove the migrated Angelchick prosthesis [10]. The advantages of this technique are that we were not supposed to dissect the tight adhesion between the stomach, the left liver lobe and the structures surrounding/nearby the esophageal-gastric junction preventing an extended operating time or larger amount of blood loss. Gastric wall incision and suture are made in healthy tissue, with no inflammation, leading to faster and safer healing. We did not have any major complications after our 3 cases series, any leak, deep space infection or post-operative bleeding. Our patients resume liquid diet in the POD 1, and were discharge in the POD 2 or 3, with no readmission, some authors advocate placement of nasogastric tube for gastric drainage up to 7 POD [11]. This favorable outcome might be related to the fact that our patients are young, active and in a better state of health, after losing a large amount of the excess weight due to LAGB placement.

LAGB erosion of the gastric wall is not an emergency if it is not complicated with signs of abdominal sepsis either gastric bleeding; our opinion is that these patients should be referred to tertiary centers with experience in bariatric and laparoscopic surgery. In a large series of 6382 cases Kirshtein et al report 14 emergencies procedures, from a total of 539 re-operations in the whole series [12].

With the increasing numbers of procedures performed we expect a raised in the number of long term complications of LAGB, in a systematic review of complications after laparoscopic adjustable gastric banding, the erosion represents an overall 1.46% in 15775 patients [13]. Regaining, epigastric pain, dysphagia in a patient with LAGB should be followed by a UGIE.

After LAGB removal there is always a regain in weight, so we have to imagine another bariatric procedure. Some authors propose re-banding during same operative procedure with the removal [14], we don't think this is feasible; we planned to perform gastric plication either sleeve gastrectomy in the near future for our 3 patients [15].

CONCLUSIONS

Eroded LAGB can be removed with a trans-gastric laparoscopic procedure; patients should be referred to tertiary centers with experience. The

procedure is safe in hands of experienced laparoscopic surgeons with selected patients. Our technique with the suspension of the gastric wall to the anterior abdominal wall prevents spillage and offers a better intra-gastric view.

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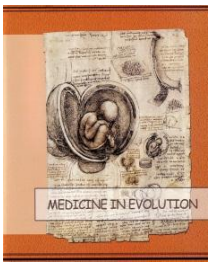
ERRATA - THE ROLE OF PRIMARY CYTOREDUCTIVE SURGERY IN ADVANCED OVARIAN CANCER



JEBEREAN ADRIAN[1], MOTOC ANDREI[1], ANCUŞA DAN[1], CARABINEANU ADRIAN[1], BUCUR ADINA[1], POPOVICI RAMONA AMINA[1], MAZILU OCTAVIAN[1]

[1]"Victor Babeş" University of Medicine and Pharmacy Timişoara

ABSTRACT

Objectives: *To determine the value of primary cytoreductive surgery in advanced ovarian cancer.*

Methods: *A retrospective clinical study in which 45 female patients, with epithelial ovarian cancer FIGO stage IIIC, operated in the Surgical Oncology Clinic of the Municipal Hospital Timisoara over a period of six years (2003-2008), were evaluated.*

Results: *The diagnosis was established based on the histopathological examination. The 45 patients were divided into two groups, Group 1 (n = 24) who underwent optimal cytoreductive surgery followed by adjuvant chemotherapy, and Group 2 (n = 21) who followed neoadjuvant chemotherapy, after being performed cytoreductive surgery. Between the studied Groups, there were not significant differences in terms of epidemiological data (area of origin, age at diagnosis and comorbidities) and neoplastic disease characteristics (histopathological type, grading). To achieve the optimal threshold after the cytoreductive surgery, 26 patients requested multiple organ resections. Long term survival was significantly higher for Group 1, 54% at 5 years, compared with only 28.5% for the 2nd Group.*

Conclusions: *Optimal cytoreductive surgery performed as the first therapeutic act and requiring the surgeon to have an aggressive attitude brings clear benefits in terms of long-term survival for patients with advanced ovarian cancer.*

Key words: *Ovarian cancer, optimal citoreductive surgery, survive, tumor residue*

Correspondence to:

Mazilu Octavian
Address: "Victor Babeş" University of Medicine and Pharmacy, Timisoara, Romania
E-mail address: mazilu_o@yahoo.com

INTRODUCTION

Ovarian cancer is a major cause of mortality and morbidity, being on the seventh place as the incidence of malignant tumors among females, with a five years survival for all stages of disease between 35-38% (1). Increased mortality is due to the fact that over 60% of patients are diagnosed in advanced stages (FIGO III-IV) (2).

The black prognosis is due to the late detection, the disease being asymptomatic until it develops disseminated peritoneal metastases. Peritoneal cavity is the main place of dissemination of the ovarian neoplasm by direct implantation in various intraperitoneal locations of neoplastic cells, which follows the peritoneal fluid hydrodynamics through the parietocolic spaces to the diaphragm and back towards the pelvis (3).

The basic treatment for patients with advanced ovarian cancer is the surgery that aims an optimal cytoreduction (postoperative tumoral residue with a diameter of maximum 1 cm) and subsequently adjuvant chemotherapy (4, 5). Unfortunately, only a relative low number of patients, between 40-50%, can follow this therapeutic model (6, 7). Patients, who cannot benefit from the beginning from the optimal tumor cytoreduction, will follow neoadjuvant chemotherapy (3-6 cycles) and, subsequently, an "interval" surgery with a cytoreductive purpose will be taken into consideration. The chemotherapy scheme used in recent years has included Cisplatin/Carboplatin and Paclitaxel and had superior results compared to others used in the past. (4, 8).

Cytoreductive surgery is an important prognostic factor in terms of disease-free survival and overall survival.

Aim and objectives:

The aim of the study was to see the the role played by the optimal tumor cytoreduction in the treatment of patients with epithelial ovarian cancer performed as a first therapeutic act, knowing that around 75% of epithelial ovarian neoplasms present chimiosensibility.

METHODS

The clinical study was conducted on a group of 45 female patients, with epithelial ovarian cancer stage IIIC, hospitalized in the General Surgery II and Surgical Oncology Clinic of the Emergency Municipal Hospital Timisoara, between 2003- 2008. Patients were selected from a total of 197 sick subjects with ovarian cancer treated in our clinic during that period of time.

Among the criteria to enter the study as subject, there were: histological diagnosis of epithelial ovarian cancer, FIGO stage IIIC, following optimal cytoreductive surgery as the first therapeutic act or after neoadjuvant systemic chemotherapy, following at least 6 cycles of adjuvant or neoadjuvant chemotherapy. Patients presenting significant comorbidities (other neoplasm diseases associated with kidney failure, liver failure) patients who interrupted the systemic chemotherapy, patients who died before performing a minimum of 6 cycles of chemotherapy, and patients older than 80 years old at the time of diagnosis were excluded from the study.

The patients studied were divided into two groups: patients who underwent optimal cytoreductive surgery as first therapeutic act (n=24) followed by adjuvant chemotherapy and patients who followed neoadjuvant chemotherapy, after being

performed cytoreductive surgery (n = 21).

The correct diagnosis was set for patients of Group 1 using the histopathological result on the excision pieces, and at Group 2, the positive diagnosis was set by staging laparotomy with biopsy at 20 patients and at 1 patient by paracentesis with positive cytological examination, increased tumoral marker CA 125 and tomography which certified the presence of ovarian tumors and of peritoneal carcinomatosis. Patients from Group 2 were considered to have unresectable tumors.

All patients were treated with adjuvant chemotherapy or neoadjuvant chemotherapy from the platinum derivates class (cisplatin/carboplatin) according to the therapeutic guidelines.

The role of primary cytoreductive surgery at patients with advanced ovarian cancer was evaluated after the survival analysis. The study is based on retrospective analysis of the observation sheets, discharge records, consultation records from outpatient facility, surgery protocols, histology reports, and oncology sheets.

RESULTS

Systematic epidemiological data of both groups are presented in Table 1. The entire group recorded an average age of 56.06 years and a rate of 44.44% had presented co morbidities, the most common being: hypertension in 28.88%, chronic ischemic heart disease 35.55%, diabetes type II at 11.11% and obesity (grades II-III) at 17.77%. In most of the cases associated pathologies occurred simultaneously.

Table 1. Epidemiological data

	Group 1 (n=24)	Group 2 (n=21)
Environment (rural area/ urban area)	10/14	8/13
Average age	57.08 (35-79)	56.05 (20-74)
Comorbidities		
Hypertension	8 (33.33%)	5 (23.80%)
Chronic ischemic heart disease	9 (37.50%)	7 (33.33%)
Diabetes type II	3 (12.50%)	2 (9.52%)
Obesity	4 (16.66%)	4 (19.04%)

From the neoplastic disease's characteristics (Table 2), all patients had epithelial ovarian cancer FIGO stage IIIC. In Group 1, the histopathological outcome presented papillary serous adenocarcinoma at 17 (70.83%) patients, adenocarcinoma type endometrioid at 2 patients (8.33%), mucinous adenocarcinoma at 2 patients (8.33%), adenocarcinoma with clear cells at one patient (4.16%), undifferentiated adenocarcinoma at 2 patients (8.33%). For Group 2, 16 patients (76.19%) had papillary serous adenocarcinoma, 2 patients (9.52%) had endometrioid adenocarcinoma, 1 patient (4.76%) had mucinous adenocarcinoma, 2 patients (9.52%) anaplastic carcinoma. Patients of Group 1 had the tumor grading G2/G3 of 15/9 patients; and in Group 2, the G2/G3 ratio was 16/5 patients.

Table 2. The neoplastic disease's hystopatological characteristics

	Group 1 (n=24)	Group 2 (n=21)
Hystipatological Type		
Serous carcinoma	17(70.83%)	16(76.19%)
Endometrioid carcinoma	2(8.33%)	2(9.52%)
Mucinous carcinoma	2(8.33%)	1(4.76%)

Carcinoma with clear cells	1(4.16%)	-
Anaplastic carcinoma	2(8.33%)	2(9.52%)
Tumoral grading		
G2	15(62.50%)	16(76.19%)
G3	9(37.5%)	5(23.80%)
|Neoplastic ascites	21(87.50%)	19(90.47%)

Both, in terms of epidemiological data and neoplastic disease's characteristics, the results reveal a similar structure of the two groups (Table 1 and 2).

The extent of the optimal cytoreductive surgery for the entire group of patients consisted in total hysterectomy with bilateral anexectomy and omentectomy, and it was associated with intestinal resection at 4 patients from Group 1 and 2 patients from Group 2; partial resection of bladder at 1 patient from Group 1; segmental resection of the sigmoid colon at 1 patient from each of the studied Groups. At 10 patients from Group 1 and 7 patients from Group 2, the ablation of tumor formation from the parieto-colic areas, the Douglas space, the gastrocolic, and gastrohepatic ligament, was performed.

From Group 1, after ending the six cycles of adjuvant chemotherapy, 17 patients had complete remission documented, at 6 patients through "second-look" surgery and at 11 patients by CT and CA-125 values normalization. Four patients had presented partial remission through second-look surgery and 3 patients had the disease in evolution.

From Group 2 all patients presented favorable response after the neoadjuvant chemotherapy, 10 patients showing complete remission with pieces of sterile resection and 11 patients had partial remission, being able to perform optimal cytoreductive surgery with residual remnants of tumor of <1 cm postoperatively.

The patients' survival was analyzed over a period of 5 years, from the time of diagnosis (Figure 1) and the results were as follows: after the first year, in Group 1 survived 21 patients (87.5%) and 19 patients (90.46%) in Group 2; after the second year, in Group 1 survived 20 patients (83.33%) and 15 patients (71.42%) in Group 2; at 3 years after the diagnosis, in Group 1 survived 16 patients (66.66%) and 8 patients (38.09%) in Group 2. At five years after the diagnosis in Group 1 survived 13 patients (54.16%) and 6 patients (28.57%) in Group 2, the difference being statistically significant (p = 0.036).

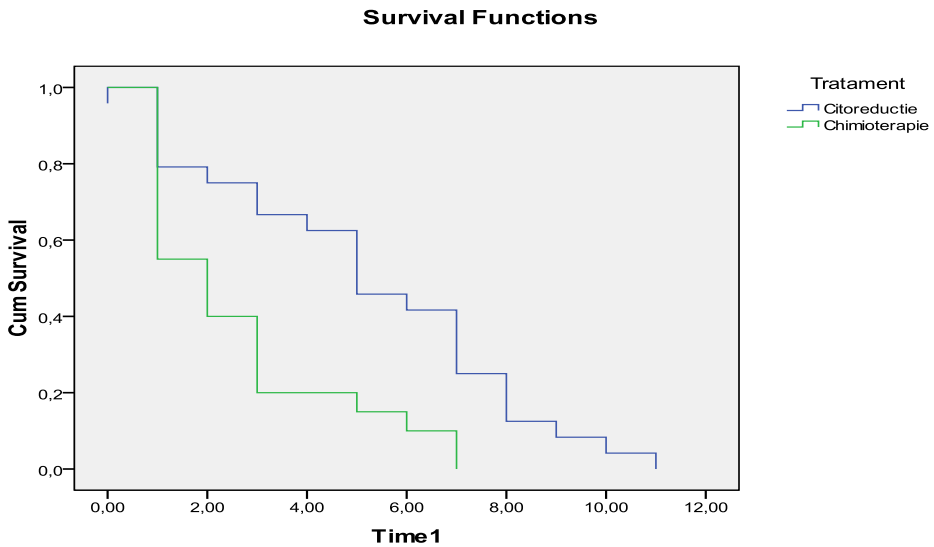


Figure 1. ***The survival curve between the groups***

DISCUSSIONS

Ovarian cancer is an important cause of morbidity and mortality in the diagnosis of malignancies due to the impossibility to put the diagnosis in the early stages of the disease.

Considering that over 60% of the ovarian cancer cases are diagnosed in advanced stages, which requires a multidisciplinary approach, mainly based on the combination of surgery with chemotherapy, the analysis and evaluation of the therapeutic possibilities is necessary in order to implement an onco-surgical protocol with a radical character which has to bring clear benefits for these patients.

The first therapeutic approach for patients diagnosed with ovarian cancer is, generally, the surgery, which aims both to put the exact diagnosis and to reduce the tumoral volume as much as possible, knowing that postoperative tumoral residue is an important factor in terms of the period "free" without disease and the overall survival.

Since the '70s, Griffiths et al (9, 10) have described the relationship between cytoreductive surgery and survival, considering the optimal cytoreductive surgery the one which obtains a postoperative tumoral residue with a maximum diameter of 1.5 cm. During the following years numerous studies confirmed the inverse relationship between residual disease after the primary surgery and the survival (11-14), considering currently tumoral cytoreduction optimal, and getting a residual postoperative tumoral residue with a diameter of maximum 1 cm. In a study on 3126 patients analyzed, du Bois et al (17) achieved an average survival of 99.1 months for patients who underwent complete resection and 36.2 months at patients who had a residue <1 cm. After primary cytoreductive surgery, patients with advanced ovarian cancer will follow adjuvant chemotherapy with regimes associating platinum and taxane derivatives.

For patients who are not candidates for the primary cytoreductive surgery, neoadjuvant chemotherapy and surgery at a certain period of time, with cytoreductive purposes, are taken into consideration. Multiple studies have presented the neoadjuvant chemotherapy's effectiveness, treatment which used platinum derivatives regimes, followed by surgery of "interval", finding an overall survival rate similar to that of patients who received primary tumoral cytoreduction followed by adjuvant chemotherapy (8, 15, 16).

The two studied groups were homogeneous, both in terms of epidemiological data (average age and comorbidities), as from the point of view of the neoplastic disease (stage of disease, histological type, and tumoral grading).

Our study highlights the benefit optimal cytoreductive surgery is brought, surgery leaves a tumoral residue under than 1 cm, performed the first therapeutic sequence. If for a period of up to 24 months after the diagnosis, significant differences weren't found, the optimal primary tumor cytoreduction on long term offers 54% for survival at 5 years, compared with 28.5% for patients who have undergone neoadjuvant chemotherapy despite tumoral chemo-sensitivities present at this.

It is also observed that in order to obtain an optimal tumoral residue, an aggressive surgery is requested, surgery which often involves multiple organ resection. The recurrences appeared later and their responses to treatment were not taken into account in the study, which benefit from the combination of surgery with chemotherapy.

The results in terms of survival of patients in both groups are within the

limits mentioned in the scientific literature.

CONCLUSIONS

The first therapeutic sequence for patients with advanced epithelial ovarian cancer must be the cytoreductive surgery, with the goal of leaving residual tumoral volume as small as possible or even absent macroscopically.

Cytoreductive surgery should be an aggressive one, as very often it requires multiple organ resections to obtain the optimal threshold.

Survival of patients with advanced ovarian cancer is closely related to the therapeutic method applied per received, and optimal tumor cytoreduction is superior in terms of this issue.

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