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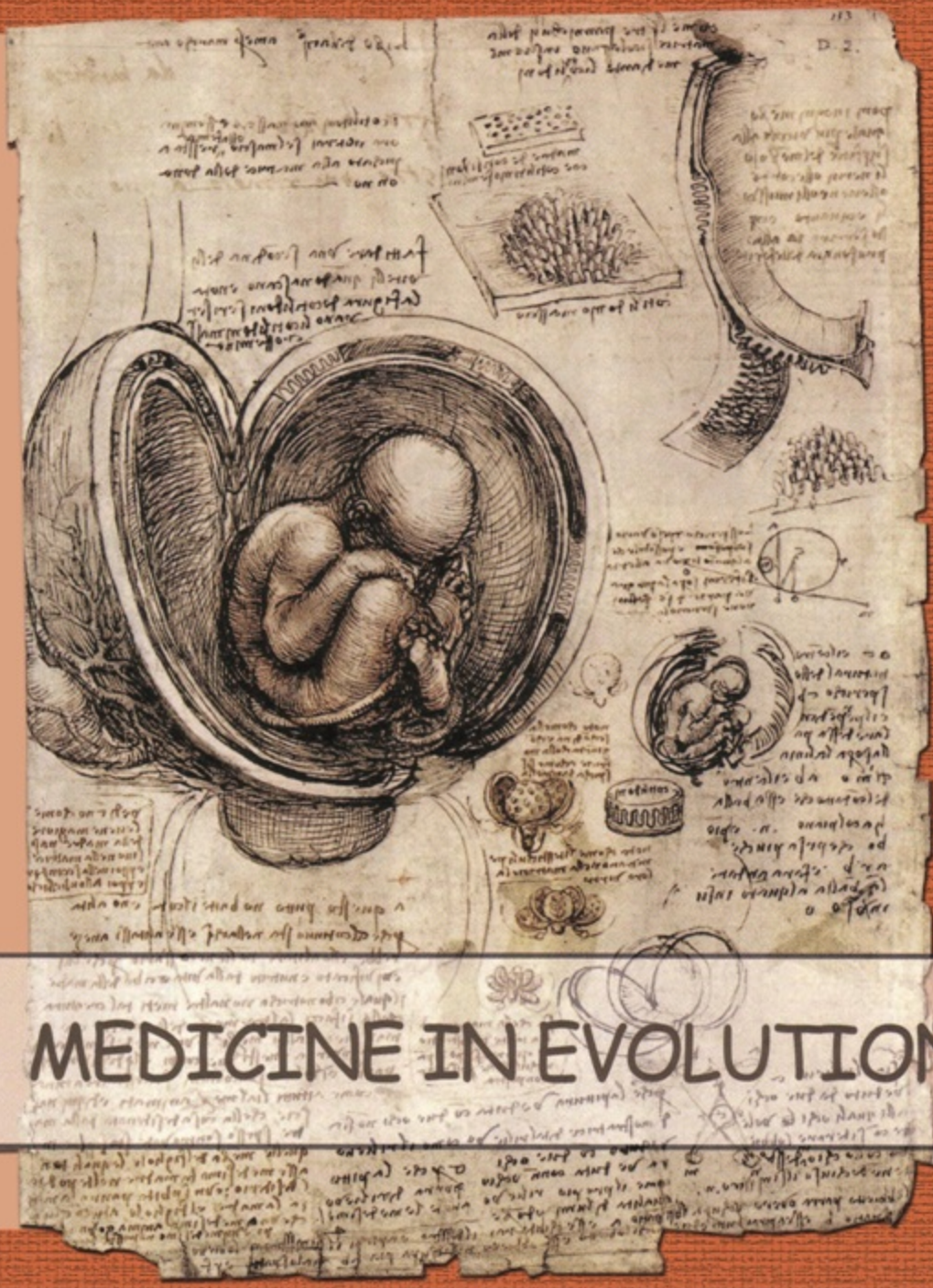

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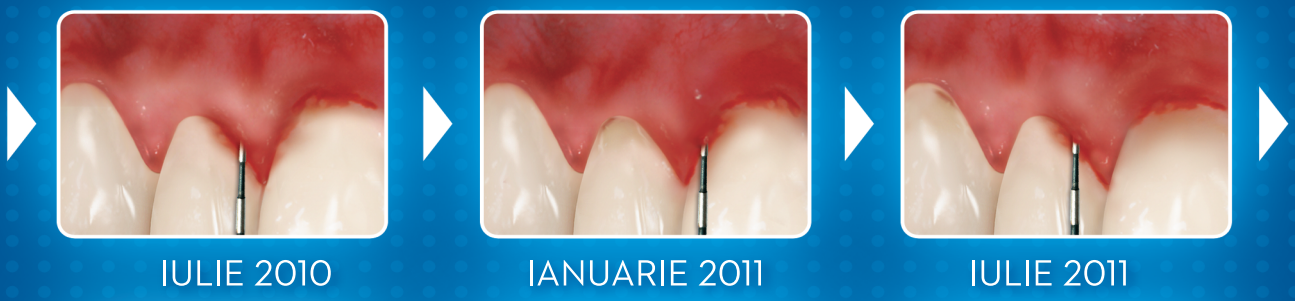
REDUCE ŞI AJUTĂ LA PREVENIREA PROBLEMELOR GINGIVALE ÎN 4 SĂPTĂMÂNI PENTRU A ÎNTRERUPE CICLUL GINGIVITEI



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Este dovedit clinic că reduce si ajută la prevenirea problemelor gingivale în 4 săptămâni pentru a ajuta pacienții să întrerupă ciclul gingivitei. Sistemul combină acțiunea chimică puternică a fluorurii de staniu stabilizate, suplimentată de apă de gură, cu acțiunea mecanică a periuței de dinți Pro-Flex, suplimentată de ață dentară, facând din acesta completarea perfectă a tratamentului din cabinetul dumneavoastră.

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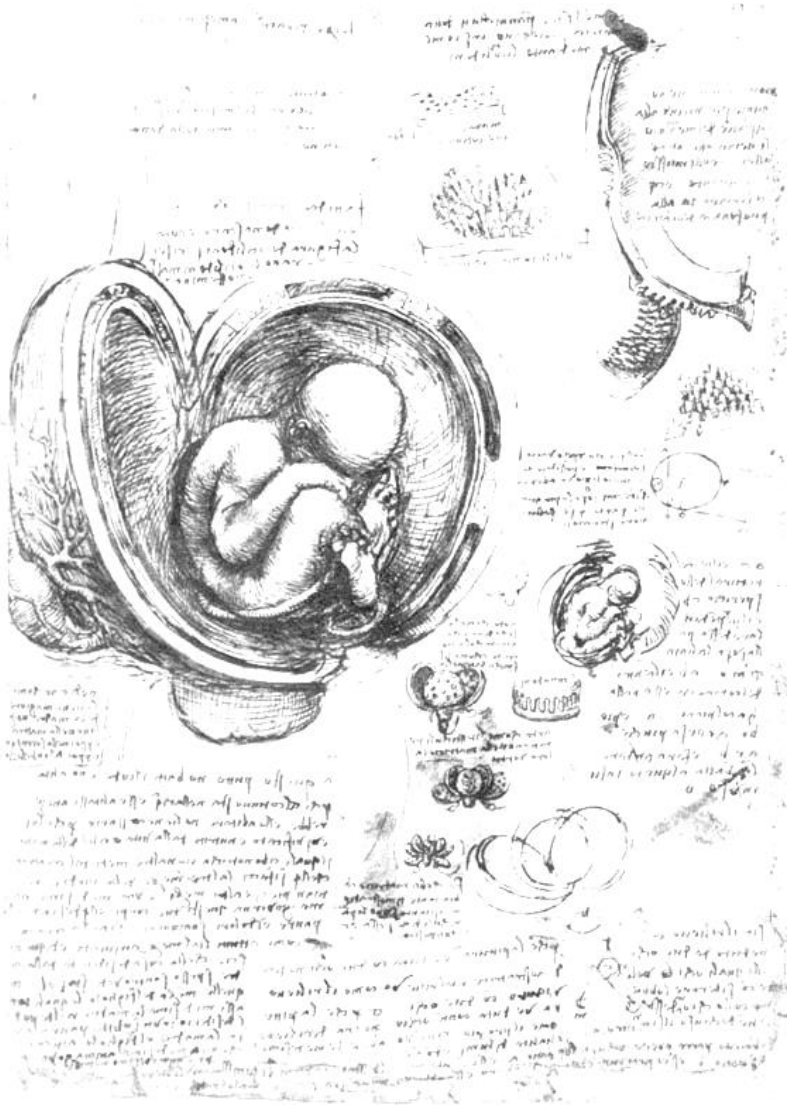

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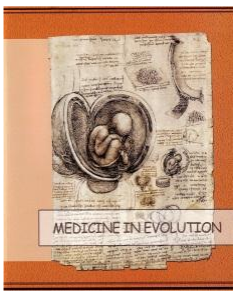
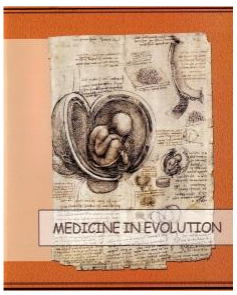


ARTICLES

Pre-and postsurgical general health and sight assessment by vfq25 score in patients with cataract surgery



Ciobotea D.[1], Şerban C.[2], Putnoky S.[1], Fira Mladinescu C.[1], Tuţă Sas I.[1], Băcean Miloicov C.[1], Popa M.[1], Vlaicu B.[1]

[1]*Discipline of Hygiene, Departament 14 Microbiology,"Victor Babeş"University of Medicine and Pharmacy Timişoara*
[2]*Discipline of Informatics and Biostatistics, Departament 3 Functional Science,"Victor Babeş"University of Medicine and Pharmacy Timişoara*

Correspondence to:
Name: Drd. Ciobotea Dana
Address: Discipline of Hygiene, Departament 14 Microbiology,"Victor Babeş"University of Medicine and Pharmacy Timişoara, Piata Eftimie Murgu nr.2
Phone: +40 788 881880
E-mail address: danukha@yahoo.com

Abstract

The study aimed to perform pre- and postsurgical investigations of a life quality score component regarding eye pathology in patients who addressed the Clinic of Ophthalmology in Timisoara in 2015. We included 53 patients with cataract, 49.1% men with the mean age M=68.6 and SD=8.81 years, and 50.9% women, mean age M=71.5 years and SD=7.66. The work methods were: transversal populational study by the Visual Function Questionnaire VFQ25; tests for visual acuity (VA); phacoemulsification as surgical intervention for crystalline replacement in the studied patients. Regarding the score obtained on the scale for general health, as component of life quality, the results showed: better presurgical scores in patients with sight deficit as compared with those with cecity; smokers had lower presurgical scores than nonsmokers, the score being more severe in smokers with a long history of active smoking; sleeping disorders such as difficulties in staying asleep, night awakenings, fatigue upon awakening are correlated to the score on general health. The score on general sight is not influenced by the clinical status during presurgical assessment. The postusrgical evolution of the two scores is statistically significant and the size of the effect >0.60 in both subscales.

Keywords: life quality, VFQ25 score, cataract patients.

INTRODUCTION

With populational aging, a better understanding of the biological basis for development and aging represents an important step to the decrease of mortality and improvement of handicap-free survival. Genetic and nongenetic factors, external such as environment, nutrition and level of healthcare control the phenotype of aging. By modulating individual susceptibility to disease and disabilities, these interactions between genetic and external factors determine life quality in terms of health and life expectancy [1].

Regardless of their degree of severity, visual disorders may limit peoples' capacity to perform daily tasks and may affect their quality of life and their capacity to interact with the external world. Blindness or cecity, the most severe form of sight disorder, may reduce the ability of people to carry out daily tasks and to move freely. Qualitative rehabilitation allows persons with various degrees of visual deficiencies to fully benefit from life, to reach goals and be active and productive as part of the present society. Most of the diseases and pathologies causing visual deficits and blindness may be prevented by adequate cost-effective interventions [2].

In the present study we aimed to investigate, during presurgical stages, two components of the life quality score, general health and visual health, from an eye-pathology perspective; during postsurgical stages, we aimed to investigate the level of improvement of these parameters after the surgical removal of the opaque crystalline in patients who addressed the Clinic of Ophthalmology in Timisoara in 2015. General health assessment proved to be a solid predictor for health status and mortality in populational studies [3].

MATERIAL AND METHODS

Material

We included a group of 53 patients diagnosed with cataract who were referred to the Clinic of Ophthamlology in Timisoara between January and April 2015. Of these patients, 49.1% are men, with a mean age M=68.6 years and SD=8.81 years, the age interval being between 50 and 82 years. The mean age differences between the two genders were not significant, p=0.206. Agewise, the two gender groups are homogeneous.

Presurgically, for the eye with the best results we recorded 69.8% of patients without visual deficit or with minor deficiencies, 20.8% with moderate visual deficiencies and 9.4% with severe defects or cecity. For the eye with the worst results we recorded 20.8% of patients without visual defects or with minor deficiencies, 24.5% with moderate defects and 54.7% with severe defects or with cecity. The surgical replacement of the crystalline was phacoemulsification. Postsurgically, visual acuity was recorded as lacking any visual deficit in all patients.

Method

Methods applied pre- and postsurgically are:

- **The transversal populational study** used the *Visual Function Questionnaire, VFQ25.* The questionnaire was developed and validated by RAND [3]. VFQ25 is a public document freely available for all researchers provided they identify the measure as such in all published materials [4,5]. VFQ25 consists of a basic set of 25 questions focusing on sight representing 11 sight-related constructs plus one general health assessment question. VFQ25 includes an appendix of additional elements in the Annex to the version with 51 questions which researchers may use to expand the scale up to a total of 39 elements. We also used the additional elements.

- **Testing for visual acuity (VA),** both corrected and uncorrected, was done using the Snellen chart and an autorefractometer.

Phacoemulsification is the surgical intervention used for crystalline replacement in the studied patients.

Data processing and interpretation involved modern methods of advanced medical statistics. Data were electronically stored using Microsoft Excel, version 2007 and processed using PASW 18 (SPSS 18) 2010. The threshold for statistical significance was set at $p<0.05$, except situations where the Bonferroni correction was applied and where the admissible threshold was explicitely stated. For ordinal data comparisons we used the Mann-Whitney and Kruskal-Wallis tests. For presurgery/postsurgery comparisons the Wilcoxon test was involved.

RESULTS

In the contex of life quality investigation using the VFQ25 score, the present paper makes an assessment of results using 2 of the 12 scales of the VFQ25 score: the selfperception of general and visual health status which were constructed by processing the questions regarding these aspects according to the instructions for use [3].

Presurgical assessment

The scale of general health has an average of 34.9 points, with a standard deviation of 16.61 points. The selfassessment of general health correlated neither to the age of participants ($p=0.055$) nor to their gender ($p=0.219$). We did find differences in the selfassessment scale of general health influenced by visual deficiency classes in the eye with the more severe clinical state, $H(2)=9.64$, $p=0.008$. We applied the Bonferroni correction and the level of statistical significance was set at 0.025. We found that patients without deficits or those with slight visual deficits have a selfassessment score of general health significantly better than patients with moderate visual deficits, $U=27$, $z=-2.59$, $p=0.010$, $r=0.52$, and than patients with severe deficits or cecity, respectively, $U=65$, $z=-2.87$, $p=0.004$, $r=0.45$, the difference ranging from medium to high (Figure 1).

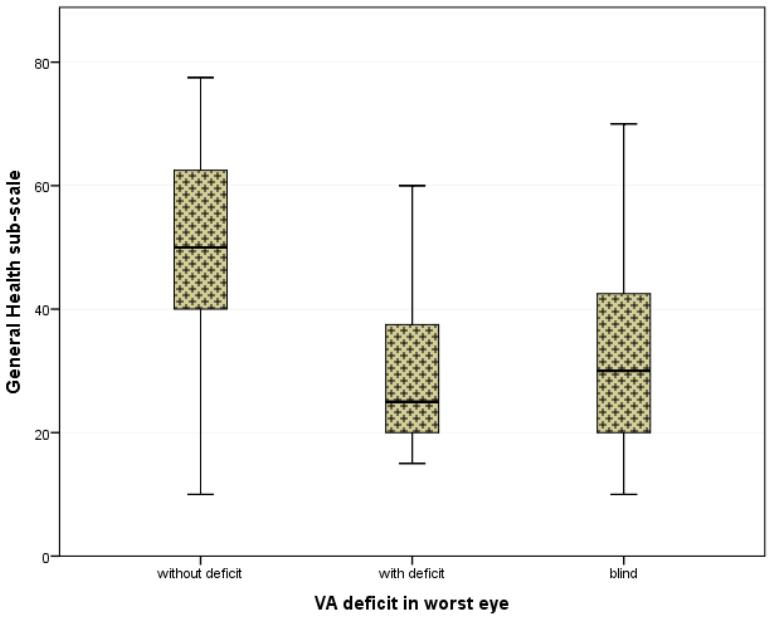


Figure 1. Distribution of scores on the „General health" subscale depending on the classification of visual deficit in the eye with the weaker clinical state

Smoking was declared by 35.8% (19) of patients, with 94.7% (18) daily smokers. For daily smokers, the number of years of daily smoking varies between 29 and 57, with an average of 43.4 years and a standard deviation of 8.37.

We found a relation between the number of years of smoking and the degree of visual deficit in the eye with the worst clinical status, H(2)=9.25, p=0.010. We additionally investigated this result. We applied the Bonferroni correction and set the threshold of statistical significance at 0.016. We found that smoker patients without deficit or with minimal visual deficits smoked for significantly less years than cecity patients, the average difference being 13.5 +/- 3.52 years, p=0.002.

Smokers selfassess their general health by significantly lower scores as compared to nonsmokers, U=201.5, z=-2.26, p=0.026, r=0.31, the difference being of medium level. Also, people who smoke daily selfassess their general health significantly lower than those who do not smoke daily, U=172.5, z=-2.69, p=0.007, r=0.36, with a similar medium level of difference.

Concerning *sleep characteristics,* 88.5% (46) declare they have problems remaining asleep, and 94.3% (50) admit awakening during the night. Only 15.1% (8) of the group answer that they wake up feeling rested and recovered. The frequency of these symptoms does not differ regarding the degree of visual deficiency, p<0.05. On the other hand, we found a significantly weaker self-evaluation of the general health in patients describing the following symptoms, as compared to those who do not describe them: difficulties in remaining asleep during the night: U=61.5, z=-2.20, p=0.026, r=0.31; night awakenings: U=18.5, z=-2.18, p=0.029, r=0.30; fatigue upon awakening U=96.5, z=-2.08, p=0.037, r=0.29, with a medium level of differences (Figure 2).

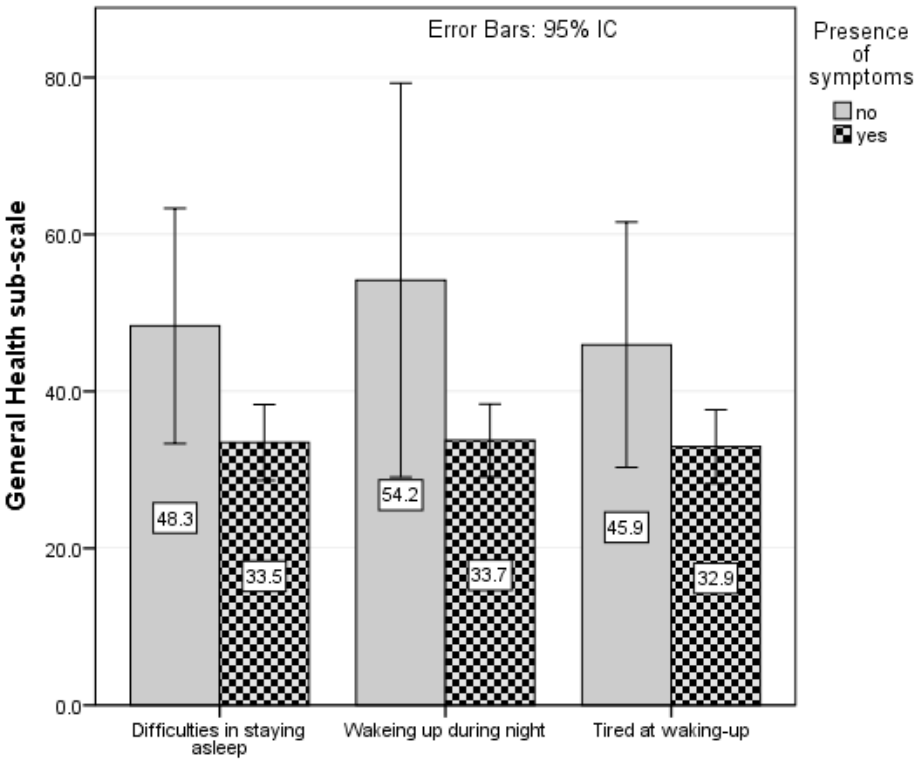


Figure 2. Distribution of scores on the"General health"scale depending on the presence of sleep disorders

The scale of the general visual status recorded an average of 35.2 points, with a standard deviation of 16.04 points. Neither the age (p=0.558), nor the gender (p=0.330) of patients, nor visual deficit classes (p=0.808) correlated to the selfassessment of the general visual status.

Postsurgical assessment

The scale of general health status has an average of 42.1 points, with a standard deviation of 16.04 points. The evolution between the initial and the postsurgical status is represented by an average difference of 7.26 points representing a significant improvement of the scale, z=-4.38, p<0.001, r=0.60, the level of difference being assessed as high. The average increase of the score is not influenced by the degree of clinical evolution, p=0.968 (Figure 4).

The scale of the general visual status has an average of 71.9 points, with a standard deviation of 13.73 points. The evolution between the initial and the postsurgical situation is represented by an average difference of 36.9 points representing a significant improvement of the scale, z=-6.23, p<0.001, r=0.86, the level of difference being considered as very high (Figure 3). The improvement in the score of general visual status was achieved with an average of 36.9 points and a SD of 12.15 points. The average increase of the score is not influenced by the degree of clinical evolution, p=0.512. The improvement is significantly lower in smokers as compared to non-smokers, U=165 z=-2.62, p=0.009, r=0.36, with a medium level of difference.

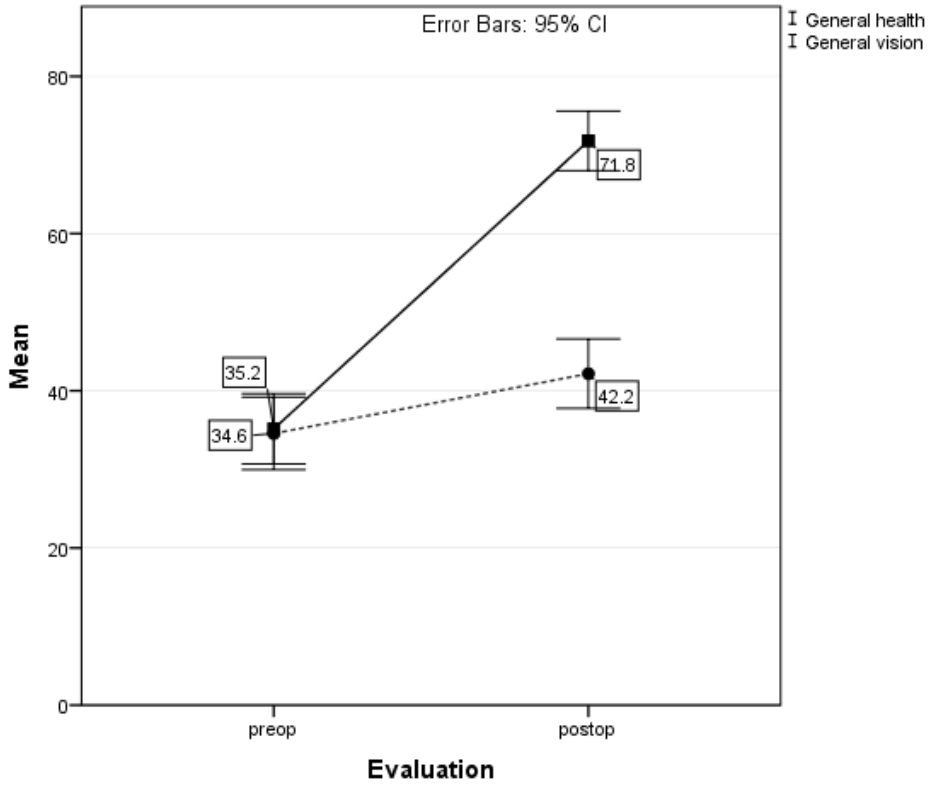


Figure 3. Distribution of the evolution of the"General health"scale between the pre- and postsurgical situation

DISCUSSIONS

In patients with cataract, the selfassessment of the visual deifict is subjective, they being differently affected by the functional limitation of sight. Our results indicate that the selfassessment of the general visual status is not influenced by the level of visual deficit, but the selfassessment of the general health is decreased in those with moderate deficit and cecity, as compared to those without deficit or with minor deficiencies.

Visual acuity is a basic assessment of sight quality and does not provide information regarding the quality of sight in real life situations under various illumination, such as solar light or front lights from cars during night driving. In a recent study [6], comparing life quality of patients with unilateral or bilateral cataract and even after considering the presence

of eye comorbidities, the authors found that the presurgical level of visual symptoms and the postsurgical improvement of visual quality were similar.

Before surgery, the prevalence of sleep disorders is very high, but nonrelated to the clinical status of visual acuity. The presence of symptoms was associated to a decreased score of the"General health"scale. Circadian disalignment caused by the low entry of light due to cataract may explain the correlation between reduced light transmission and sleep disorders [7]. In a prospective study [8], before surgery, 43.9% of patients had a low quality of sleep, with a Pittsburgh Sleep Quality Index (PSQI) score>5.5.

Smoking was identified as a risk factor in the deteriminism of cataract in both experimental and monitoring studies. Bormusov et al. [9] demonstrated under experimental conditions that smoking is an independent risk factor for cataract, with dose-response effects. The Beaver Dam Eye Study [10,11], a longitudinal study with a monitoring period of over 20 years, after corrections for age, income and severity of the senile macular degeneration, found that the status of current or past smoker was linked to a more pronounced decrease in the number of lost letters as determined upon the visual acuity examination. Another study [12] also showed that visual acuity under all illumination conditions, is significantly lower in persons who smoked with low or medium intensity as compared to non-smokers. In our study, the correlation between the number of years of daily smoking and the state of visual acuity was statistically significant. In our opinion, the two scales on life quality are affected by the smoking status as an effect of smoking on the organism [13,14], the status of the General health being significantly lower in smokers as compared to non-smokers.

The reduced improvement in the scale of General visual status observed in smokers as compared to non-smokers may be explained by the influence of free oxygen radicals generated by smoking on postsurgical healing [15,16].

The comparisons between pre- and postsurgical evolutions on the two scales of life quality are significant and the size of the effect is high on the general health scale and very high on the general visual health scale. Assessing the quality of life of patients in whom cataract surgery was performed, Polack et al. [17] found significant improvements, at very high levels, regardless of the initial state of visual acuity, similar results being also found in our study.

In a study including patients with cataract in Austria and Germany [18] with an average age of 74.1 years, difficulties in using their hands were detected in 42% of cases and in identifying denivelated surfaces in 30% of cases. Patients with bilateral surgery for cataract achieved marked improvements in sight and satisfaction on life quality. A subgroup of patients who had a lower limitation of activity before surgery were already content after the intervention on the first eye.

In a 13 years model, the surgical intervention on the first eye offered a plus of 1.62 QALY (quality-adjusted life years) and in 20.8% of patients an increase of life quality. Bilateral cataract surgery offered 2.81 QALY in the 13 years model and a 36.2% increase in life quality. Rönbeck calculated in 2012 a direct cost of 2653 $ for unilateral cataract surgery in the USA, price which was adjusted with 34.2% less than in 2000 and with 85% less than in 1985 [19].

CONCLUSIONS

The clinical status of sight is correlated presurgically to the score of General health status, and non-associated to the dimension of the General visual status. The evolution from pre- to postsurgical status of the two dimensions is statistically significant and with a high and very high level, respectively, but these are not influenced by the clinical status generated by the intervention.

Presurgically, the score of the General health status is influenced by the quality of sleep and by smoking, exhibiting a dose-response relationship.

Postsurgically, smoking affects the perception of clinical improvement as evaluated by the dimension of the General state of sight, probably a cummulative effect on eye structures and on postsurgical healing.

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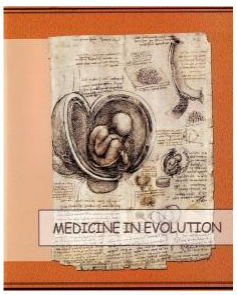
Endovenous laser treatment used in the surgery of venous insufficiency conditioned by varicose veins



Crăciun L.[1], Bernad E.[2], Bordianu A.[3], Crăciun C.[4], Ionita I.[5], Petre I.[2]

[1]*Vascular and general surgery, Timisoara*
[2]*Department of Obstetrics and Gynaecology,"Victor Babes"University of Medicine and Pharmacy Timisoara*
[3]*Department of Plastic Surgery and Reconstructive Microsurgery,"Carol Davila"University of Medicine and Pharmacy, Bucharest, Romania*
[4]*General surgery, Hospital Caransebes*
[5]*Department of Internal MedicineI, Discipline of Hematology,"Victor Babes"University of Medicine and Pharmacy Timisoara*

Correspondence to:
Name: Craciun Codruta
MD PhD
Address: Piata Eftimie Murgu nr.2
Phone: +40 724321413
E-mail address: med_lavinia@yahoo.com

Abstract

Endovascular laser therapy uses a modern technique to guide the laser using an ultrasonic device. The laser is inserted into the varicose vein, guided by the ultrasound machine, whilst the energy released by the intense pulsed laser light selectively destroys abnormal veins. The targets of the laser waves are hemoglobin and the water in the blood. Vascular laser causes the increase of the blood vessel temperature, which determines the closure of the veins. The study provides a retrospective assessment and is based on the analysis of the data supplied by the clinical-, imaging-, functional-, and morpho-pathological examination, as well as on the results of the complex surgical treatment using EVLT on 60 patients with severe CVI of the lower extremity.

Keywords: endovascular laser therapy, chronic venous insufficiency, varicose disease.

INTRODUCTION

Severe chronic venous insufficiency (CVI) of the lower extremity is one of the most common medical problems, affecting up to 25% of the adult population of industrialized countries (1,2). Venous trophic ulcer, as final and most dramatic manifestation of severe CVI, affects 0,3% - 1% of the western countries' population (3,4), and is associated with significant reductions in quality of life.

Nowadays, chronic venous insufficiency is becoming more common, being found in about 50% of the world population, respectively in 32% of the Romanians. The condition has various clinical manifestations, ranging from mild to complications seriously affecting the quality of people's lives. CVI has a considerable clinico-economical impact in the western countries caused by the high prevalence and significant morbidity, the elevated costs of diagnosis and treatment, and the loss of working days. Therefore, approximately 2%-3% of the European countries' budget allocated to health represents costs of CVI management (5,6,7). CVI leads to essential economic losses, amounting to around 4,6-6 million working days per year. (8,9).

CVI is conditioned by varicose veins, post-thrombotic syndrome or venous system abnormalities – the last two with less practical importance.

Varicose disease is the most common form of CVI; its prevalence is higher in industrialized countries and in northern Europe. In the Framingham study, the incidence of varicose veins is estimated at 2,6% in women and 1,9% in men.(10,11,12)

MATTER AND METHODS

We performed a retrospective study over a 5-year period (01.01.2005-31.12.2009) on patients hospitalized and surgically treated for varicose veins of the lower limbs; the study is based on a review of records and surgical protocols from the analyzed time period.

The study provides a retrospective assessment and is based on the analysis of the data supplied by the clinical-, imaging-, functional-, and morpho-pathological examination, as well as on the results of the complex surgical treatment using EVLT on 60 patients with severe CVI of the lower extremity. Patients were treated at the 1st Surgical Clinic of the Clinical Emergency Hospital, Timisoara. The research group included patients with severe CVI and incompetent perforator veins, located in the trophic lesions region of the shin, which underwent EVLT.

According to the CEAP classification, our research group is presented in chart 1:

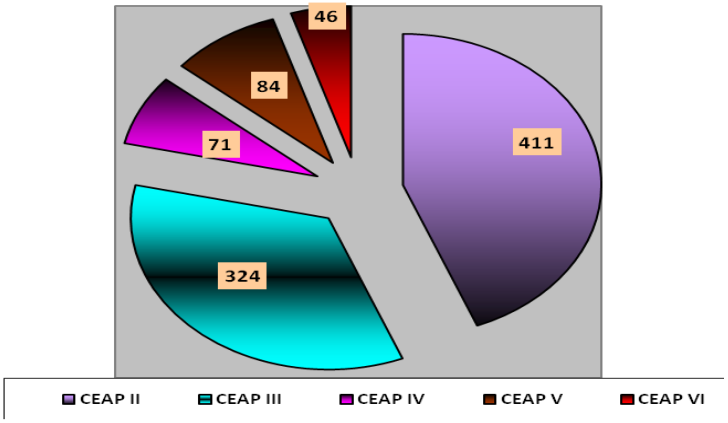


Chart 1. Case distribution according to the CEAP classification

Endovenous laser therapy is a thermal ablation technique using a laser fiber places within the vein.

The procedure is done with mild sedation and local anesthesia and lasts from 45 to 60 minutes. A catheter holding a laser fiber is inserted into the vein containing the defective valve, the laser energy is applied and the vein is sealed by the laser; the fiber and the catheter are then withdrawn from the vein. A special compression stocking is worn for about one week to facilitate healing. Most patients are back at work the next day.(13,14)

RESULTS AND DISCUSSIONS

Of the 60 patients included in the study, 42 (70%) cases were women, while 18 (30%) men. The age of patients was 56,06 years on average. Most patients were fit for work, while 33,85% were aged over 50.

Effect on a leg was found in 48 patients (80%) and on both legs in 12 (20%). When EVLT was performed on both legs, clinical and instrumental data was evaluated for each individual member. Thus, in total, there were 92 examined extremities. Primary etiology (varicose veins) of CVI was found in 47 cases (78,3%), and secondary etiology (post-thrombotic syndrome) in 13 (21,6%).

The clinical picture, recorded in the research group patients, was made evident by the multitude of complaints, which did not correspond with the clinical manifestations commonly associated with the presence of lower limb chronic venous pathology. Signs corresponding to the clinical criteria of the CEAP classification, in the research group patients, were defined as recommended by the International Union of Phlebology (Rome, 2007): CIV class (hyper pigmentation, eczema, lipodermatosclerosis, and white atrophy), CV class (healed trophic ulcer) and CVI class (active trophic ulcer). Most active venous trophic ulcers are characterized by an important diameter (>2 cm), major surface (>5 cm2), great depth, significant microbial contamination.

The majority (84,61%) of patients noted the presence of repeated stationary hospitalizations for symptoms conditioned by CVI. Obviously, the studied patients showed advanced CVI for a long time, with significant severity, repeated hospitalizations and insistence on complex treatment, but with reduced efficiency.

Finding of the VSM associated reflux was recorded in 52 cases and VSm in 8 cases, while the simultaneous presence of the reflux in both saphenous trunks was observed in 5 cases. The association of the perforator reflux with only the vertical deep one was found in 14 cases. The presence of the pathological reflux in the three venous systems of the lower limb, at the same time, was identified in 9 cases. The duplex scan results, thus, indicate the high frequency of the perforator reflux – superficial and/or deep reflux association. This confirms that the advanced CVI, with active trophic ulcer as its most severe complication, develops on the background of a long and progressive pathological process which affects all anatomical components of the lower limb venous system.

According to the results of the studies conducted by R. Mendes and coauthors (2008), the interruption of the vertical superficial reflux in patients with CVI primary etiology may lead to the competency restoration of up to 80% of previously insufficient perforators. Those perforators' incompetence was considered independent of superficial reflux, these presenting, at best, a valve apparatus anatomical dysfunction. It is obvious that in patients with severe CVI most perforators will remain incompetent after the saphenous reflux closure. Results of the study show the importance of preoperative identification and mandatory subsequent closure of the pathological venous reflux, in patients with severe CVI.

Australian Medical Services Advisory Committee (MSAC) established in 2008 that the endovenous laser treatment for varicose veins"seems to be more effective in the short term, and, overall, at least as effective as junction ligation for the treatment of varicose veins". Also, in the statistics found in the available literature, it was noted that"rates of occurrence of

severe complications, such as DVT, nerve damage and numbness, post-op infections and hematoma, appear to be higher after ligation and stripping only after EVLT".(15) A study on 516 veins treated by Elmore and Lackey, over a +70 month period, reported a success rate of 98,1%. In our case, as the EVLT treatments was applied on a number of 5 patients, over a time period of about 38 months, the obtained result was not the desired one.

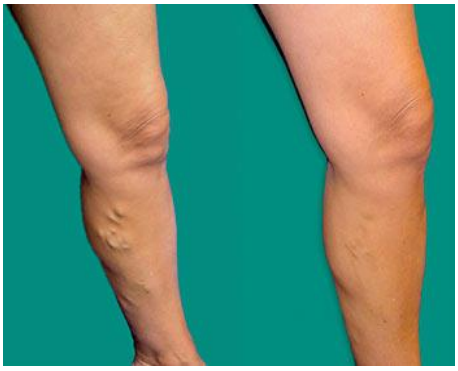


Figure 1. Pre- and post-surgery picture. G.S., 48 yo - CVI CEAP II. Hydrostatic varicose, lower left limb, 2nd stage

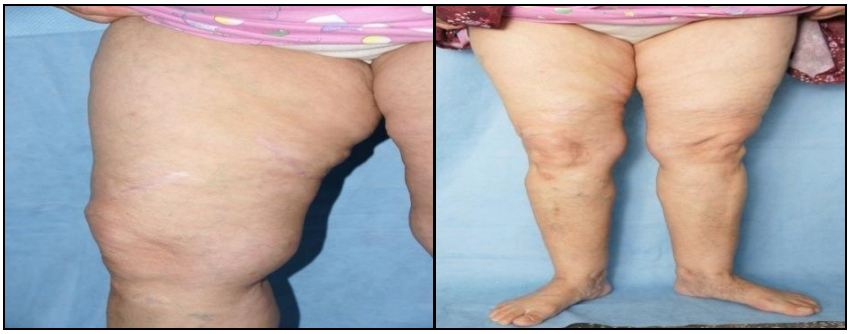


Figure 2. C.V., 57 yo - CVI CIV. Hydrostatic varicose, lower left limb; Recurrent varicose, lower right limb. Cystocele: Obesity, 3rd degree

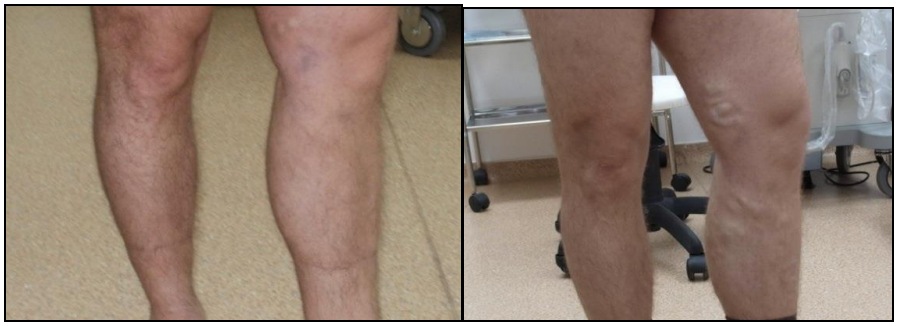


Figure 3. Pre- and post-surgery picture (two weeks after surgery)

CONCLUSIONS

Laser therapy (ILVO – intralumenal vein occlusion) is a minimally invasive procedure that does not require hospitalization; the recommended anesthesia is a local one, thus removing the risks and complications of other types of anesthesia and the adverse effects of anesthetic drugs, representing a quantum leap in ambulatory surgery of hydrostatic varicose.

Given the nature of these new minimally invasive procedures, treatment can be easily repeated in order to complete the results of the first surgery, in the rare cases of relapse. An ultrasound will confirm the need for EVLT treatment. In some individuals, the symptoms are more subtle. In both cases, the reflux is present and easily demonstrated through ultrasonography.

It is the most modern surgical treatment of varicose veins without stripping and consists of thermal photocoagulation with tissue contraction and destruction of the collagen in the vessel wall, thereby leading to the obliteration and/or destruction of the treated veins.

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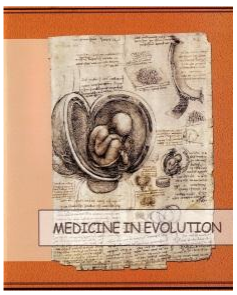
Morbidity and mortality in extremely low birth weight newborn



Manea A.M.[1,2], Cioboată D.[2], Dobre M.[2], Bilav O.[2], Boia M.[1,2]

[1]*"Victor Babeş" University of Medicine and Pharmacy Timişoara*
[2]*„Louis Turcanu" Children's Emergency Hospital, Timisoara, Romania*

Correspondence to:
Name: Marioara Boia
Address: Str. Gospodarilor nr. 42. Giroc 2
Phone: +40 740137597
E-mail address: marianaboia@yahoo.com

Abstract

Premature birth, defined as birth that occurs before 37 weeks of gestation, is one of the most important determinants of neonatal morbidity and mortality. Development of modern methods of neonatal intensive care in recent decades has led to increased survival rates among premature newborns, especially premature infants with extremely low weight at birth. These procedures generally aimed at survival and immediate recovery of premature, are known to have a negative impact on blood circulation brain in very low birth weight premature and can generate hypoxic / ischemic changes in central nervous system, leading to neurological complications and major impact on neonatal mortality. The authors wish to establish the incidence of extreme prematurity and the impact of procedures in intensive care unit on neurologic status of extremely low birth weight newborn.

Keywords: extreme prematurity, complications, mortality.

INTRODUCTION

Premature birth, defined as birth that occurs before 37 weeks of gestation, is one of the most important determinants of neonatal morbidity and mortality with long-term negative consequences. It is estimated that every day, more than 41,000 children worldwide are born before the normal gestational age (1).Prematurity account for 75% of mortality and more than half of perinatal morbidity (2).The risk of acute neonatal illness decreases with gestational age, reflecting the fragility and immaturity of the brain, lungs, immune system, vascular system and gastrointestinal system of premature.

Hypoxic-ischemic lesions, impaired autoregulation of cerebral blood flow, inflammatory and infectious perinatal aggression can lead to intraventricular hemorrhage and periventricular leukomalacia and on a long term to cerebral palsy, cognitive deficits, behavioral disorders and epilepsy (3).

Intraventricular hemorrhage incidence increases with decreasing gestational age. At newborns with extreme prematurity and weighing 500-999 grams, IVH occurs in about 45% of cases(4).

Periventricular leucomalacia (PVL): an ischemic lesion of periventricular white matter, characteristic to premature, its incidence is higher in premature infants with extremely low birth weight.

During hospitalization approximately 65 percent of infants with birth weights less than 1,000 grams have at least one infection They contract these infections at birth from their mothers or after birth through their lack fully developed immunoprotective functions.(5)

The most common hematologic complication in preterm infants is anemia of prematurity and it occurs due frequent blood sampling, the shorter survival of red blood cells in preterm infants and a greater need for red blood cells with growth. Preterm infants often need red blood cell transfusions, but very low birth weight and extremely low birth weigh newborn need sometimes multiple transfusions (6). These procedures that generally aim the survival and immediate recovery of the premature are known to have a negative impact on cerebral blood flow at very low premature thus increasing the risk of neurological complications..All these, adding also neonatal infection which is constantly present, generate hypoxic/ischemic modification at the level of CNS with potential for lesions, leading to neurological complications with major impact on neonatal mortality.

Objectives

The study wants to establish:the incidence of extremely low birth weight premature comparative to other categories of premature; repartition by sex; the impact of procedures in the neonatal intensive care unit on the neurological status of newborn with extreme low birth weight.

MATERIAL AND METHODS

The study was carried out in the Premature -Neonatology Department of the Clinical Emergency Hospital for Children „L. Țurcanu”and Neonatology”Bega”Department of the Emergency County Hospital Timisoara. over a period of 2 years (2012-2013).

The study included a group of 213 premature babies and a control group consisting of 88 apparently healthy newborns.

The lots were divided by weight, as follows:

- lot 1: ELBW newborn with 42 premature (< 1000 grame)
- lot 2: VLBW newborn with 84 premature (<1500 grame)
- lot 3: LBW newborn with 87 premature (<2500 grame)

The three groups were compared with a control group 4 control, which included 88 newborns (>2,500 kg).

RESULTS

The values of the APGAR scores are rising significantly, with increasing weight of the premature infants. There were significant differences between the Apgar score in preterm ELBW group and the other 3 groups studied: VLBW, LBW and control (table 1)

Table 1. APGAR score values for the 4 groups

Variable	Lot	N	Mean	Std. Deviation	Std. mean error	95% confidence for the mean		Minim	Maxim
						Lower limit	Upper limit		
APGAR Scor	ELBW	41	3.1	1.54	0.24	2.6	3.6	1.00	6.00
	VLBW	84	5.8	1.73	0.19	5.4	6.1	1.00	9.00
	LBW	88	6.7	1.45	0.15	6.4	7.0	1.00	9.00
	CONTROL	88	8.7	0.78	0.08	8.6	8.9	7.00	10.00
	Total	301	6.5	2.27	0.13	6.3	6.8	1.00	10.00

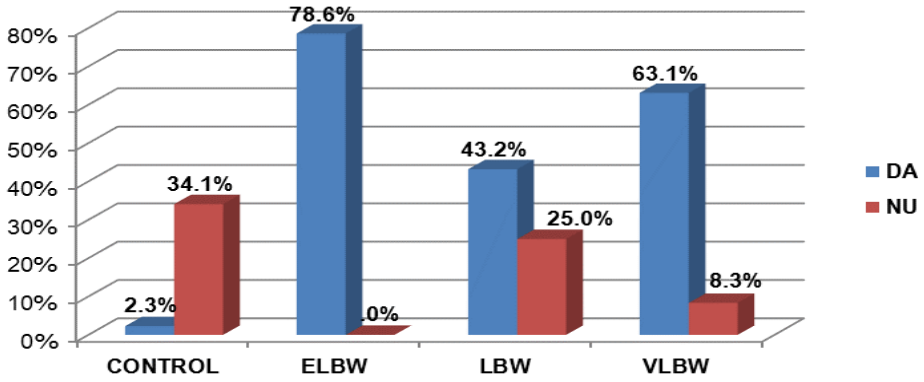


Figure 1. VPPO2 values in the 4 groups

There were significant differences between the proportions of the 4 groups by the necessity of using VPPO2. Also, the highest percentage of usage of VPPO2 was in the group with ELBW premature (fig.1).

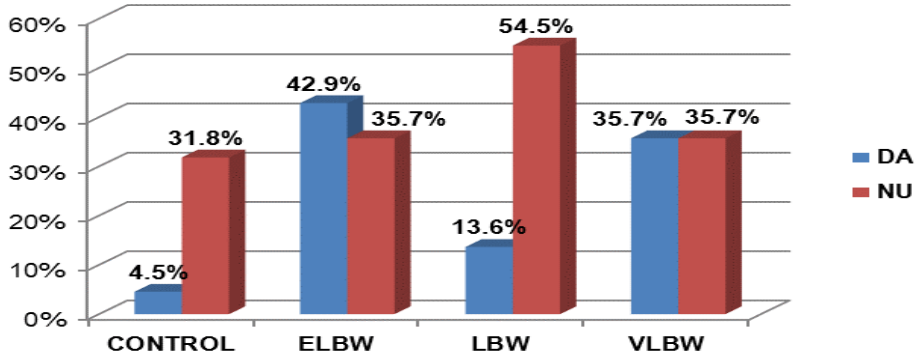


Figure 2. Erythrocyte mass values at the 4 groups

There are significant differences between the proportions of the 4 groups depending on the need of red blood cell transfusion. The percentage of premature who required red blood cell transfusion was the most increased in the group of ELBW premature newborns compared with the other groups and the control group (fig. 2).

It resulted in significant differences between the sentences of the four groups according to the type of infection (table 2)

Table 2. Comparisons between the 4 groups depending on the infection

Lot	Infection								Total
	-	Fungi	Gram -	Gram - Fungi	Gram +	Gram + Fungi	Gram + Gram -	NO	
control	27	1	2	0	3	0	0	55	88
	30.7%	1.1%	2.3%	0%	3.4%	0%	0%	62.5%	100%
ELBW	0	2	1	1	5	2	2	29	42
	0%	4.8%	2.4%	2.4%	11.9%	4.8%	4.8%	69%	100%
LBW	8	1	2	1	10	5	1	60	88
	9.1%	1.1%	2.3%	1.1%	11.4%	5.7%	1.1%	68.2%	100%
VLBW	6	3	9	0	3	6	7	50	84
	7.1%	3.6%	10.7%	0%	3.6%	7.1%	8.3%	59.5%	100%

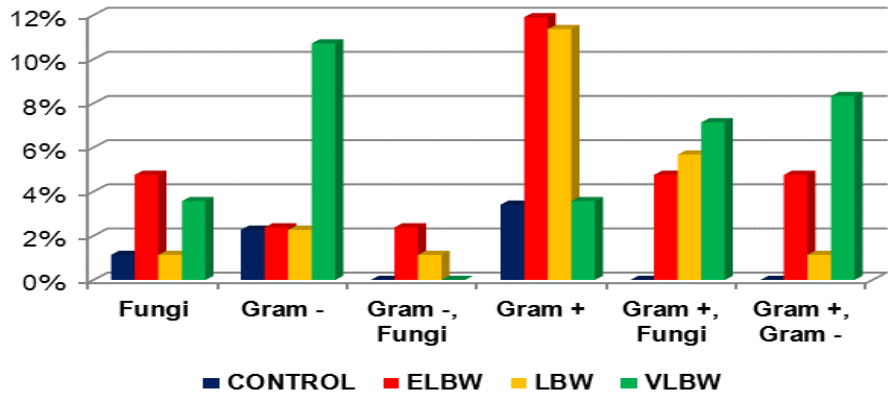


Figure 3. Comparisons between the 4 groups depending on the infection

Gram + and fungal infections were present in a higher percentage in the group of ELBW premature, while infections with Gram - Gram + associated with fungi and gram - in association with gram + were present in the VLBW group (fig.3).

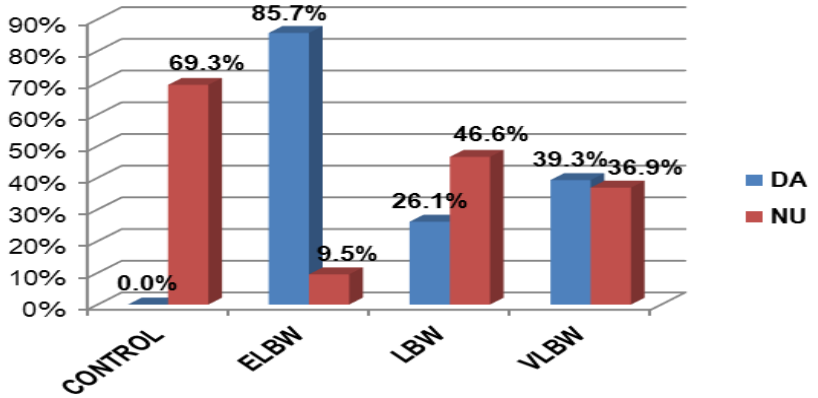


Figure 4. Neurological complications rates in the 4 groups

There are significant differences between the 4 groups according to the presence of neurological complications. In the ELBW premature lot the neurological complications were present in a proportion of 85.7% (fig. 4)

CONCLUSIONS AND DISCUSSIONS

1. The APGAR scores values are increasing significantly with increasing birth weight of premature infants. There were significant differences between Apgar score at ELBW preterm group and the other 3 groups studied: VLBW, LBW and control.

2. There were significant differences between the 4 groups according to MER transfusions.

3. The study confirmed the impact of immediate neonatal adaptation (Apgar score) and of certain techniques and therapeutic procedures (VPPO2, transfusion red blood cells) in the general neonatal management on the clinical outcome of premature newborn.

4. All these procedures mentioned that generally aim the survival and immediate recovery of the premature are known to have a negative impact on cerebral blood flow at very low premature thus increasing the risk of neurological complications.

5. There are significant differences between the 4 groups according to the presence of neurological complications. In the group of ELBW preterm the rate of complications was present in a proportion of 85.7%.

6. There were found significant differences between the 4 groups depending on the survival rate, death occurring in 61% in premature infants ELBW.

7. The objective analysis of the particularities of premature newborns leads to the early interpretion of the warning signs in a way that detecting complications allows promptly clinical and therapeutic approach.

8. The early track of neurological complications leads to a reduced rate of long term sequels, of neurological and motor disable as well as of mortality, all these being proportional with early approach.

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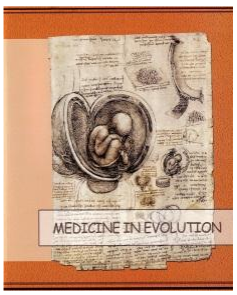
Contrast-enhanced ultrasound – a well-established tool in the assessment of the severity of acute pancreatitis?



Ardelean M.[1], Ardelean O.[2], Sporea I.[1], Sirli R.[1], Popescu A.[1], Danila M.[1], Timar B.[3], Buzas R.[2], Lighezan D.[2]

[1]Department of Gastroenterology and Hepatology,"Victor Babeş"University of Medicine and Pharmacy, Timişoara, Romania
[2]Municipal County Hospital,"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania
[3]Department of Informatics and Biostatistics,"Victor Babes"University of Medicine and Pharmacy, Timisoara, Romania

Correspondence to:
Name: Ovidiu Ardelean
Address: 60 C, Octavian Goga str, ap. 1, 300525 Timisoara, Romania
E-mail address: ovi.ardelean@gmail.com

Abstract

Introduction: Acute pancreatitis (AP) remains a pathological entity often met in the clinical field, sometimes with a high severity. Early detection of severe cases is important, because it can provide information regarding the evolution and therapeutical approach.

Aim: of our study is to investigate the applicability of CEUS in the assessment of acute pancreatitis, as well as its diagnostic accuracy in the evaluation of the severity of pancreatitis, using Computed Tomography as a reference standard method.

Material and Methods: A retrospective, monocentric study was performed in 79 consecutive patients admitted in our Department between Oct. 2009 and Oct.2014. All the cases respected the same approach: standard US and CEUS in the same session, followed by CT examination 48h after the onset of the disease. A CEUS final diagnosis was established after the contrast agent completed its course by comparing the vascular enhancement pattern of each lesion following contrast US, with the typical one described in the EFSUMB guidelines from 2008, updated in 2011. We compared the results of the enhancement pattern in our study with a second line contrast imaging method (CT), considered to be the reference method. AP severity was graded according to Balthazar index. Seven patients were excluded from the study because of a chronic pancreatitis (2), incomplete ultrasound imaging of the pancreas (2) and for having a MRI as a reference method (3).

Results: Finally 72 patients (mean age 51.3+/- 14.2 years) met the inclusion criteria. The rate of a conclusive diagnosis in our study was 68 out of 72 (94.4%) CEUS cases according to the enhancement pattern stated in the EFSUMB guidelines. In 63 out of 72 cases (87.5%), there was a perfect concordance between CEUS and CT. Necrosis was found by CT in 51.4% of the cases. There was a significant correlation between CT and CEUS for the extent of necrosis ($r= 0.945$, $p<0.001$) and for the CT severity index, based on Balthazar grade ($r= 0.951$, $p<0.001$). The sensitivity, specificity, positive predictive value and negative predictive value for detecting severe acute pancreatitis were 94.6%, 100%, 100% and 94.6%.

Conclusion: CEUS has shown to be of clinical value in the assessment of pancreatic necrosis and has a high diagnostic value in the evaluation of AP severity. The concordance between CEUS and CT turned to be 87.5% in our study, which leads to the conclusion that CEUS is comparable to CT in the evaluation AP severity, in cases in which the pancreas can be evaluated by US.

Keywords: Contrast-enhanced ultrasound, acute pancreatitis, necrosis, severity index.

INTRODUCTION

Acute pancreatitis (AP) remains a pathological entity with high mortality (2%-15%), going to 30% into severe forms (1). The detection of severe cases is important, because it can provide prognostic information and it may have therapeutic implications. Early diagnosis of severe necrosis can reduce mortality and morbidity (2).

Ultrasonography (US) is the first imaging method used in assessment of AP onset and complications. It is non-invasive and non-radiating, very well accepted by the patients, extremely effective in emergency unit (1,2). US assesses the changes in pancreatic parenchyma: size, shape, echogenity, echostructure, Wirsung's duct, complications. (3).

At present moment, computed tomography (CT) is considered the reference standard for diagnosis and staging AP, recommended within 72hours after the symptom onset. CT allows the detection of pancreatic necrosis and fluid collections (2,3,4). Other imaging technique with a safer profile than CT, such as magnetic resonance (MRI) has also been used to detect severe cases. This technique is as accurate as CT in detecting pancreatic necrosis and staging acute pancreatitis severity, avoiding radiation exposure and iodinated contrast allergies (3).

Recently, CEUS has been proven to be a valuable technique which can provide information on the vascularization of the pancreatic parenchyma and can differentiate between areas of inflammation and areas of necrosis. It is a non-irradiant method that can be performed repeatedly providing real-time information (2). It is known that the perfusion of the pancreas is well correlated with the enhancement of the gland's parenchyma. The blood supply of the pancreas is entirely arterial; thus, the enhancement of the gland begins almost together with the aortic enhancement (between 12-20s after contrast injection). Afterwards there is a progressive wash-out of contrast medium (3). A report stated that CEUS has comparable results in AP as CT provides (5).

The **aim** of our study is to investigate the applicability of CEUS in the assessment of AP, as well as its diagnostic accuracy in the evaluation of pancreatitis severity, using CT as a reference standard method.

MATERIAL AND METHODS

A retrospective, monocentric study was performed in 79 consecutive patients admitted in our Department between Oct. 2009 and Oct.2014. The study was conducted in full accordance with the Declaration of Human Rights (Helsinki, 1975) and with its further revisions (2000 revision-Edinburgh), and was approved by the local ethical committee. Patients gave their written consent prior to CEUS examination, in order to use their data in different further studies.

Patients

Inclusion criteria consisted of the following: patients older than 18, diagnostic of AP based on clinical criteria and confirmed by biology, ultrasonography examination, CT examination (according to our Department's protocol) (it's a protocol established by our department- we investigate an AP first with biology, US, CEUS and CT). Each patient underwent a B-mode US examination that evaluated the pancreatic parenchyma: it's echostructure, size, shape; the bursa omentalis, the presence of peripancreatic or distal collections and/or complications. If the pancreas was well seen in standard US, in the same session a pancreatic CEUS examination was performed. CT exam was available in each patient and considered the"gold standard"for establishing the final diagnosis.

Exclusion criteria consisted of the following: improper visualization of the pancreatic parenchyma, US signs of chronic pancreatitis, unavailable CT as a reference method or for

having MRI as a gold standard method which couldn't provide a Balthazar score, acute heart failure, pregnancy, acute coronary syndrome, history of allergic reactions. Seven patients were excluded from the study because of a chronic pancreatitis (2), incomplete ultrasound imaging of the pancreas (2) and for having a MRI as a reference method (3).

Methods

The diagnosis of acute pancreatitis (AP) consists mostly in imaging techniques- ultrasonography (US), contrast-enhanced ultrasound (CEUS), computed tomography (CT) and magnetic resonance (MRI).

All the cases respected the same approach: standard US and CEUS in the same session, followed by CT examination 48h after the onset of the disease. Ultrasonography and CEUS were performed in a highly experienced center, by 4 experienced physicians, 3rd level according to the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) classification of expertise levels. Firstly, each patient underwent abdominal US to observe the size, shape edge, echostructure of the gland, aspect of bursa omentalis (shape, size), the presence of abdominal fluid collections, ascites or pleural effusion (2,3) and complications.

CEUS was performed on an Accuson S2000 US system (Siemens, Erlangen, Germany) with a low mechanical index: 0.09 to 0.11. We considered all the inhomogeneous lesions of the pancreatic and peripancreatic areas (that didn't have the same aspect as the pancreas - i.e, which were hyper or hypoechoic) including cystic lesions, as complications of AP.

The protocol for contrast enhanced examination consisted of a bolus of 2.4 ml of second generation contrast agent-sulphur hexafluoride filled microbubbles with a phospholipid peripheral shell- SonoVue (Bracco, Milan, Italy) which was injected into an antecubital vein, followed immediately by 10ml of normal saline solution (0.9% NaCl). Real-time observation of the lesion's blood perfusion was no less than 120s, during which the patient was instructed to maintain smooth breathing. Dynamic images were preserved for later analysis. A"real-time", dynamic observation of the contrast enhanced phases – arterial (early stage of enhancement, 10-30 seconds) and late (delayed stage of enhancement, 30-45 until 120 seconds following contrast injection) – began immediately after the contrast bolus (2,3,6,7). The assessment of the contrast agent in the area of interest was made considering the pancreatic parenchyma as reference (1). A CEUS final diagnosis was established after the contrast agent completed its course, by comparing the microvascular enhancement pattern of our lesions with the typical ones described in the EFSUMB guidelines from 2008, updated in 2011 (8,9). We compared the results of the enhancement pattern in our study with a second line contrast imaging method (CT), considered to be the reference method and identified the accuracy of CEUS in the characterization of the severity of an AP.

Pancreatic necrosis found both on CEUS and CT was evaluated as a non-enhanced area in the pancreatic parenchyma. A small, peripancreatic hypoechoic halo that enhanced after contrast was considered in CEUS as peripancreatic inflammatory changes (Balthazar's C), while if the halo was better seen after the contrast- didn't enhance, it was interpreted as a small collection (Balthazar D). Acute pancreatitis severity was graded according to Balthazar's criteria for the extent of pancreatic and extrapancreatic fluid collections, degree of necrosis, and the combined severity index. The severity index described for CT was also used for CEUS (5, 10). In establishing a correlation between CEUS and CT in detecting accurately an AP, we excluded from the studied group the CEUS cases with MRI standard imaging method (3 patients). So 72 CEUS cases remained in the final statistics.

According to the enhancement pattern as compared with the surrounding parenchyma, the area of interest was categorized as iso- or nonenhancing. As stated in EFSUMB guidelines, the enhancement pattern should be compared to the surrounding

parenchyma. The lesion might be hyperenhancing, isoenhancing, hypoenhancing or nonenhancing

1. Isoenhanced: the lesion's enhancement was similar to the surrounding pancreatic parenchyma (according to the echogenity of the image presented in US);
2. No enhancement: the lesion did not enhance at all following contrast.

Criteria used for assessing lesions in an AP (2, 9):

Acute pancreatitis	Ultrasonography	CEUS
Inflammatory aspect	Hyperechoic	Isoenhanced (stated in EFSUMB guideline 2008)
Necrotic aspect	Hypoechoic	No enhancement
Fluid collections	Anechoic	No enhancement

If the pancreatic region was clearly visible on US, CEUS was used in the follow up of AP after CT staging, in order to reduce the number of CT examinations, according to EFSUMB guidelines 2011 (9).

Statistical analysis

Data were collected and analyzed using the SPSS v.17 software suite (SPSS Inc. Chicago, IL, USA). Data are presented as mean ± standard deviations for continuous variables with Gaussian distribution. For analyzing the diagnosis quality of pancreatic CEUS we used sensitivity (Se – the number of true positive divided to the total number of positives), specificity (Sp – the number of true negatives divided to the total number of negatives), positive predictive value (PPV – the number of true positives divided to the total number of positives at test) and negative predictive value (NPV – the number of true negatives divided tot the total number of negatives at the test). Accuracy was defined as the percentage of correctly classified patients from the total analyzed ones. A value of $p<0.05$ was considered statistically significant and was taken into consideration. The Spearman's rank correlation coefficient was used to assess the relationship between CEUS and CT findings (the areas and the extent of the necrosis lesions).

RESULTS

We investigated 79 CEUS examinations in 79 patients. Out of the 79 cases, we excluded 7 cases, 2 for being a chronic pancreatitis, 2 for not having in US a proper window for visualization, and 3 for having a MRI as a gold standard method, which couldn't provide a Balthazar score.

So, finally 72 cases in 72 patients were taken into consideration.

The patients' characteristics are presented in Table I.

Table I. The patients characteristics

Mean age	51.3+/-14.2 yrs
Sex ratio	29 F (40.2%) 43 B (59.7)
AP's etiology	25 alchool abuse (34.7%) 39 biliary (54.2%) 4 hypertrigliceridemia (5.5%) 4 unknown (5.5%)
Reference gold standard method	72 CT (100%)
CEUS diagnosis	Necrosis- 35 (48.6%) Normal pancreatic parenchyma- 26 (36.1%) Collection- 4 (5.5%) Cystic lesions- 3 (4.2%) Inconclusive- 4 (5.5%)
Final diagnosis by CT	Necrosis- 37 (51.4%) Normal pancreatic parenchyma- 26 (36.1%)

	Collection- 5 (6.9%) Chronic pancreatitis- 1 (1.4%) Cystic lesions-2 (2.7%) Cystic tumor- 1 (1.4%)

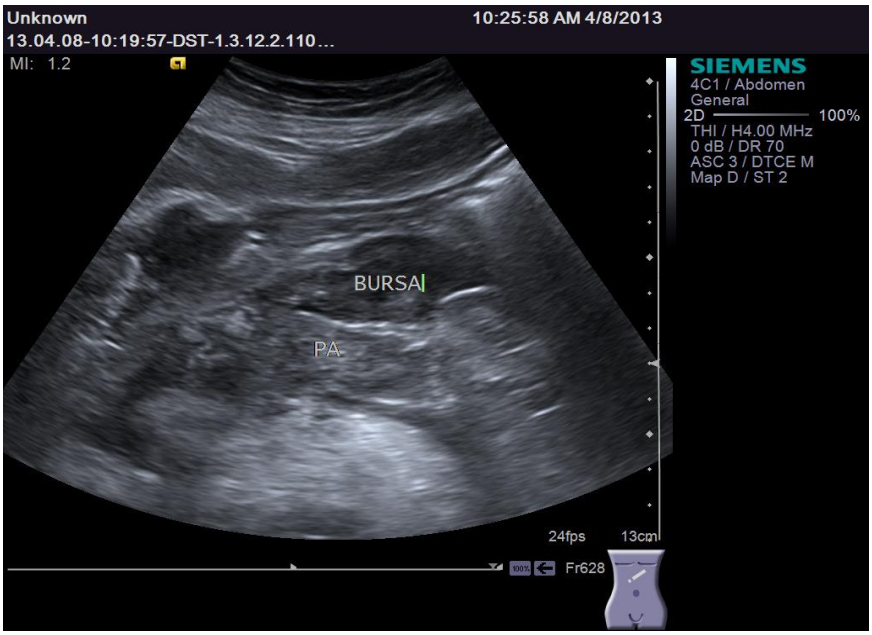


Figure 1. Infrapancreatic, inhomogeneous, liquid collection in an acute, severe pancreatitis. Large omental space in front of the pancreas in standard US Scan

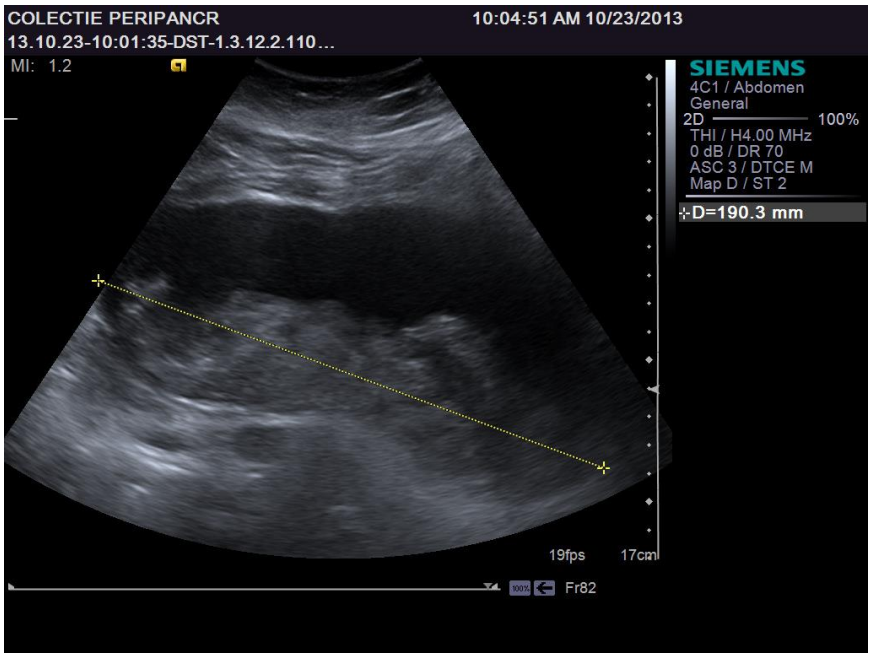


Figure 2. Large, inhomogeneous peripancreatic collection in an acute pancreatitis (body and tail of the pancreas) in standard US Scan

The rate of a conclusive diagnosis in our study was observed in 68 out of 72 (94.4%) CEUS cases according to the enhancement pattern stated in the EFSUMB guidelines (8, 9). In 63 out of 72 cases (87.5%), there was a perfect concordance between CEUS and CT as the"gold standard"imaging method regarding both the necrotic areas and peripancreatic inflammatory aspects.

CEUS and CT findings in patients with AP are presented in Table II.

Table II. CEUS and CT findings in patients with AP

	CEUS	CT
Balthazar grade		
B	23	21
C	7	9
D	5	7
Necrosis		
None	37	35
<30%	24	22
30-50%	7	9
>50%	4	6

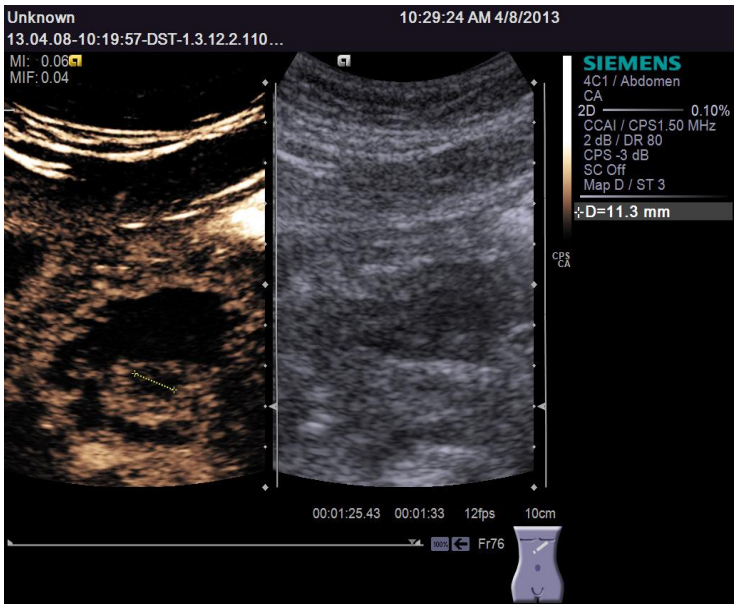


Figure 3. A necrotic lesion in the body of the pancreas during an acute episode of severe pancreatitis in CEUS examination

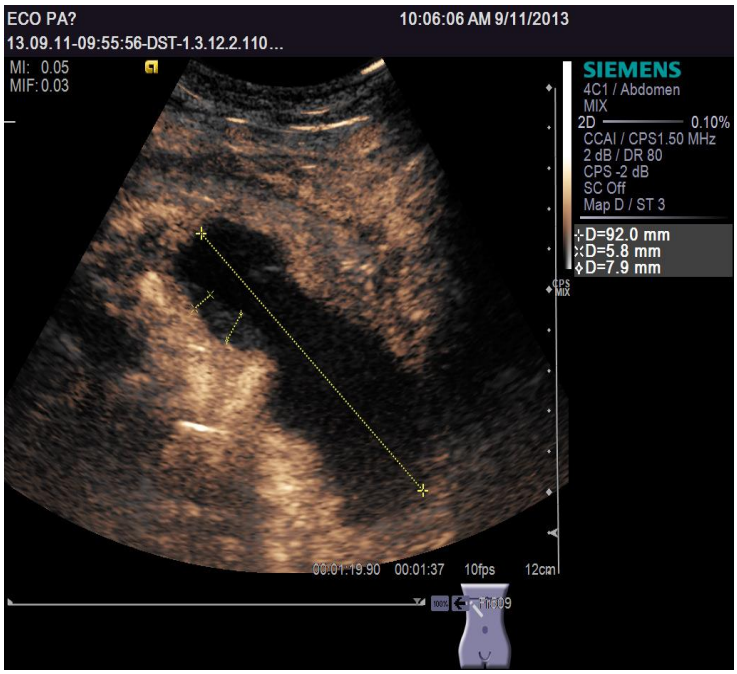


Figure 4. Necrotic area that occupies the whole pancreatic lodge in CEUS examination

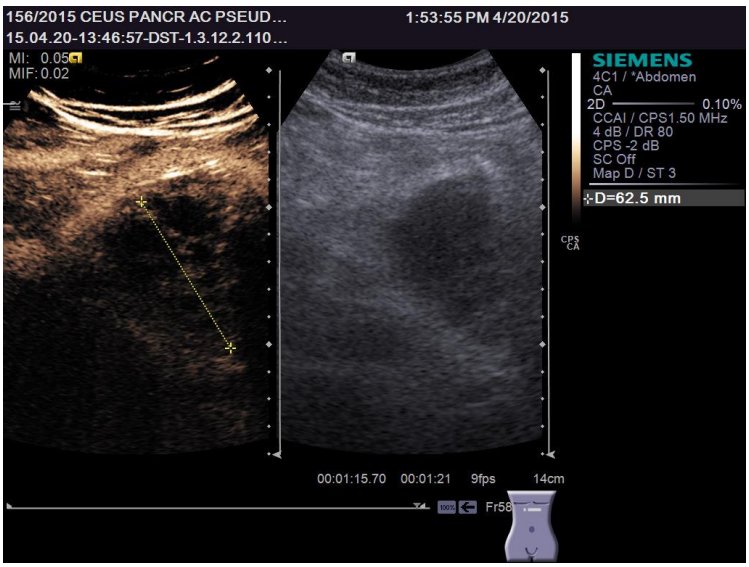


Figure 5. Large collection in CEUS examination in an acute pancreatitis

Necrosis was found by CT in 51.4% of the cases. Regarding the areas of necrosis, all but 2 cases were correctly diagnosed by CEUS (r= 0.945, p<0.001). In these 2 cases the extent of necrosis was less than 30%, being overestimated by CEUS, localized in the body and tail of the pancreas. The sensitivity, specificity, positive and negative predictive value for detecting necrosis by CEUS are included in the table 3. The severity of necrosis was estimated similarly by CEUS and CT in all patients, except for 4 cases of necrosis, where the grade of necrosis was underestimated by CEUS. In 2 patients with necrosis localized in the body and tail, the CT percentage of necrosis was estimated to be 30-50%, while CEUS showed less than 30% necrosis. In another 2 patients, with necrosis located in the pancreatic head and tail considered more than 50% on CT, CEUS estimated the necrosis as being 30-50% of the gland (r=0. 896, p<0.01).

A strong correlation between CEUS and CT findings was found regarding the CT severity index, based on the Balthazar grade (r=0.921, p<0.001). The sensitivity, specificity, positive predictive value, negative predictive value for detecting severe acute pancreatitis are also presented in Table III. The comparison of CT and CEUS results in estimating the spread of acute fluid collections and the extent of necrosis (Balthazar's grade) revealed a significant correlation between the two imaging techniques (Table IV).

Table III. Necrosis and Balthazar grade (severity)

NECROSIS	**Result**	**95% CI**
Sensitivity	94.6%	81.8% to 99.3%
Specificity	100%	90% to 100%
Positive Predictive Value	100%	90% to 100%
Negative Predictive Value	94.6%	81.8% to 99.3%
SEVERITY	**Result**	**95% CI**
Sensitivity	75%	47.6% to 92.7%
Specificity	100%	93.6% to 100%
Positive Predictive Value	100%	73.5% to 100%
Negative Predictive Value	93.3%	83.8% to 98.1%

Table IV. Spearman's correlation coefficient between CT and echo enhanced ultrasound findings

Parametres	**CT vs CEUS**
Severity Index	r=0.921
Balthazar's grade	r=0.945
Extent of necrosis	r=0.896

DISCUSSIONS

Ultrasonography is a preferred imaging method in the evaluation and follow-up of pancreatic complications at the onset and during an AP, because of its ability to detect necrotic or pseudocystic lesions, while the qualitative diagnosis with US has turned to be a little difficult (10). Thus, the role of US in the first days of illness is limited because differentiation between necrotic and non-necrotic areas can't be made (3). The dynamic character of US examination is very useful during the evolution of AP. Until now, the mainstream diagnostic method for pancreatic lesions has been CT, which shows a higher sensitivity and specificity in the detection and staging of lesions (10).

The introduction of CEUS has led to major improvements in the diagnostic capabilities of US. CEUS takes advantages of its special features: the high contrast and spatial resolution, the use of a blood-pool microbubble contrast medium and the real-time, dynamic evaluation of pancreatic lesions' enhancement, filtering the background tissue signals (11).

Our study confirms the value of CEUS in detecting pancreatic necrosis and a reliable method in predicting the severity of an episode of acute pancreatitis. The Se, Sp, PPv and NPv in our study are almost the same as the one stated in Rippoles T et al. study (3). 94.6%, 100%, 100% and respectively 94.4% in our study are slightly better than the values described by Ripolles: 86%, 97%, 95% and 90%. This fact might be because in our study we only assessed the presence of necrosis by imaging appearance, while in Rippoles et al. (3) study, there was a significant correlation between pancreatic necrosis and Ranson criteria. Also the pattern of our study didn't refer to the Ranson criterias, like Rippoles (3) did. More biological markers were used to score and predict the presence of necrosis. As also stated, in the study of Lu Q1 et al (12), the Se and Sp (90%, 95%) in the diagnosis of pancreatic parenchyma necrosis appears to have almost the same values as in our study (94.6%, 100%). The values slightly differ from our study, possibly because this present Japanese paper is a prospective, double-blind study. Another study, that confirms the great feasibility of CEUS in detecting pancreatic necrosis is presented by Zhihui Fan et al. (10) where the conclusion of the study is that there is no significant difference between CEUS and CT in diagnosing necrotic areas in an (AP) ($p>0.05$) with a Se of almost 90%, a Sp of 91.9% and accuracy of 88.9%. (10).

The correlation between CEUS and CT regarding the extent of the necrosis was significant ($r=0.945$) and with the Balthazar grade ($r=0.951$). This was similar with the study of Rippoles et al (3) where the correlation between CT and CEUS was estimated for the extent of necrosis ($r=0.893$) and Balthazar grade ($r=0.926$).

For detecting necrosis, there was a discordance between our study and the one of Rickets et al's study (5). In their study the necrosis was detected with CEUS in all cases, while we missed 2 cases with mild necrosis (94.5% sensitivity). This might explain the false-negative cases. Being located in the body and tail, these regions might be hard to be assessed because of the interposition of abdominal gas. The pancreatic borders on US, and thus on CEUS are less precise than on CT, especially after contrast injection. Therefore, small areas of necrosis localized in the periphery of the gland can be missed or misinterpreted as a small collection in CEUS (3). As stated in Lu Q's study (12), the time intervals between CEUS and CT examinations might be a possible cause of missed cases of the two imaging techniques.

There were 4 cases of necrosis underestimated by CEUS in our study. In 2 patients a diffuse enlargement of the gland was noticed on US, while on CEUS just a small peripancreatic halo appeared and being interpreted as Balthazar B. The CT showed inflammatory changes in the peripancreatic fat. Taking into account that we considered in our study CT the"gold standard method", we considered the results presented by CT as definitory and we compared our CEUS' results referring to the CT's ones. In the other 2 underscored cases CEUS presented the results as being Balthazar C, while the CT showed peripancreatic inflammatory modifications with a small collection. So, possible causes of the

false-positive cases might be of peripancreatic fluid lesion, areas that might be reversible in time. (13).

As for the number of collections, CEUS missed 1 collection, that was smaller than 2 cm. As Rippoles T et al's study (3) suggested, collections are better depicted by CEUS, because contrast agent increases the differences in the echogenicity between the pancreatic parenchyma and the collections, which do not enhance.

On the other hand, the present paper reveals an excellent correlation (95%) between CT and CEUS for detecting the CT severity index, based on the Balthazar score. As presented in Lu Q' study, the perfect correlation matches in 94%, with Se, Sp, PPv, NPv similar to those presented in our study. The result differ from that of Rickes et al, who found discordance between the two techniques in 5 patients (15%) (5). Although CT was considered as the gold standard in acute pancreatitis assessment to determine the diagnostic accuracy of CEUS, it is not clear whether it is really the reference standard in predicting severe acute pancreatitis for all cases (in Rickes' study, Ranson criterias were included).

The main limitation of the study was the relatively small number of cases taken into study; larger studies should be performed in order to implement CEUS as a single method in assessing the severity of an AP. But the present results are confident and promising. Together with other clinical information, these ultrasound parameters and their statistical analysis could help develop an ultrasonographic severity score in AP. CEUS examination for the detection of parenchyma necrosis, similar to CT examination, should be made 48h after the onset of the symptoms, in order to avoid underestimation of necrosis, due to the meteorism caused by the adynamic ileus. In our study we did not record at what time following AP onset the CEUS examinations were performed. Also, the video sequences of CEUS are more difficult to be handled than the static images of the CT. The patients' distribution might be different from other research groups, as most of the patients referred to our department had different courses of disease.

Last, another limitation of CEUS might be the occasionally restricted image resolution of deep regions and poor sonographic visualization of the gland due to overlying abdominal gas or to large amounts of abdominal fat. (11).

Current clinical guidelines state that CT is the imaging method of choice for the diagnosis and evaluation of an AP. CT shows complete visualization of the peripancreatic, retroperitoneal region and offers the clinician an image of the possible complications (3).

CEUS can be useful where CT is contraindicated, in patients with idiosyncratic reactions to iodinated agents, renal failure. Moreover, CEUS can be repeated as many times as it is necessary, in order to avoid extra radiation dose. That's why CEUS can be used as a follow-up imaging method in an AP.CEUS is a not very expensive method, available any time and US machine is mobile, allowing the investigation to be done at the patients' bed(3).

CONCLUSIONS

CEUS has shown to be of clinical value in the assessment of pancreatic necrosis and has a high diagnostic value in the evaluation of AP severity. The concordance between CEUS and CT turned to be 87.5% in our study, which leads to the conclusion that CEUS is comparable to CT in the evaluation of an AP severity (when the pancreas can be well seen by US). Therefore, CEUS can be an alternative, when CT is contraindicated. Further, larger studies are needed in order to introduce CEUS in the diagnostic algorithm for an AP.

None of the authors have any conflict of interest to disclose regarding this paper.

All the authors agreed to the publication of this paper

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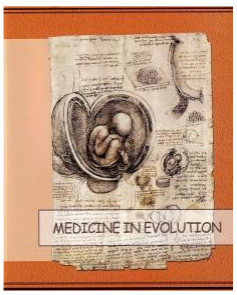
Cardiovascular risk profile of a group of high income patients addressed to a private clinic



Diaconu C.C.[1], Balaceanu A.[2]

[1]University of Medicine and Pharmacy"Carol Davila", Internal Medicine Clinic, Clinical Emergency Hospital of Bucharest, Romania
[2]University of Medicine and Pharmacy"Carol Davila", Internal Medicine Clinic, Clinical Emergency Hospital"Sf. Ioan", Bucharest, Romania

Correspondence to:
Name: Camelia Diacon
MD, PhD
Address: Clinical Emergency Hospital of Bucharest, 8 Calea Floreasca, Bucharest, Romania, Zip code 0114612
Phone: +40 726 377 300
E-mail address: camiluciemi@yahoo.com

Abstract

Introduction. Cardiovascular diseases are the leading cause of death in European countries. The profile of cardiovascular risk factors may differ between high income individuals and those with lower socioeconomic status. **The purpose of the study** was to evaluate the burden of cardiovascular risk factors in an adult population with high socio-economic level.

Material and methods. The study included 74 patients addressed to a private clinic from the north part of Bucharest, between June 1st-October 1st, 2014. In all these patients the physical exam and ECG were performed, together with usual blood tests. Their medical records were searched from the family doctor database.

Results. The mean age of the patients was 33.5±7.8 years old. The distribution by sex was: 52.70% women and 47.30% men. The distribution of the main cardiovascular risk factors in the group of study was: smoking 41.89%, dyslipidemia 39.19%, family history of cardiovascular diseases 29.73%, low physical activity 24.30%, obesity 16.21%, arterial hypertension 12.16%, type 2 diabetes 8.10%. Low physical activity was more frequent in women compared with men (28.20% versus 20%). Also, more women than men were dyslipidemic (48.71% versus 28.57%). Instead, more men than women had hypertension. Only 62.06% of dyslipidemic patients had hypolipemiant drug treatment.

Conclusions. Smoking was the main cardiovascular risk factor in our study, followed by dyslipidemia, family history of cardiovascular diseases, and lack of physical activity. Dyslipidemia and low physical activity were more frequent in women. Hypertension was more frequent in men. More than 1/3 of dyslipidemic patients did not have hypolipemiant treatment, mainly due to the fear of secondary effects.

Keywords: cardiovascular risk factors, smoking, dyslipidemia.

INTRODUCTION

Cardiovascular diseases are still the leading cause of death in European countries. The profile of cardiovascular risk factors may differ between high income individuals and those with lower socioeconomic status. Studies have shown inequalities in mortality and morbidity related to socioeconomic status, due to socioeconomic differences in smoking, excessive alcohol consumption and access to healthcare services. Since 1989, Romania has experienced a period of rising income inequality and major changes in the social and healthcare systems. Higher levels of income inequality at a national level are associated with poorer health across the society as a whole. Many analyses of the relationship between health and economy have shown that health is very unevenly distributed across society and that significant differences exist between people of different socio-economic status. Many risk factors, such as psycho-social factors, lower level of education, unhealthy food, bad working and living conditions, are more frequent in the lower socio-economic categories.

The **objective of the study** was to evaluate the burden of cardiovascular risk factors in an adult population with high socio-economic level (as measured by education, income and occupation).

MATERIAL AND METHODS

The study included 74 patients addressed to the family doctor of a private clinic from the north part of the capital of the country, the most developed area, between June 1st-October 1st, 2014. In all these patients the physical exam and ECG were performed, together with usually blood tests (complete blood count, lipid profile, blood sugar). Their medical records were searched from the family doctor database. Education level was categorized as higher secondary education (up to 12 years) and tertiary education (faculty). All the patients included in the study had a monthly income at least 3 times higher than the average gross wage in the Romanian economy (2298 RON in 2014). The level of physical activity was self-reported as low, normal or regularly doing sport.

RESULTS

The mean age of the patients was 33.5±7.8 years old. The distribution by sex was: 52.70% women and 47.30% men (Fig.1). The distribution of the main cardiovascular risk factors in the group of study was: smoking 41.89%, dyslipidemia 39.19%, family history of cardiovascular diseases 29.73%, low physical activity 24.30%, obesity (body mass index ≥ 30 Kg/m^2) 16.21%, arterial hypertension 12.16%, type 2 diabetes 8.10% (Fig.2). Low physical activity was more frequent in women compared with men (28.20% versus 20%) (Fig.3). Also, more women than men were dyslipidemic (48.71% versus 28.57%) (Fig.4). Instead, more men than women had arterial hypertension. Only 62.06% of dyslipidemic patients had hypolipemiant drug treatment.

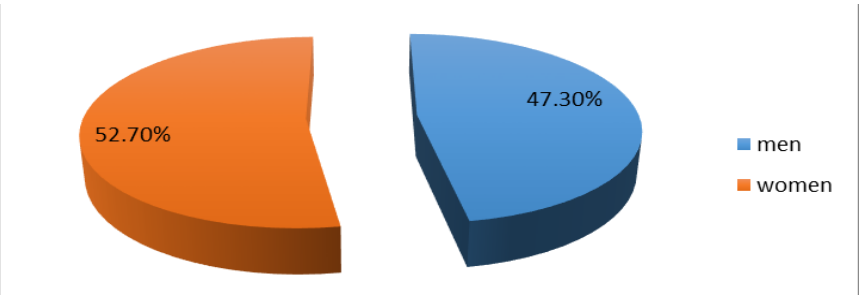


Figure 1. The distribution by sex in the group of study

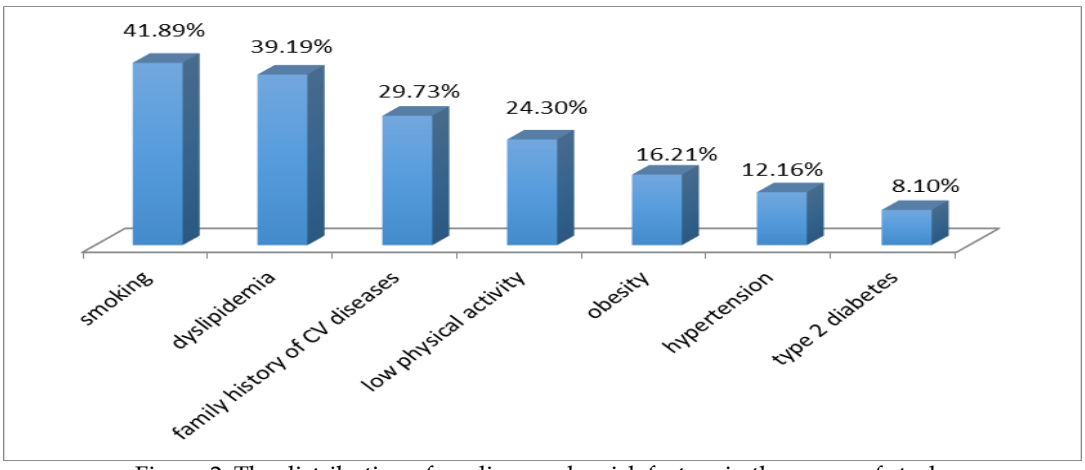


Figure 2. The distribution of cardiovascular risk factors in the group of study

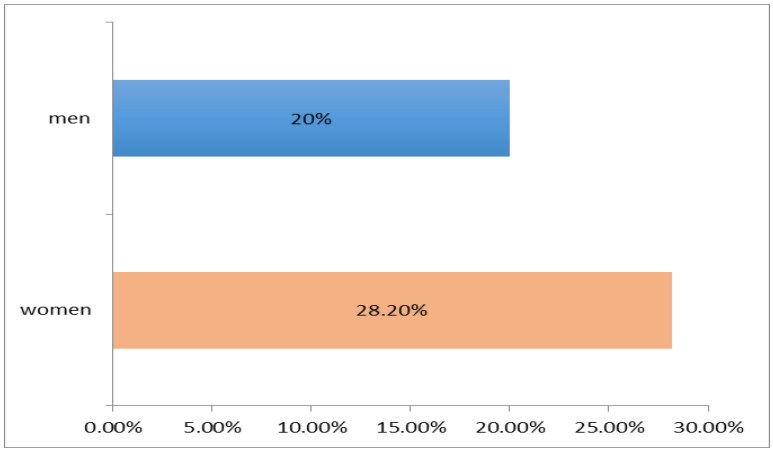


Figure 3. The percentage of men and women with low physical activity

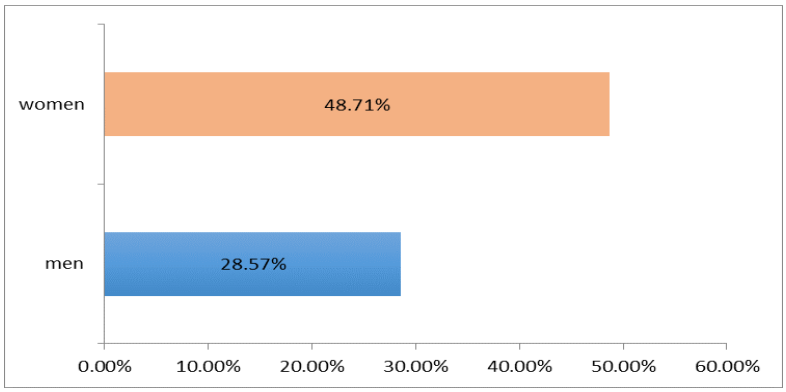


Figure 4. The percentage of men and women with dyslipidemia

DISCUSSIONS

In patients with cataract, the selfassessment of the visual deifict is subjective, they being differently affected by the functional limitation of sight. Our results indicate that the selfassessment of the general visual status is not influenced by the level of visual deficit, but the selfassessment of the general health is decreased in those with moderate deficit and cecity, as compared to those without deficit or with minor deficiencies.

Between 1930s and 1950s the rate of cardiovascular diseases increased in developed countries. In the same time, this rate was low in less developed countries, with middle- or low-income[1,2]. After 1970s, the rate of death from cardiovascular diseases decreased in some

high income countries, mainly as a result of a better control of cardiovascular risk factors and improved treatment of cardiovascular diseases[3].

One study that enrolled 156,424 persons from 628 urban and rural communities in 17 countries (3 high-income, 10 middle-income and 4 low-income countries) assessed the cardiovascular risk using the INTERHEART Risk Score, a validated score for quantifying risk factor burden without the use of laboratory testing[4]. Participants were followed for incident cardiovascular disease and death for a mean of 4.1 years[4]. The incidence of major cardiovascular events was highest in low-income countries, despite the fact that these countries had the lowest risk factor burden[4]. In contrast, the incidence of non-major cardiovascular events was highest in high-income countries[4]. In the same study, the percentage of smoking in men was highest in low-income countries as compared to high-income countries (41.8% versus 16.4%)[4]. In our study, surprisingly, 41.89% of patients (both men and women) were current smokers, a percentage much higher than that reported in high-income countries. 39.19% of our patients had dyslipidemia, a percentage close to that reported in high- and middle-income countries (47.8% and 31.7%)[4]; in the same study, the percentage of dyslipidemia was 17.3% in men from low-income countries[4]. Despite diagnosed dyslipidemia, more than 1/3 of our patients refused the drug treatment, due to concerns related to side effects. Hypercholesterolemia increases the risk of heart disease and stroke[5]. Worldwide, one third of coronary heart disease is attributable to high cholesterol levels[5]. According to World Health Organization, the prevalence of hypercholesterolemia increases in parallel with the income level of the country[5]. In low-income countries, approximately 25% of adults have hypercholesterolemia, while in high-income countries, over 50% of adults have increased total cholesterol[5].

In our study, the frequency of hypertension was 12.16%, lower than that reported in the study of Yusuf et al (49% in men and 37.4% in women from high-income countries)[4]; a possible explanation is the younger mean age of our patients (33.5±7.8 years old versus 53.3±9.4 years old). Globally, nearly one billion people have hypertension; 2/3 of these live in developing countries[6]. The prevalence of hypertension is likely to increase, in 2025 the estimated numbers of hypertensive patients being 1.56 billion[6].

Regarding the low level of physical activity, our study has found a percentage higher than that reported in high-income countries (in men 28.20% versus 10.8%, in women 20% versus 11.7%). More women than men reported a low physical activity. This aspect may be improved by a better medical education of our patients regarding the cardiovascular risks of physical inactivity. 150 minutes of moderate physical activity each week is estimated to reduce the risk of ischemic heart disease by approximately 30% and the risk of diabetes by 27%[7,8]. Also, physical activity lowers the risk of stroke and hypertension[6]. In all World Health Organization region, men are more active than women[7]. 16.21% of patients included in our study were obese. In high-income countries, 25.6% of men and women were obese, in middle-income countries 14.4% of men and 21.6% of women and in low-income countries 4.9% of men and 11.6% of women[4]. Regarding this characteristic, the profile of our patients was similar to that of middle-income countries.

Most non-communicable diseases are strongly associated with four major behavioural risk factors: smoking, physical inactivity, unhealthy diet and the harmful use of alcohol[7]. All these risk factors may lead to arterial hypertension, overweight/obesity, hyperglicemia and dyslipidemia. In terms of attributable deaths, the leading non-communicable risk factor is arterial hypertension (to which 13% of global deaths are attributed), followed by smoking (9%), hyperglycaemia (6%), physical inactivity (6%), overweight and obesity (5%)[5].

The 2013 American College of Cardiology/American Heart Association guidelines recommend that global risk should be the starting point of risk assessment and an opportunity to increase the patients' awareness about their cardiovascular risk[8,9].

CONCLUSIONS

Smoking was the main cardiovascular risk factor in our study, followed by dyslipidemia, family history of cardiovascular diseases, and lack of physical activity. Dyslipidemia and lack of physical activity were more frequent in women. Arterial hypertension was more frequent in men. More than 1/3 of dyslipidemic patients did not have hypolipemiant treatment, mainly due to concerns related to secondary effects of statins. It is the role of the physician to educate the patients about the need for treatment and to correctly inform about the risk of side effects. Epidemiological studies on different social categories can provide information to guide prevention strategies both at individual and general population level. There is a need for common efforts between public healthcare system and private sector in order to address the cardiovascular diseases epidemic and to decrease morbidity and mortality. In a country with limited financial resources for healthcare system such as Romania, preventive cardiology may be the key factor for reducing the costs associated with cardiovascular morbidity and mortality.

Declaration of interest: none.

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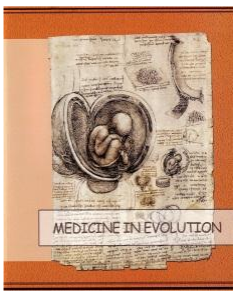
Asymptomatic gigantic lung tumor: Case report



Paraschiv B.[1], Ionescu C.[2], Diaconu C.[3]

[1]University of Medicine and Pharmacy"Carol Davila", National Institute of Pneumology"Marius Nasta", Bucharest, Romania
[2]Internal Medicine Clinic, Clinical Emergency Hospital of Bucharest, Romania
[3]University of Medicine and Pharmacy"Carol Davila", Internal Medicine Clinic, Clinical Emergency Hospital of Bucharest, Romania

Correspondence to:
Name: Camelia Diacon
MD, PhD
Address: Clinical Emergency Hospital of Bucharest, 8 Calea Floreasca, Bucharest, Romania, Zip code 011461
Phone: +40 726 377 300; +40 21 599 2300
E-mail address: camiluciemi@yahoo.com

Abstract

Lung cancer causes one in five deaths by cancer worldwide. Most patients with lung cancer present symptoms in advanced stages. The initial evaluation is essential in making a timely diagnosis and accurate staging so that proper treatment can be initiated. We present the case of a 64 yo man with a 40 pack-years smoking history, without respiratory symptoms, who was admitted for severe pain in the right leg. The initial evaluation revealed a rupture of a intramedullary nailing which migrated in the abdomen. The chest imaging showed a gigantic left lung tumor with chest wall invasion. The patient was referred for biopsy to the oncology clinic. The particularity of the case consists of its clinical presentation: gigantic lung tumor with no respiratory symptoms, who was admitted for right leg pain due to a femoral intramedullary nailing rupture.

Keywords: lung cancer, smoking, asymptomatic.

INTRODUCTION

Lung cancer has been known for several decades as the most common cancer worldwide[1]. The highest estimated incidence in men is in Central and Eastern Europe[1]. Given the asymptomatic presentation until advanced stages, lung cancer remains the most common cause of death by cancer in the world, with a mortality rate of 19.4%[1].

CASE PRESENTATION

We present the case of a 64 year-old man who was admitted for severe pain in the right leg, fatigue, weight loss (6 Kg during the last 6 weeks). The medical history of the patient included arterial hypertension, diabetes mellitus under insulin treatment, chronic hepatitis C, peripheral arterial disease and right femural fracture surgically stabilized with intramedullary nailing 30 years ago. The patient had a smoking history of 40 pack-year but stopped smoking 6 months prior to presentation. The physical examination revealed pulmonary dullness in the inferior half of the left thorax, without crackles, the respiratory rate was 16 breaths/minute, the oxygen saturation was 98% while breathing ambient air, blood pressure 140/80 mmHg, heart rate 78 beats/minute, arterial pulse present in both legs, but weak at dorsal pedal and posterior tibial artery, bilaterally, due to peripheral artery disease. The rest of the physical examination was within normal limits. Laboratory tests showed hyperglicemia (seric glucose 227 mg/dL, HbA1c 7.35%), mild hepatic cytolysis (ALT 40 U/L, AST 97 U/L), mild inflammatory syndrome (leucocytes 15 800/mmc, ESR 25 mm/h). The ECG revealed a synus rhythm with QS aspect in DIII and aVF. The echocardiography showed a mild degenerative mitral regurgitation, with diastolic dysfunction of the left ventricle, important calcification of the mitral annulus. The X-ray of the right hip revealed the rupture of the intramedullary nailing, with migration of its superior half into the abdomen (Figure 1).The thoracic X-ray showed a large, homogeneous opacity, located in the inferior half of the left lung (Figure 2). The differential diagnosis included a community acquired pneumonia with secondary pleural effusion, atelectasis, tumor. A high-resolution computed tomography (HRCT) scan was performed, which revealed a gigantic left lung tumor with invasion of the left thoracic wall, bilateral pulmonary nodules (compatible with secondary determinations), osteolytic lesions of the left ribs and scapulae (Figure 3). The orthopedic consult did not recommend the surgical treatment of the nailing rupture, due to high surgical risk. The patient was referred for pulmonary biopsy to the thoracic surgery clinic. A large-cell lung carcinoma was diagnosed.

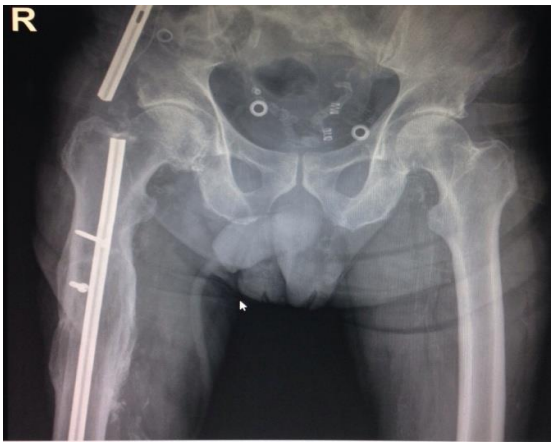


Figure 1. The migration of the intramedullary nailing

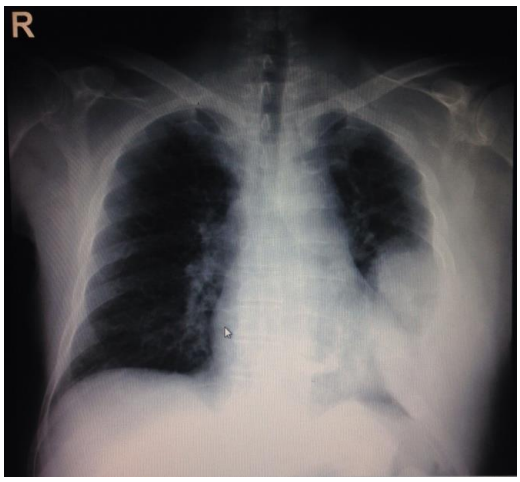


Figure 2. Large, homogeneous opacity in the inferior half of the left lung

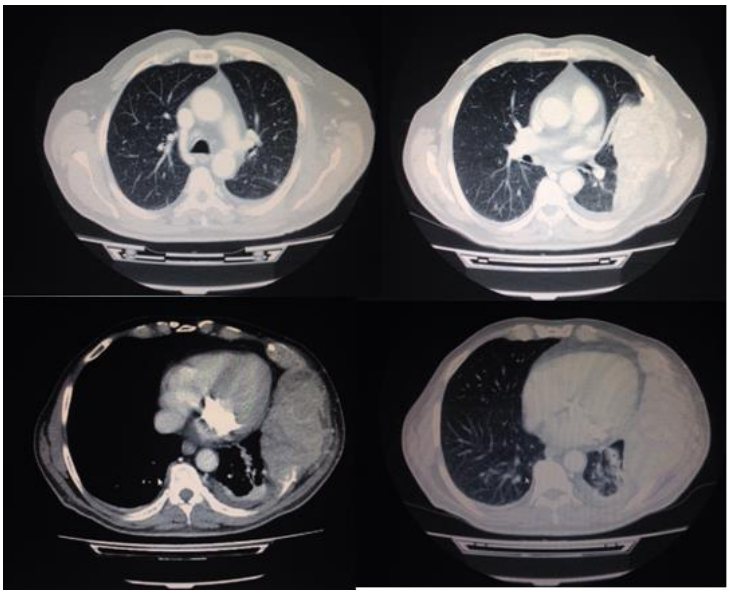


Figure 3. HRCT scan - gigantic left lung tumor with chest wall invasion

DISCUSSIONS

Lung cancer has been associated with a number of environmental and lifestyle risk factors, but the most important remains smoking[2]. Our patient had a smoking history of 40 pack-years, without any other identifiable risk factor for lung cancer. There are four major histologic cell types in lung cancer: adenocarcinoma (38%), squamos cell carcinoma (20%), small cell carcinoma (13%) and large cell carcinoma (5%)[3]. Therapeutic approach depends on the histological type of the tumor. Other factors that influence the therapeutic approach are: TNM classification of the cancer, clinical status of the patient, lung volumes, comorbidities[4]. Most patients with lung cancer present clinical signs and symptoms only in advanced stages[2]. Symptoms usually are secondary to local invasion of the tumor, local or distant metastasis or paraneoplastic syndromes[5,6]. Any delay in diagnosis may lead toward losing a curative option. There have been recent efforts for establishing a proper diagnostic approach in patients at risk for developing lung cancer[7]. In patients over 50 years old, with a smoking history of a minimum 20 pack-years, with a cessation of less than 15 years and one additional risk factor, screening should be done with HRCT scan (level one recommendation)[7]. The additional risk factors include: diagnosis of chronic obstructive pulmonary disease, environmental or occupational exposure, personal cancer history, family history of cancer, pulmonary fibrosis.

Despite advanced disease, with local invasion in chest wall, ribs and scapulae, and secondary determinations in both lungs, our patient did not have any respiratory symptom. The only symptom was the right leg pain. Given the patient risk factors (age over 50, smoking history more than 30 pack-years with only 6 months cessation), lung cancer systematic screening might have been necessary in this case. The most important strategy to improve prognosis is a rapid diagnosis with accurate staging, followed by proper treatment[4,6].

The usual diagnostic approach of lung cancer is based on imaging and biopsy with histopathological exam. A thoracic HRCT is mandatory in order to obtain information regarding tumor size, lymph node involvement, thoracic metastases[8]. The histopathological confirmation can be obtained by bronchoscopy, thoracotomy, or lymph node biopsy via endobronchial ultrasound (EBUS), mediastinoscopy, or biopsy from a distant metastasis[9]. The use of PET-CT scan has not yet been established as a mandatory investigation during lung cancer initial evaluation[10]. In our case, a HRCT scan was performed, which confirmed the lung tumor; the patient was then referred for lung biopsy with histopathological exam. Laboratory tests also play a role in the initial evaluation of lung cancer. They may suggest the presence of a metastasis or a paraneoplastic syndrome.

CONCLUSIONS

In **conclusion**, lung cancer has still the highest mortality rate amongst deaths by cancer, mainly due to lack of clinical signs and symptoms in early stages[1]. We presented the case of a giant pulmonary tumor with invasion of the chest wall, multiple pulmonary secondary determinations and osteolitic lesions, without any respiratory or thoracic symptoms, despite advanced disease. The lung tumor was diagnosed incidentally, with the occasion of admission for right leg pain. Appropriate screening methods should be used in patients at high risk for lung cancer, in order to improve prognosis.

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Declaration of interest: none.

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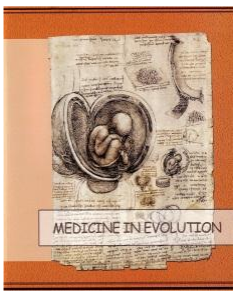
Gigantic post-mastectomy keloid scar- A case report



Ciobanu A.[1], Georgescu T.A.[1,2], Sajin M.[1,2], Tampa M.[1,3], Georgescu S.-R.[1,3], Costache M.[1,2], Dumitru A.[1,2]

[1]*Department of Pathology, Emergency University Hospital, Bucharest, Romania*
[2]*"Carol Davila University of Medicine and Pharmacy", Bucharest, Romania*
[3]*Department of Dermatology,"Victor Babes"Hospital for Infectious and Lung Diseases, Bucharest, Romania*

Correspondence to:
Name: Prof. Mariana Costache
MD, PhD
Address: Department of Pathology,"Carol Davila"University of Medicine and Pharmacy, 8 Eroilor Sanitari Avenue, 050474 Bucharest, Romania
Phone: +40 21318 07 62
E-mail address: m_costache_dermatopat@yahoo.com

Abstract

Keloids are manifestations of abnormal wound-healing responses, presenting as raised, red or flesh-colored, firm nodules, extending beyond the borders of the original wound. The cause of keloid formation is unknown. Microscopically, a keloid is characterized by the presence of distinctive thick, eosinophilic, homogeneous collagen bundles associated with fibroblasts with plump nuclei. We report a case of a gigantic keloid (278/45/36 mm) in a post-mastectomy 56-year-old female. Postoperatory gross examination revealed an aspect of irregular scar tissue mass, with increased consistency and above-mentioned dimensions. Microscopically, the aspect was, beyond doubt, that of a keloid. Although keloids are common benign fibrous proliferations that don't normally raise interest, the dimensions in this case are the biggest that our clinic has encountered in the past 10 years' experience.

Keywords: keloid, scar, mastectomy, benign.

INTRODUCTION

A keloid is an abnormal manifestation of wound healing. Scar tissue is formed at the site of cutaneous injury (on the site of trauma or surgical incision). It does not regress spontaneously and grows beyond the original margins of the scar. Keloids are raised, red or flesh-colored, firm nodules, often symptomatic (pruritus, tenderness), that should be differentiated from hypertrophic scars, which are also abnormal responses to injury, but the latter do not grow beyond the boundaries of the initial wound and may regress in time [1,2]

The term *keloid*, meaning"crab claw"(Greek) was first mentioned in 1806 by baron Jean-Louis Marie Alibert who was the court physician of King Louis XVIII of France, in an attempt to illustrate the way this lesion expands laterally from the original scar into normal tissue. He called them cancroïde, later changing the name to chéloïde to avoid confusion with cancer [3].

Keloids are benign dermal fibroproliferative tumors with no malignant potential, composed of wide bands of collagen with large, brightly eosinophilic, glassy fibers, parallel fibroblasts and myofibroblasts. Blood vessels are typically prominent with a vertical arrangement, perpendicular to the skin surface. Epidermis is thinned, lacking rete ridges [1,4,10].

The cause of keloids is not well known. There are hypotheses suggesting associations with race, age, skin tension lines, trauma, and hormonal factors. Keloid-derived fibroblasts seem to over express various growth factors: VEGF, TGF- β1, TGF-β2, CTGF and growth factor receptors: PDGF-α receptor [5, 11]

CASE PRESENTATION

We report the case of a gigantic keloid scar in a 56-year-old female, localized on the left anterior thoracic wall. The patient has a history of breast carcinoma, diagnosed 2 years earlier. After right mastectomy, performed for therapeutical purposes, she also requested left mastectomy, for aestethic reasons. Although unaffected by cancer or radiotherapeutic treatment, the scar on the left mammary gland developed viciously, extending beyond the incision lines.

CT exam revealed confluent tissue masses on the thoracic wall, extending from the midline to the axilla, having polycyclic aspect and raising the suspicion of a soft tissue secondary determination.

Postoperatory gross examination revealed an aspect of irregular scar tissue mass, with increased consistency and measuring 278/45/36 mm.

Microscopical examination revealed eosinophilic, broad, homogeneous collagen bundles arranged in a haphazard array and an increased number of fibroblasts along the collagen bundles, similarly oriented. The overlying epidermis was thin and vascularity was reduced compared with normal healing wounds (Fig 1-3).

Considering the cancer history, any uncontrolled growth could have been a relapse. That is why a differential diagnosis had to be made. First of all, the existence of a metastasis had to be excluded. Although, clinically, the lesion pleaded for the diagnosis of a keloid, imagistic examination could not eliminate a soft tissue determination. Eventually, the histopathologic exam confirmed benign, fibroproliferative pseudotumoral masses consistent with the diagnosis of keloid.

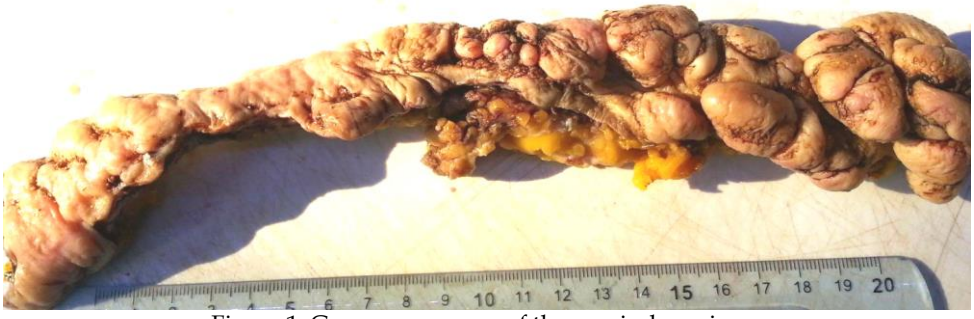


Figure 1. Gross appearance of the surgical specimen

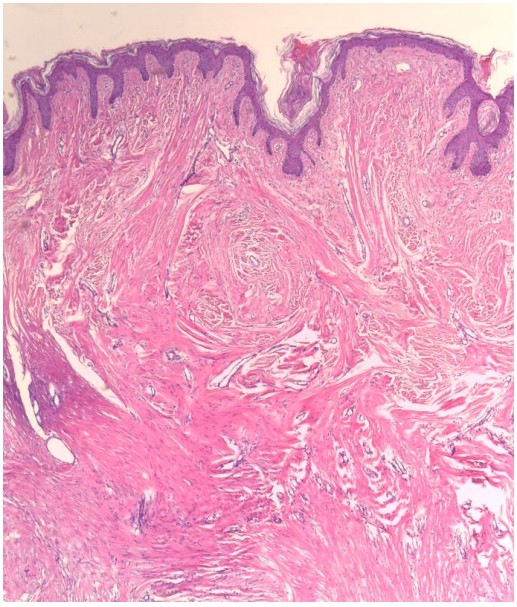


Figure 2. Keloid scar. Wide bands of collagen with large, brightly eosinophilic, glassy fibers arranged in a nodular fashion. H.E stain. Ob.x4

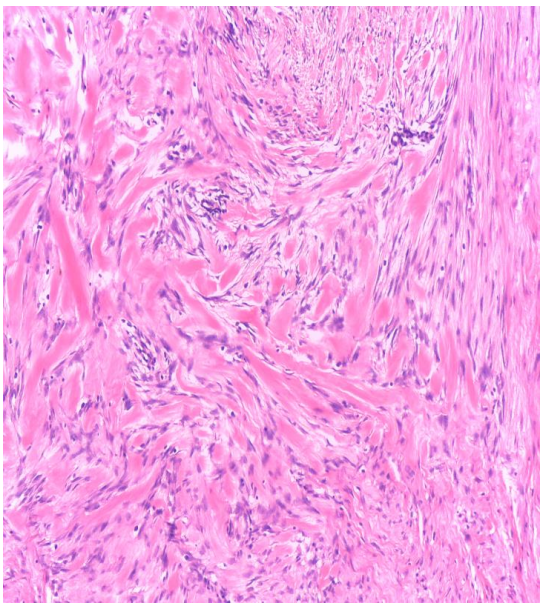


Figure 3. Central core of the keloid nodule comprising closedly-packed hyalinized fibrous tissue, broad bands of collagen and an increased number of fibroblasts. H.E stain. Ob.x10

DISCUSSIONS

Tipically, fibrosis is related to the final stage of an inflammatory reaction, and may be reactive, benign, or pathological. For the last category, fibrosis is linked to the destruction of collagen fibers due to an inflammatory reaction. This process may be microscopic or may result in a clinically visible scar. Hypertrophic scars and keloids are expressions of aberrant wound-healing responses that share some resemblance. Both lesions are elevated, pink flesh-colored to red or brown, and firm nodules. Hypertrophic scars are usually asymptomatic and do not grow beyond the boundaries of the original wound. Keloids can be symptomatic and generally extend beyond the area of healing trauma. The cause of keloids is as far as we know, idiopathic: various hypotheses suggest associations with race (far more frequent in Afro-American, Asian, and Hispanic population), age (more often young adults), skin tension lines, trauma, hormonal and genetic factors. Keloid is the result of an overgrowth of granulation tissue (collagen type 3) at the site of a healed skin injury which is then slowly replaced by collagen type 1 [6,7]

Histopathologically hypertrophic scars are characterized by fibrillary collagen arranged in a parallel bundle fashion to the epidermis, in association with an increased number of fibroblasts having the same alignment. Also, blood vessels have a typical vertical arrangement perpendicular to the skin surface. Commonly, the epidermis overlying

hypertrophic or atrophic scars is thinned, lacking rete ridges [8,9]. In recently developed scars the superficial dermis may have an increased amount of mucin, imparting a slight basophilic to amphophilic color with routine stains such as haematoxylin-eosin [1,8]

The main difference between keloid and hypertrophic scar is the prominent presence of distinctive, characteristically thickened, eosinophilic, homogeneous, coarse collagen bundles associated with fibroblasts having more rounded shape nuclei than those seen in scars. Mucin and rare calcifications may be found in keloids between thickened collagen bundles or more often at the periphery of the lesion [1,2,9,10].

Classical differential diagnosis of hypertrophic scars and keloids includes dermatofibroma, morphea, connective tissue nevus, fibromatosis, and some desmoplastic tumors such as desmoplastic or nodular melanoma [1]. In our case, considering the gross appearance and patient's cancer history, we also included in the differential diagnosis a possible relapse of breast cancer as an epidermotropic metastase. Eventually, the microscopic examination revealed standard features of a keloid scar, excluding without any doubt a breast cancer metastasis. Also, considering the patient's age and the fact that this was her first and only keloid scar, we could link the breast cancer therapy (which included a radical-modified mastectomy, followed by chemo and radiotherapy) to be the major trigger for the development of keloid scars in this particular case. Patients with cancer history, unusual features, such as advanced age, lack of trauma preceding keloid formation, or the presence of a keloid-like lesion in uncommon sites, should prompt the clinician to seek histopathological confirmation of the diagnosis in order to avoid missing potentially malignant conditions.

The best treatment for keloids is prevention in patients with a known predisposition. This includes preventing unnecessary trauma or surgery whenever possible. Any skin infections should be treated as early as possible to minimize areas of inflammation. Should keloids reoccur, the most effective treatment is superficial external beam radiotherapy (SRT), which can achieve cure rates of up to 90% of treated cases. Alternatively, cryotherapy or cryosurgery could be used as a minimal invasive treatment. These methods are easy to perform and have shown promising results with least chance of recurrence. Additionally, intralesional injection of corticosteroids does appear to improve inflammation and pruritus [7,12,13].

CONCLUSIONS

Although a keloid would not seem spectacular, the dimensions in this case are impressive, and our clinic did not encounter such a gigantic specimen in the past 10 years' experience. In addition, the association with cancer history in the region made it imperative to carefully look for possible metastases.

***Conflict of interests**: none declared*

***Financial support**: none declared*

We undersign, certificate that the procedures and the experiments we have done respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2000 (5), as well as the national law

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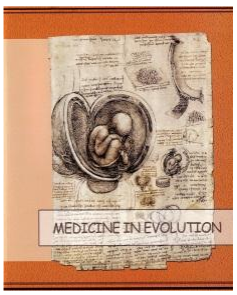
Indication and clinical outcomes of a pulmonary rehabilitation program



Dantes E.[1,2], Fildan A.P.[1,2], Tudorache E.[3], Oancea C.[3], Iliescu M.[1]

[1]*Faculty of Medicine,"Ovidius University", Constanta, Romania*
[2]*Pneumology Clinic, Constanta Hospital, Romania*
[3]*University of Medicine and Pharmacy"Victor Babes", Timisoara, Romania*

Correspondence to:
Name: Ariadna Petronela Fildan
Address: Ovidius University, Faculty of Medicine, Constanta
Phone: +40 741157526
E-mail address: ariadnapetrofildan@yahoo.com

Abstract

Background: Pulmonary rehabilitation (PR) is a multi-disciplinary program, which addresses symptomatic patients with chronic respiratory disease and decreased daily activities. The expected outcomes are the improvement of respiratory symptoms; increase exercise tolerance and improving Health Related Quality of Life (HRQOL); lowering medical costs; relieve anxiety and depression; reduce the frequency and severity of exacerbations.

Objective: Identifying the inclusion criteria for pulmonary rehabilitation program of the patients admitted to our clinic and describing the evaluation process before and after the PR program.

Materials and Methods: It was evaluated: inclusion and exclusion criteria of patients hospitalized with chronic respiratory diseases for the PR program, evaluation methods pre- and post- PR, used instruments, types of interventions and outcomes.

Results: 670 patients with pulmonary non-tuberculous disorders were included in the PR program. Diagnosis indication were severe and very severe forms of COPD, suppurated bronchiectasis, chronic asthma and diseases caused by direct affection of the mobilization capacity of the thorax: chest deformities, Kypho-scoliosis, ankylosing spondylitis, obesity, pleurisies after drainage and outstretched pachypleuritis, post-tuberculous syndrome and post-surgical thoracic sequelae. Contraindication were represented by decompensated cardiovascular disease, hemoptysis, unstable hypertension, myocardial infarction in the last 3 months, acute or chronic infectious disease, severe musculoskeletal impairments, marked cognitive decline, patient refusal to participate in the program. The pulmonary rehabilitation program improved quality of life, increased exercise capacity, and reduced symptoms for the most patients that have participated in the program.

Conclusions: By performing PR in our hospital we aimed to assess the socio-professional reinstatement of the patients, and to improve their functional and psychological status.

Keywords: pulmonary rehabilitation; indication, chronic obstructive pulmonary disease (COPD); bronchiectasis.

INTRODUCTION

Incidence and prevalence of the obstructive disease are continuously growing and according the WHO data, until 2020, COPD will become the third cause of death worldwide[1,2]. Chronic respiratory diseases affect the quality of life through the negative impact of the respiratory function (FEV_1 loss), high frequency of exacerbations, and subsequent number of hospitalizations and reduce exercise tolerance[1].

Pulmonary rehabilitation (PR) addresses symptomatic patients with chronic respiratory diseases that often have impaired activities of daily living[3]. A pulmonary rehabilitation program should be individualized and pursue a specific purpose based on the patient needs. The objectives of such a program are: improving respiratory symptoms (dyspnea and fatigue), increase exercise tolerance, enhanced quality of life related to health, reduce anxiety and depression, reduce the number of exacerbations, lower the health costs, resulting a professional and recreational reinstatement[4]. Studies show utility and benefits of PR in patients with chronic pulmonary diseases, suffering of skeletal muscle dysfunction, sedentary life style due to continuously increase in dyspnea and fatigue.

MATERIAL AND METHODS

This retrospective study has analyzed the activity performed in our pulmonary rehab department from March 2014 until September 2015. The study was conducted by a multidisciplinary team, consisting of pulmonologist specialized in pulmonary rehabilitation, physiotherapist specialist, cardiologist and dietitian, psychotherapist.

Inclusion criteria consist in: symptomatic hospitalization patients with chronic respiratory diseases, age over 18 years that presented impairment of daily life activities. Clinical and functional evaluation of the patients included complete medical history, vital function measuring (blood pressure, pulse rate, oxygen saturation), spirometry with bronchodilator test, ECG, chest radiography, co-morbidities assessment, quality of life questionnaires (ACT for asthma and CAT for COPD), SF-36 (Quality of Life Survey), 6 minutes walk test (6MWD) and BODE index calculation.

Exclusion criteria: decompensated cardiovascular disease, hemoptysis, unstable hypertension, myocardial infarction in the last 3 months, acute or chronic infectious disease, severe musculoskeletal impairments, marked cognitive decline, patient refusal to participate in the program.

Dyspnea and fatigue were assessed using visual analog scales (VAS). The 6MWD was performed respecting the indications and contraindication of the test, before and after the rehabilitation program. 6MWD is a validated instrument applied to evaluate the exercise impact of the rehabilitation program and oxygen saturation (SpO_2) and heart rate were assessed to establish the necessary maximum level of exercises.

For each patient an individualized rehabilitation plan was established, choosing safe procedures, physical training, muscles stretching exercises and breathing techniques. The program aimed the symptom relief, enhanced quality of life, improvement of exercise tolerance, and endurance and increasing the distance walked in the 6MWD, after 8 weeks of PR program. The rehabilitation program also included medical education workshops for patients and caregivers, treatment explanations and ways of correcting the habits that could influence the chronic obstructive disease (smoking – anti-smoking program, occupational exposure to pollutants), oxygen therapy indication, lifestyle and nutrition.

RESULTS

In 2014, 207 patients with non-TB pulmonary disorders participated in the pulmonary rehabilitation program and 463 patients in 2015 (table 1).

Table 1. Patient distribution from the PR program according to their disease

	Total	COPD	Pleural effusion; pachypleuritis	Bronchiectasis Lung abscess	Chest deformities	PID	Chronicasthma	Post TB syndrom
2014 N= (%)	207	139 (67)	21 (10)	11 (5,3)	5 (2,4)	5 (2,4)	7 (3,3)	19 (9,1)
2015	463	359 (77)	39 (8)	21 (4,5)	7 (1,5)	5 (0,2)	11 (2,3)	21 (4,5)

The distribution of patients who participated in the PR program in 2014 according to their pathology was: 67% patients with COPD (139 pts), 10% patients with drained pleurisy or pachypleuritis (21 pts), 9.1% bronchitis syndrome post TB (19 pts), 5.3% with suppurative bronchiectasis or lung abscess (11 pts), 3.3% chronic asthma (7 pts), 2.4% fibrosis and chest deformities (5 pts). In 2015 the distribution was: 77% patients with COPD (359 pts), 8% pleural disorders (39 pts), 4.5% post-Tb syndromes (21 pts), 2.3% chronic asthma (11 pts), 4.5% with bronchiectasis (21 pts), and 1,5 % patients with chest deformities (7 pts). Clinical and functional characteristics of the patients who were enrolled in the program are shown in table 2.

Table 2. Clinical and functional characteristics of the patients included in the PR program

	2014	2015
Male/female	165/42 (79,7 vs. 21,3%)	325/138 (70 vs. 30%)
Interval age	23-95	25-87
Mean age	62	57
BMI:	12,8-39 kg/m2	14-40 Kg/m2
Mean FEV1 in COPD patients	42%	39%
Patients with 6MWD done	107 (52%)	319 (69%)
Mean interval of PR program	10	15

Patients participated in one of the rehabilitation programs below, selected depending on the severity of the disease.

KT 1 – exercises for the upper limbs, inhalation on the extension of the thorax and exhalation compressing the thorax,

KT 2 – exercises for the upper and lower limbs, simple movements accompanied by deep abdominal breaths,

KT 3 – diaphragmatic breathing exercises,

KT 4 – exercises for upper limb + lower limbs plus stationary bike,

KT 5 – exercises for the upper and lower limbs + treadmill (walking training),

KT 6 – exercises for the upper and lower limbs + multifunctional machine,

KT 7 – exercises for the upper and lower limbs plus stationary bike + treadmill + multifunctional machine,

KT 8 – stationary bike plus treadmill + multifunctional machine.

Patient evaluation after the program showed an average VAS score decreased for both fatigue and dyspnea (table 3) and increased in walking distance from 335 to 433 m (figure 1).

Table 3. VAS scale score before and after PR program

BORG SCALE 0-10 points	Fatigue PRE 6MWT	Fatigue POST 6MWT	DYSPNEA PRE 6MWT	DYSPNEA POST 6MWT
PRE-PR	1.35	4.19	2.1	4.23
POST-PR	1.15	2.38	1.15	2.15

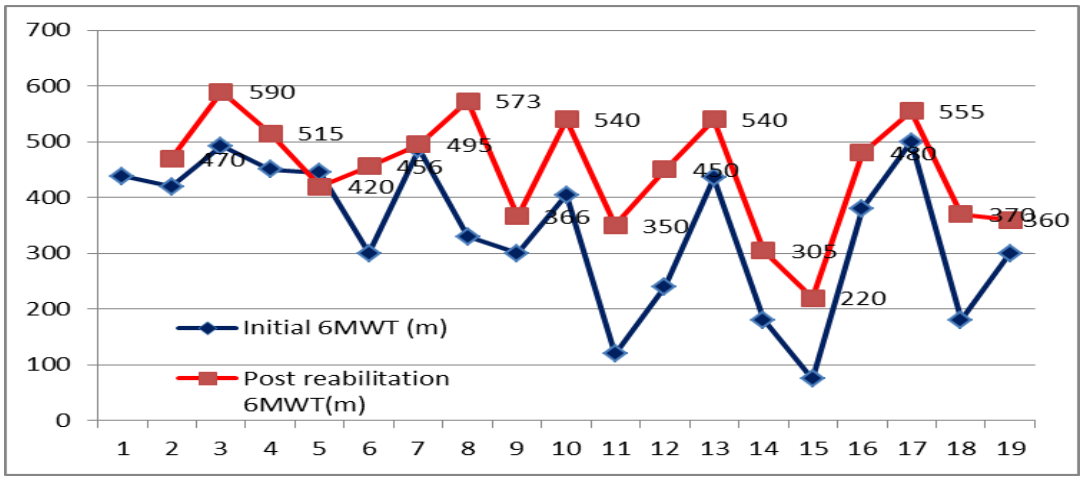


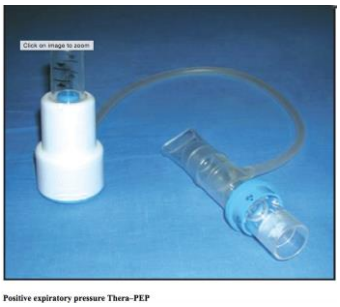
Figure 1. Example of absolute distance walked by patients before and after the PR program

Patients with chronic bronchiectasis and bronhoreea were assessed by pulmonologist through computed tomography to objectify and evaluate the extent of lesions and to appreciate the presence of stagnant mucus in the bronchial tree. All patients with bronchiectasis were evaluated functionally, by spirometry, and bacteriologically, using sputum examination.

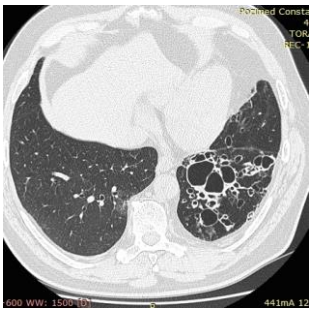
For these patients, 3 types of interventions were done: bronchial secretions removal techniques (mobilization and airway clearance), exercises and aerosol therapy with saline solution.

The techniques used this purpose were: ACBT (airway clearance breathing technique) in 91% of the cases, autogenous drainage, postural drainage and chest percussion. For some of them we use medical devices witch function on positive expiratory pressure principle (figure 2).

Figure 1. Postural drainage and chest percussion



Positive expiratory pressure breathing (PE)



Lower left lobe chistic bronchiectasis

Duration and frequency of PR sessions were adapted to each patient, approximately 20-30 minutes per session. Patients were informed and trained regarding the recommended clearance technique and advised to choose the preferred technique.

The contraindications were represented by unstable angina, hemoptysis, pleurisy, foreign body, aortic aneurysm, rib fractures, severe osteoporosis.

Follow up was performed after 3 months from the first consultations, in order to asses the results of the program and to improve patient adherence to treatment.

The following results were obtained from the PR program:

- Transition from total rest to independent motion
- Gradual transition from supine to standing
- Independent walking, when orthostatism can be maintained easily by the patient
- Increasing the distance traveled and the duration of effort
- Independence from oxygen
- Increased quality of life

Another important component of PR is education. The program included individual sessions and group medical education, both for the patient and family, explaining the benefits of exercises, indication of oxygen, administration methods of the treatment, correction of habits that can influence the dynamics of the disease (smoking cessation, avoidance of allergens, occupational exposure to pollutants), influence of co-morbidities (cardiovascular, osteoporosis), lifestyle and nutrition.

DISCUSSIONS

PR indications were represented by severe and very severe forms of COPD, with FEV_1 under 50%, suppurated bronchiectasis, chronic asthma, diseases caused by the direct affections of the mobilization capacity of the thorax – chest deformities, Kypho-scoliosis, ankylosing spondilytis, obesity, pleurisies after drainage, extended pachipleurities, post TB syndromes, post operative sequelae. Contraindications were: uncompensated cardiovascular and respiratory diseases, unstable hypertension, myocardial infarction in the last 3 months, acute or chronic infectious diseases, severe musculoskeletal impairments, marked cognitive decline, and patient refusal to participate in the program.

The rehabilitation program included daily sessions of respiratory exercise training, both for the muscles involved in the breathing act and for the upper and lower limbs associated with respiratory therapy (learning and practicing relaxation postures and breathing techniques, abdominal breathing, drainage of bronchial secretions), exercise programs adapted to various musculoskeletal deficit. Each patient with chronic obstructive disease was taught how to perform diaphragmatic breathing, to inhale slowly through the nose and exhale prolonged with pursed lips; diaphragmatic control was performed with the hands of the physiotherapist placed on the patient's chest.

The results of this study, supported by data from literature [5-8], showed that implementing a PR in COPD patients have important results in improvements in exercise tolerance, quality of life, endurance walking and symptom relief. These techniques are inexpensive, readily available and require simple equipment. The PR should be supervised by a physiotherapist, and the exercise programs should be prescribed based on an exercise test, and progressed in a standardized manner [9].

The duration of our respiratory rehabilitation program was variable and determined by the multidisciplinary team. A series of inconveniences have been reported due to the absence of a standardized program regarding the actual session time, which in present, is depending on the hospitalization period. In the case of our program, compared to other studies [10-12], the PR was short. In patients with severe diseases, immobilized in bed, the 6 minutes walking distance test could not be performed, these patients received only a partial assessment of the dyspnea and fatigue scales.

The postural drainage is a very important technique used frequently in patients with bronchiectasis, and it aims to mobilize the bronchial secretions, being conditioned by the compromised ciliary activity, coughing and viscosity of sputum. Different positions are recommended depending on the affected lobe segments, the aim being to direct the bronchial secretions with the help of gravity, from the small and large bronchi, to the oral cavity [13]. Chest percussions prevent the adhesion of bronchial secretions to the chest wall, favoring their elimination. In order to increase the tracheobronchial clearance, to decrease viscosity of phlegm and sputum volume growth, the patients in our study followed treatment with bronchodilators and/or hypertonic saline solution 3% through nebulization, this method being currently used in different rehabilitation programs [13, 14].

In order to facilitate mobilization and removal of bronchial secretions, the patient in our study used several medical devices: oscillating respiratory devices, external percussion vests, flutter, etc. Positive expiratory pressure breathing (PE) was performed in bed every 1-4 h, in combination with aerosol therapy and oxygen. Our study demonstrated improvement in exercise capacity and in decreasing in symptoms of dyspnea and fatigue. Same results were obtained by other studies, which showed short-term improvements in exercise capacity and quality of life, with a combination of endurance, strength training and inspiratory muscle training [15] or regular airway clearance therapy [16]. Lee et al. demonstrated in his prospective study that exercise training in bronchiectasis is associated with short term improvement in exercise capacity, dyspnea and fatigue and fewer exacerbations over 12 months [17].

For the patients with ineffective cough, we used Cough Assist, a device of mechanic insufflations/exhalation, with gradual application of positive pressure in the airway, and then, rapid transition to negative pressure. This method is a component of a PR program, which has the effect of bronchial mucus mobilization, followed by significant improvement in cough-related quality of life [18].

Our findings suggest that pulmonary rehabilitation program can lead to a significant improvement in exercise capacity, endurance walking and symptom relief.

CONCLUSIONS

By performing PR in our hospital we aimed to asses the socio-professional reinstatement of the patients, and to improve their functional and psychological status. Each patient was advised to continue the rehabilitation program at home, by performing daily breathing exercises, diaphragm mobilization and bronchial drainage techniques combined with walking or cycling.

We observed that after the pulmonary rehabilitation program, all the patients that have participated, had decreased breathlessness and fatigue and improved exercise capacity. Patients also mentioned an improved quality of life and reduced symptoms of anxiety and depression.

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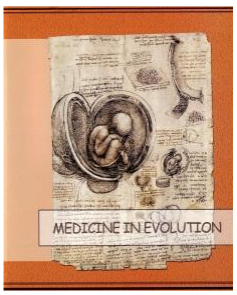
Chronic obstructive pulmonary disease: comorbidity or risk factor for lung cancer?



Fildan A.P.[1], Tofolean D.E.[1], Tudorache E.[2], Crisan A.[2], Mazilu L.[1], Dantes E.[1]

[1]*Faculty of Medicine, Ovidius University, Constanta*
[2]*"Victor Babes" University of Medicine and Pharmacy, Timisoara*

Correspondence to:
Name: Doina Tofolean
Address: Ovidius University, Faculty of Medicine, Constanta
Phone: +40 722488722
E-mail address: tofoleandoina@yahoo.com

Abstract

Background: COPD and lung cancer share common risk factors such as age, smoking and occupational exposure. In the presence of neoplastic disease, obstructive pulmonary pathology is frequently under diagnosed and untreated, leading to decreased quality of life. In addition, in current clinical practice, COPD is considered a smoking related disease and often ignored as an independent risk factor for lung cancer.

Aim: The aim of this study was to determine the prevalence of COPD diagnosis among patients newly diagnosed with lung cancer and to evaluate it as an independent risk factor.

Materials and Methods: Patients diagnosed with lung cancer in the Clinical Pneumology Hospital of Constanta, for a period of five years, were evaluated versus smoking patients with other lung pathology: respiratory tract infections, bronchiectasis, asthma, obstructive sleep apnea.

Results: There were 170 smokers patients diagnosed with lung cancer, including 142 men and 28 women, with a mean age of 61.08 years. The diagnosis was confirmed through histological or cytological specimens in 85% of the cases in which 63. 8% met ATS/ERS criteria for COPD. In the control group, the percentage of patients with COPD was 8.7%.

Conclusions: With other known risk factors for lung cancer, COPD can be considered as an independent risk factor. The extensive use of spirometry in smokers, with early diagnosis of COPD and imaging monitoring lead to the early identification of those with the greatest risk of lung cancer.

Keywords: chronic obstructive pulmonary disease, lung cancer, risk factor.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and lung cancer are major public health problems worldwide. COPD is the only cause of death in the top five that is increasing since 1990 [1]. COPD prevalence, morbidity and mortality varies, and are directly related to the prevalence of tobacco smoking except in developing countries, where air pollution resulting from the burning of biomass fuels plays also an important role in the emergence of this disease.

Prevalence estimated in the United States ranges from 10 to 16 million adults, but the condition may be under-diagnosed [2]. Lung cancer accounts for 12% of all cancers diagnosed worldwide, making it the most common malignancy after the non-melanoma skin cancer. Also, lung cancer is the leading cause of cancer deaths in both men and women, and is estimated to be responsible for nearly one in five (1.59 million deaths in 2012, 19.4% of the total) [3]. Because of the high fatality, with the overall ratio of mortality to incidence of 0.87 [3], lung cancer remains one of the cancers with extremely poor prognosis.

Tobacco smoking is associated with 90% of the cases of lung cancer [4] and, it is also, the most important risk factor for COPD [5]. Lung cancer and COPD are linked by the common exposure of tobacco smoke. It has been shown that 50-70% of patients diagnosed with lung cancer suffer from COPD [6]. It is not certain whether the association between lung function reduction and lung cancer is real or simply a shared smoking history.

The role of chronic airway inflammation in the causal pathway for both lung cancer and COPD has been suggested [7]. Inflammation in COPD can be considered as a consequence of repeated airway epithelial injury and repair, which enhance cell turnover rates and potential propagation of DNA errors, resulting in amplification of the carcinogenic effects of cigarette smoke [8]. Patients with chronic airflow obstruction have an impaired mucociliary clearance of carcinogenic substances from tobacco smoke. This leads to an increased exposure of the bronchial epithelium to carcinogens and promotes pathologic changes, epithelial to mesenchymal transition, leading ultimately to lung tumorigenesis [9]. Given this hypothesis, it has been shown that COPD patients treated with inhaled corticosteroids have reduced incidence of lung cancer, suggesting that the inhibition of inflammation can halt lung carcinogenesis [10].

The severity of COPD could influence the incidence of lung cancer [11]. A positive correlation between the severity of airflow obstruction and lung cancer incidence has been demonstrated by the results of the First National Health and Nutrition Examination Survey, a large study who collected data from a 22-yr follow-up of 5402 subjects [6], while other studies reported a lower incidence of stage IV COPD GOLD among patients with lung cancer diagnosis than the incidence of stage I [12].

The histological characteristics of lung cancer in patients with COPD are different from those without COPD [9, 11-14]. Smokers subjects with airflow obstruction have a higher risk of developing squamous cell carcinoma [13,14], although adenocarcinoma is associated with passive exposure to tobacco smoking, light smokers and females [11,15].

The above observations suggest that the COPD diagnosis should represent an alert for both, patients and doctors, regarding the risk of lung cancer development. In current clinical practice, COPD is often considered only a smoking related disease and ignored as an independent risk factor for lung cancer.

The objective of this study is to determine the prevalence of COPD diagnosis among patients newly diagnosed with lung cancer and to evaluate it as an independent risk factor.

MATERIAL AND METHODS

Patients diagnosed with lung cancer at Constanta Clinical Pneumology Hospital between January 2009 and December 2013 and who had undergone spirometry prior treatment, were included in the study. These patients were >40 yrs of age, Caucasians, in which histologic or cytologic proof of primary lung cancer was confirmed in 85% of cases. Tobacco smoke exposure was evaluated as current smoking status, number of cigarettes smoked per day, years of tobacco smoking, and age that started to smoke. Nonsmokers with lung cancer were excluded from this study.

Histology was categorized as non small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC was further classified into adenocarcinoma (ADK), squamous cell carcinoma, and other types of cancer (NOS) (generally large cell carcinoma, or bronchoalveolar subtypes). The pathologic stage of lung cancer at the presentation time was classified according to the 7th lung cancer TNM classification and staging system [16]. Lung cancer was grouped as stage I, stage II, stage IIIA (all surgically resectable), stage IIIB, and stage IV (surgically unresectable).

The pulmonary function tests (PFTs) were performed and interpreted using the American Thoracic Society/European Respiratory Society (ATS/ERS) revised guidelines [17]. Patients were considered to have COPD when the FEV1/FVC ratio was < 70%, and were classified according to Global Initiative for Chronic Obstructive Disease (GOLD) criteria [2]. PFTs were performed after with-holding short- and long-acting bronchodilators for a minimum 6 and 12 hours, respectively. Among patients with lung cancer, spirometry was performed within 3 months of lung cancer diagnosis, prior to surgery, in the absence of partial or complete lung collapse or pleural effusions visible on chest x-rays. Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were recorded for at least three maneuvers using flow-volume loops. The best pre-bronchodilator FEV1 and FVC test results were used for analysis, after conversion to percentages of predicted normal values.

Control subjects were recruited from smoking patients diagnosed with other lung pathology: respiratory tract infections (others than pulmonary tuberculosis), bronchiectasis, obstructive SAS, at the same hospital, during 2011-2013. Patient demographics, clinical history, and smoking history were obtained by completing an investigator-administrated questionnaire at our institution. We selected subjects aged between 40 and 80 years, with a minimum 10 pack-yrs smoking history.

Lung cancer cases and control cases were matched one for one for each of the following parameters: age within 5 years, sex, and smoking history within 5 pack-yrs. All participants gave written informed consent and the study was approved by the hospital ethics committee.

A comparison of the distributions of patients and clinical characteristics between cases and controls was performed using unpaired t tests for continuous variables. All test results with a p value of <0.05 were considered to be significant. Chi-squared test was used for discret variables.

RESULTS

The study included 170 smokers patients diagnosed with lung cancer, 142 men and 28 women, with a mean age of 61.08 years. Between January 2011 and December 2013, 170 smokers with others respiratory pathologies were recruited. The two groups of patients were matched for age, sex and smoking history. In the matched comparison, weight was higher among controls ($p<0.05$) and current smoking less among controls ($p<0.05$) when compared with lung cancer cases (table 1).

Table 1. Demographic characteristics and smoking history of control and lung cancer groups

Parameter	Control cases	Lung cancer cases	p-value
Patients n =	170	170	
Males %	84	84	
Ages yrs±SD	62.11±8.7	61.08±8.6	0.35
Height cm±SD	169.4±7.7	169.5±8.3	0.65
Weight kg±SD	73.16±16.3	67.73±13.3	<0.05
Smoking history			
Current smokers%	52	75	<0.05
Cigarettes/day±SD	20.66±9.26	21.84±8.60	0.88
Pack/yrs±SD	38.30±11.37	42.82±27.44	0.31
Age staring smoking±SD	20.75±5.12	19.73±2.66	0.87

The values of forced expiratory volume in 1 second, FEV1% predicted and FEV1/FVC were significantly different between the lung cancer and control smokers groups (table 2). Lung cancer cases had a greater airflow limitation, regardless of COPD severity, compared to the control group (figure1). More than half of the patients in both groups were classified in stages I and II COPD GOLD.

Table 2. The values of lung function parameters among control and lung cancer groups

Lung function	Control cases	Lung cancer cases	p-value
FEV_1 L	2.28±0.68	1.75±0.61	<0.05
FEV_1 %	86±18.44	65.5±17.13	<0.05
FEV1/FVC	80.6±11.05	66.68±12.14	<0.001

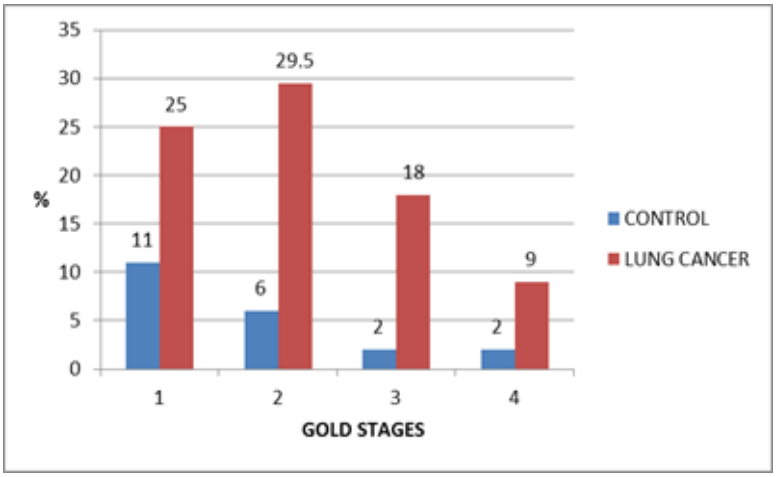


Figure 1. Patients distribution by severity of airflow obstruction (GOLD stages)

The prevalence of COPD was higher among patients diagnosed with lung cancer compared to controls (63.8% vs 8.7%, p<0.001) (fig 3 and fig 4). FEV1 and FEV1/FVC were significantly lower in the lung cancer group compared to the smokers control group (65.5% vs 86%, p<0.05; 66.6% vs 80.6%, p<0.05). 68% of patients diagnosed with lung cancer were simultaneously identified by spirometry with airflow obstruction; only 32% were previously diagnosed with COPD.

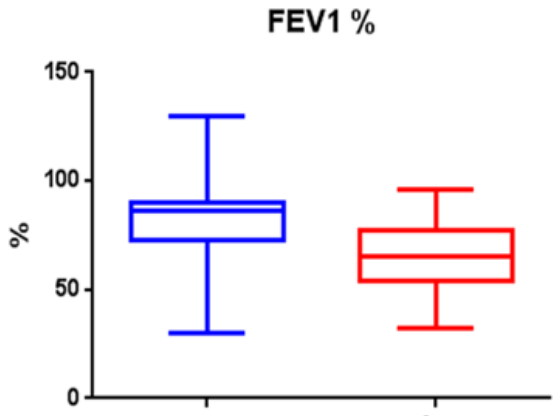


Figure 3. Difference in FEV1% between control and lung cancer groups

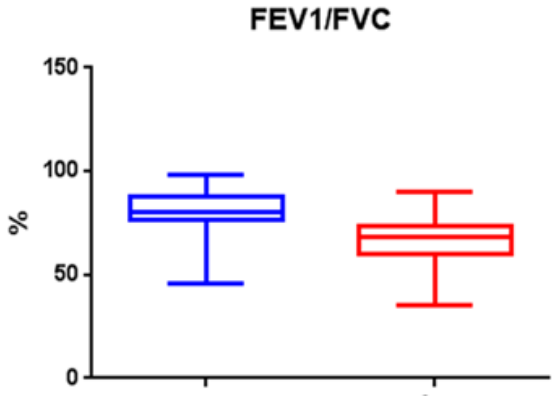


Figure 4. Difference in FEV1/FVC between control and lung cancer groups

Figure 5 shows the prevalence of COPD diagnosis in our lung cancer cases, classified by histology types. Patients diagnosed with adenocarcinoma had a lower incidence of airflow limitation (47.7%), compared with patients with squamous cell carcinoma (65.7%). Regarding the frequency of COPD diagnosis among different TNM stages of lung cancer, no significant differences between patients in stage I, II, III or IV were found (fig 6). The highest incidence of COPD diagnosis was noticed in patients with stages IIIB (68.9%) and IV (69.5%), considered surgically unresectable cases of lung cancer.

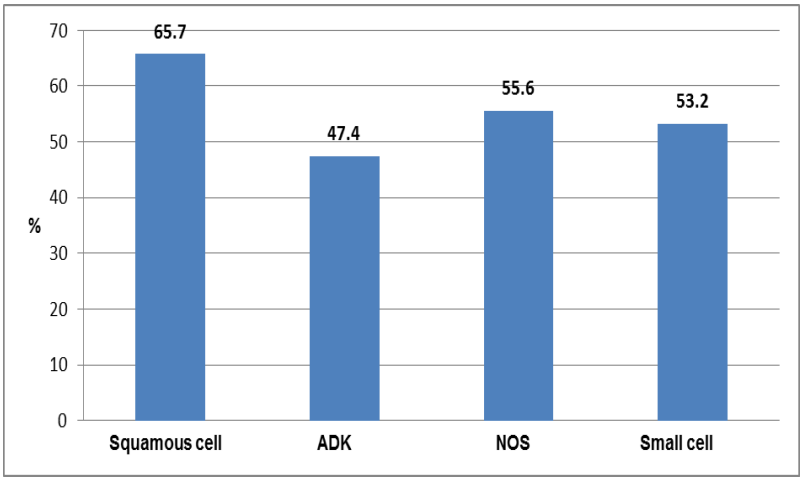


Figure 5. Prevalence of COPD in patients diagnosed with different histopathologic types of lung cancer

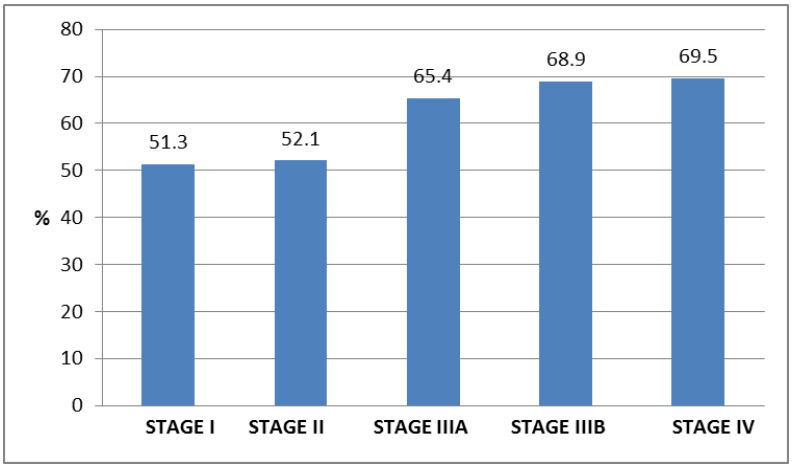


Figure 6. Prevalence of COPD in patients diagnosed with different TNM stages of lung cancer

DISCUSSIONS

The results of this study show that the prevalence of COPD (based on GOLD 2+) was 63.8% in 170 lung cancer cases and 8.7% in our matched sample of smoking controls with no lung cancer. The findings from this study supplement results from the literature [6–11, 18-20], which highlights the fact that lung cancer and COPD are linked by more than the common exposure of tobacco smoke.

A number of studies [6-9, 18-20] have reported a high prevalence of airflow obstruction in patients with lung cancer. In these studies, approximately 40–70% of lung cancer cases have coexisting COPD. Given the high prevalence of reduced FEV1 in smokers with lung cancer (50–80%) compared with those randomly selected from community studies (15–20%), Young suggests that FEV1 (a physiological marker of airway damage) is an important biological marker of a smoker's susceptibility to lung cancer [20]. The risk of developing lung cancer has been reported to be of four to six times higher in the presence of COPD, compared with smokers with normal lung function [18-20]. We found similar results, with a comparable COPD prevalence of 63.8% in patients diagnosed with lung cancer. Many studies suggest that impaired lung function (based on reduced FEV1) is more important than age or smoking exposure (measured as pack-yrs) [6, 18-20].

The exact mechanism of the impact of airflow obstruction on the development of lung cancer is unknown. The role of chronic airway inflammation in the causal pathway for both lung cancer and COPD has been suggested [7]. The epithelial response to cigarette smoke may represent attempts by the airway epithelium to protect itself and repair the injury caused by cigarette smoke [21-23]. These repeated processes of injury and repair of the epithelium enhances cell turnover rates and potential propagation of DNA errors, resulting in amplification of the carcinogenic effects of cigarette smoke [8]. Squamous cell metaplasia impairs mucociliary clearance and increases the exposure of the bronchial epithelium to carcinogens and promotes pathologic changes, epithelial to mesenchymal transition, leading ultimately to lung tumorigenesis [9].

In this study, 25% of the patients diagnosed with lung cancer had mild airflow obstruction, 29.5% moderate obstruction, while only 18%, respectively 9% had severe and very severe obstruction. These results are similar with those founded by de Torres el al. [12]. He reported a lower incidence of stage IV COPD GOLD among patients with lung cancer diagnosis than the incidence of stage I. They suggested that an active and non-tolerant immune system could be an important factor against tumorigenesis and lung cancer progression [11, 12]. Conversely, the results of the First National Health and Nutrition Examination Survey, a large study who collected data from a 22-yr follow-up of 5402 subjects, demonstrated a positive correlation between the severity of COPD and lung cancer incidence [6]. Multivariate proportional hazards analysis of the data in this study demonstrated that patients with mild airflow obstruction had a relatively higher risk to develop lung cancer (HR 1.4, 95% CI 0.8–2.6), and moderate or severe obstruction had even a higher incidence compared with normal pulmonary function (HR 2.8, 95% CI 1.8–4.4).

Analyses stratified by histopathological classification of lung cancer show different characteristics of lung cancer in COPD patients from those without COPD [9, 11, 13]. Smokers subjects with airflow obstruction have a higher risk to develop squamous cell carcinoma [13, 14], although adenocarcinoma is associated with passive exposure to tobacco smoking, light smokers and females [11, 15]. In our study we found similar patterns, the association between COPD and squamous cell carcinoma being present in 67.5% of cases, while COPD and adenocarcinoma in only 47.4% of cases ($p<0.05$). Other studies revealed similar histology-specific findings [9, 11-15]. One of these studies [12] reported that, although adenocarcinoma was the most frequent histological type in COPD GOLD stage I subjects, the most prevalent type of lung cancer in COPD GOLD stage II and III patients was squamous cell carcinoma.

The results of our study show that the patients diagnosed with pathologic stages I and II of lung cancer (surgically resectable) had a high prevalence of airflow obstruction (51.3% and 52.1%). These findings, supported by similar results from literature [6,9, 21], suggest the fact that the presence of severe lung function limitation in the early stages can act as a contraindication of surgical treatment.

We found that 68% of patients diagnosed with lung cancer were simultaneously identified by spirometry with airflow limitation, suggesting the fact that COPD is often undiagnosed and unrecognized as an important risk factor for lung cancer development. This argues strongly for the routine use of spirometry in smokers to identify those with COPD and those with a significantly elevated risk for lung cancer, both of which have previously been shown to assist in smoking cessation [19-21, 23].

The above observations and the results suggest that the COPD diagnosis should represent an alert for both, patients and doctors, regarding the risk of lung cancer development. In current clinical practice, COPD is often considered only a smoking related disease and ignored as an independent risk factor for lung cancer. The close link between lung cancer and COPD identified in this and other studies is not just about a shared tobacco smoking exposure, but likely to consider a shared genetic susceptibility to chronic smoking-induced inflammation. Age, smoking and presence of airflow obstruction, could represent the future parameters to be used in lung cancer screening.

CONCLUSIONS

With other known risk factors for lung cancer, COPD can be considered as an independent risk factor. The extensive use of spirometry in smokers, with early diagnosis of COPD and imaging monitoring lead to the early identification of those with the greatest risk of lung cancer.

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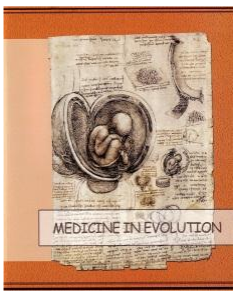
Metatypical carcinoma – a controversial tumour. Case report



Georgescu S.-R.[2], Mitran M.I.[2], Mitran C.I.[2], Sarbu M.I.[1], Matei C.[1], Tampa M.[1,2]

[1]*"Carol Davila University of Medicine and Pharmacy", Bucharest, Romania*
[2]*Dermatology Department,"Victor Babes"Hospital of Infectious and Tropical Diseases*

Correspondence to:
Name: Mircea Tampa
MD, PhD
Address: 37 Dionisie Lupu Street, Bucharest, Romania
E-mail address: tampa_mircea@yahoo.com

Abstract

Metatypical carcinoma is an infiltrative slow-growing tumour, which mainly involves the chronically sun exposed areas of the skin, being located especially on the face. The diagnosis of MTC is based on the histopathological examination, the tumour exhibiting features of both basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). It is an invasive tumour with a high tendency for recurrences and metastases. We present the case of a 75 year-old woman, who was admitted to our clinic for the occurrence of a proliferative lesion located on the right side of her chin. Following the histopathological examination the diagnosis of MTC was made. The early detection of the tumour permitted an appropriate management with a good prognosis.

Keywords: metatypical carcinoma, basal cell carcinoma, squamous cell carcinoma.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common cutaneous malignancy accounting for 80% of skin malignancies. Exposure to ultraviolet rays represents the most important risk factor. Therefore it is mainly located on the sun exposed areas of the skin. Clinically, BCC displays many forms, the most important being the nodular, superficial and morpheaform types (1). BCC originates in the basal layer of the epidermis and the hair follicle. Histopathologically, cells with a small amount of cytoplasm and large basophilic nuclei are noticeable. Mitoses, apoptotic cells and occasionally cellular atypia are identified (2). It rarely metastasizes, but it may be responsible of local invasion, which may extend even to the bone tissue (3).

Squamous cell carcinoma (SCC), a more aggressive tumour, with a lower incidence than BCC, appears as a papule or nodule, with or without hyperkeratotic surface, skin-coloured or pink. It may be ulcerative and bleed if it is traumatized (4). As BCC, it is most commonly located on the sun exposed areas of the skin. Histopathologically, SCC is characterized by the proliferation of atypical keratinocytes and the presence of pearls of keratin, forming cellular masses that invade the dermis. Local recurrences are often seen and SCC has a high propensity for metastatic spread (5).

Metatypical carcinoma (MTC) was described for the first time in 1910 by M. Cormac, who noticed that it displayed features of both BCC and SCC (6). Subsequently, some investigators disputed the existence of this tumour type. Today, MTC is considered a separate entity, but some controversies regarding its definition still persist (7).

CASE PRESENTATION

A 75 year-old woman presented to our clinic for the occurrence of a round-oval proliferative lesion located on her chin. The lesion had appeared 5 months earlier, increasing gradually in size, being painless and nonpruritic. The medical history was irrelevant. She denied the chronic exposure to sunlight and she was not a smoker.

Physical examination revealed a healthy woman with the vital parameters within the normal range. A local examination showed a round-oval proliferative lesion, 0.5/0.7 in size, with a translucent surface and small nodules in the periphery, located on the right side of her chin. The superficial lymph nodes were not enlarged. Presumptive diagnosis of BCC was made. The tumour excision and a biopsy were performed. The biopsy specimen demonstrated tumour cell proliferation with characteristics of both BCC and SCC. The cells were arranged in strands, invading the reticular dermis and a polymorph inflammatory infiltrate was seen (Figure 1).

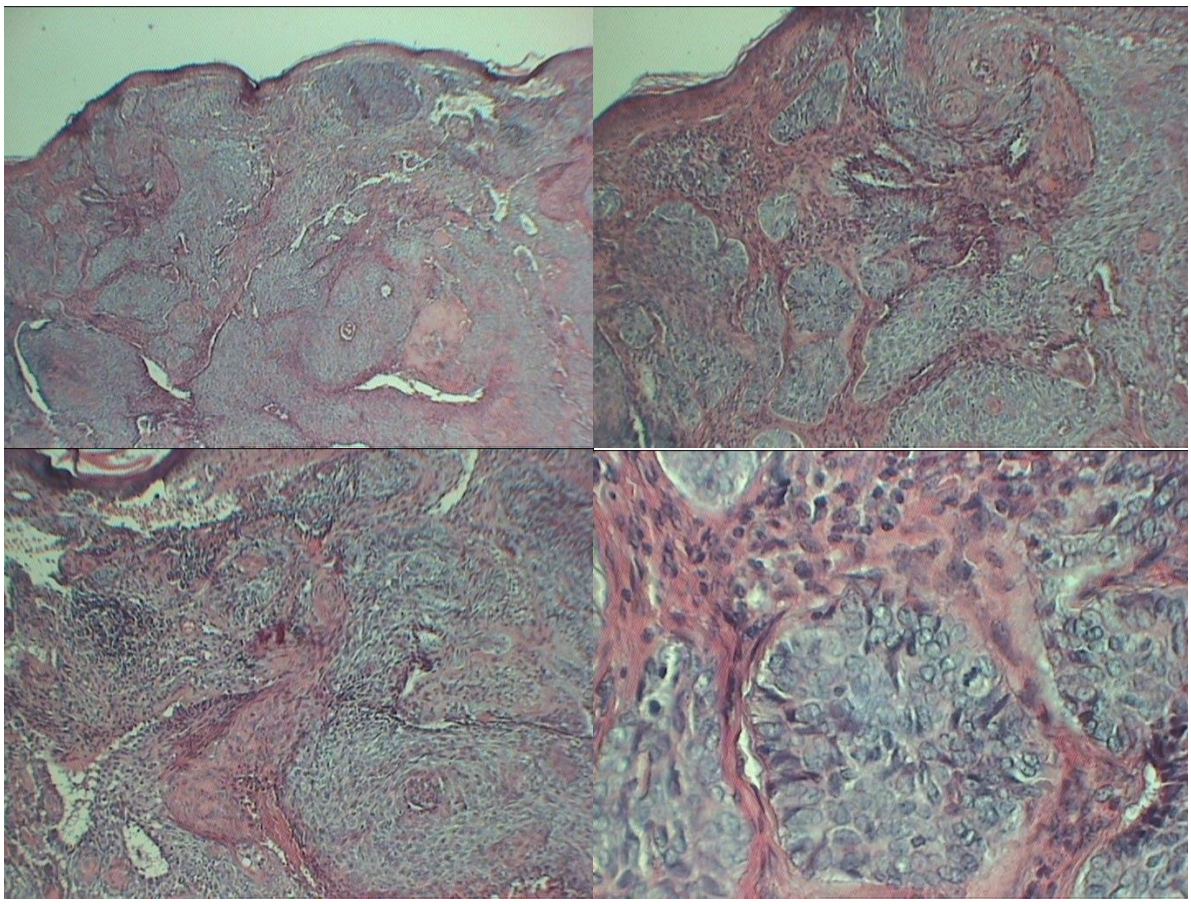


Figure 1. Histopathological appearance. Hematoxylin and eosin stain. Tumour cell proliferation with characteristics of both BCC and SCC: basaloid cells with a small amount of cytoplasm and big and pallid nuclei. Increased mitotic activity; in the SCC area there is an abundant eosinophilic cytoplasm with large nuclei and prominent nucleoli, active mitoses and intercellular bridges

Based on histopathological findings the diagnosis of metatypical carcinoma was made. The patient underwent radiotherapy with favourable evolution. A follow up plan was established in order to diagnose recurrences or metastases in an early stage.

DISCUSSIONS

MTC, also known as basosquamous carcinoma, is an invasive tumour with increased capacity of recurrence and metastasis (8). The definition of MTC is controversial, several hypotheses being postulated over time. Some investigators advocated that MTC is a tumour composed of two distinct types of tumours, BCC and SCC, with different origins, while others suggested that it is a form of keratinising BCC (9). Taking into account its aggressive behaviour, some authors classified MTC as a metastatic BCC (10). Today, MTC is considered a lesion which exhibits histopathological characteristics that resemble BCC and SCC simultaneously in the same lesion, with or without a transition zone (11). Further studies are needed to clarify its origin. It is unclear if the tumour appears de novo or develops on a pre-existing BCC (9).

MTC is a slow growing tumour, accounting for 1.5% of skin neoplasms. Clinically, it does not exhibit specific features, but often resembles BCC; therefore the diagnosis is based on the histopathological characteristics (12). A higher incidence was observed in males, in the study of Leibovitch 64% of patients being males. In terms of age, MTC was more frequently diagnosed in older persons, especially in the seventh decade of life (13).

Studies have shown the involvement of cephalic extremity in 82-96% of cases, the tumour being located especially on the central area of the face (9, 13). The most commonly

affected are the nasal, auricular and periocular regions. In our case, the lesion was located on the right side of the chin, a location less often described. MTC can be also found on the oral mucosa, in which case it may progress in a more aggressive manner than SCC (14). The main factors highlighted as being involved in the etiology of MTC are the chronic sun exposure and smoking (15). Our patient does not present any of these risk factors.

Many authors have described the aggressive behaviour and the increased ability to metastasize of MTC. These features are mainly due to the presence of cells with characteristics of SCC, which are prone to metastasize, but the immune status and the size of the lesion play also an important role (12). Studies have shown an increased number of recurrences, ranging between 10 and 48%, and a metastasis rate of up to 7.4%, similar to that recorded in patients with SCC. By contrast, the metastasis rate of BCC varies between 0.0028 and 0.55% (16, 17). Metastases commonly involve the lymph nodes and the lungs. The metastasis risk increases with the size of the lesion, therefore lesions more than 10 cm large present a metastasis risk of up to 50% (7). The main risk factors for recurrence are the presence of positive resection margins, the male gender, and the lymphatic and perineural invasion (16). In our case the lesion was early diagnosed and the resection margins were negative.

The histopathological appearance of MTC reveals basaloid cells, larger than the cells observed in BCC, which are characterized by a small amount of cytoplasm and big and pallid nuclei (9). In addition, an increased mitotic activity and a higher number of apoptotic nuclei are present (18). The cells from the SCC area are defined by an abundant eosinophilic cytoplasm with large nuclei and prominent nucleoli, active mitoses and intercellular bridges. The palisade, a typical feature of BCC, is weakly represented or absent. The pluripotent basal cells apparently support the development of this tumour (8, 13). In addition, MTC displays an infiltrative character and presents a stroma rich in fibroblasts and collagen (8). There are two subtypes of MTC, intermediate and mixed (19, 20). In the intermediate subtype, there is a transition zone between the two cell populations, while the mixed subtype is defined by areas of squamous cells within the BCC areas (19). In our case the histopathological examination revealed a mixed subtype.

Since not all the cases are diagnosed, the real incidence remains unknown. Sometimes the lesion is not biopsied or the biopsy is not correctly performed. Some authors have emphasized that characteristic changes of MTC are encountered only in the deeper layers of the tumour, and if the biopsy involves only superficial layers, histopathological findings may mislead to the diagnosis of BCC. In addition more attention should be given to aggressive BCC cases, because behind them a case of MTC may be found (7). Thus, in the study conducted by Farmer and contributors 17 cases initially diagnosed as metastatic BCC were re-analysed and in 80% of them basosquamous areas were identified (21).

Some immunohistochemical studies have revealed that in fact there is a transition zone between BCC and SCC areas, which suggests that the pluripotent cells of BCC turn into cells with an aggressive pattern and differentiate into areas of SCC (13). In addition it has been noticed that there are certain markers expressed by these cell populations. Thus, the BCC cells are positive for Ber EP4 and the SCC cells for CAM5.2 and both types of cells express the AE1/AE3 marker. In the transition zone the expression of specific markers decreases (17).

In order to distinguish between BCC and MTC, the analysis of the expression of keratin was suggested as being useful, therefore the MTC cells exhibit a lower expression of it, and BCC cells express keratin 8 and 17 (19). There are studies about the markers which are associated with an aggressive behaviour; they have revealed that the increased expression of cyclin D1 and decreased expression of Bcl 2 represent markers for invasion and poor prognosis for BCC and also for MTC (6).

Recently, the first case of a collision tumour composed of MTC and melanoma has been reported in the medical literature. The tumour was diagnosed in a 60 year-old man, Fitzpatrick skin type III, with chronic sun exposure (22).

Vismodegib is an inhibitor of the hedgehog pathway, approved by the FDA in 2012, for the treatment of advanced and metastatic BCC. Interestingly, during the treatment with Vismodegib, the occurrence of an SCC at the site where previously there had been a BCC has been reported but it has not been revealed whether the tumour process was based on basal cells transformation or it developed independently. Furthermore, based on genetic evidences, Ransohoff and contributors have recently described a case of BCC, which acquired specific phenotypic features of SCC under treatment with Vismodegib (23).

Surgery with safe margins of resection is the treatment of choice. However, the majority of the lesions are located on the face and in some instances the excision with safe margins may become difficult, having important esthetic implications. There is no consensus regarding the safe margins but the aggressive behaviour of the tumour requires a larger excision. In the case of large tumours or lymphatic and perineural invasion, radiotherapy is necessary as an adjuvant therapy (11, 19, 24). Some authors recommend the examination of sentinel lymph node, especially for advanced lesions (11). It is important to draw up a plan to follow up the patient in order to diagnose recurrences or metastases in an early stage (25).

Mohs surgery is recommended for recurrent or large tumours and if the localization of the tumour imposes the preservation of the tissue, especially when the face is involved (8). In the study performed by Leibovitch and contributors the patients had been treated using Mohs surgery and the 5-year local recurrence rate was 4.1%, much lower than in conventional surgery (13).

CONCLUSIONS

MTC is a rare tumour, which clinically resembles BCC, but taking into account its evolution, with a significant risk of recurrence and metastasis it mirrors an SCC. The histopathological examination is the key of the diagnosis. However the lack of accurate criteria and the histopathological peculiarities often make the diagnosis difficult. In order to achieve a correct diagnosis, the collaboration between the dermatologist and the histopathologist is meaningful. Aggressive BCC should raise the suspicion of a possible MTC. The particularity of the above case is the occurrence of an MTC on the chin, in a patient without evident risk factors. The early diagnosis allowed the excision of the tumour with clear histologic margins, without esthetic implications.

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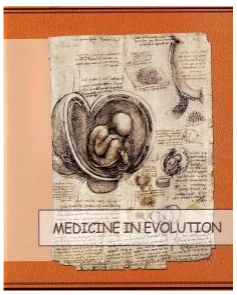
The psychological profile of mothers of children with diabetes. Basis for support and intervention program



Vintilă M.

West University of Timişoara, Romania

Correspondence to:
Name: Professor Mona Vintilă
PhD
Address: Bvd. Vasile Pîrvan, no. 4, Timişoara, Romania, Postal code: 300223; West University of Timişoara, Romania
Phone: +40 722684236
E-mail address: mona.vintila@e-uvt.ro

Abstract

Diabetes is a typical example of a chronic disease that the whole family must learn to live with, since it affects the lifestyle of each family member and the family organization, especially when the one diagnosed with diabetes is the child. The aim of this study was to identify the changes that mothers of children with diabetes pass through in terms of parental stress, couple satisfaction and health perception by comparing them with mothers of healthy children.

These results show some changes in the psycho-socio-relational registry of mothers of children with diabetes, changes that need to be known to be taken into account and to initiate support and intervention programs for disease acceptance and coping to the new conditions of life imposed on the family by the child's condition.

Keywords: diabetes mellitus, parental stress, mothers.

INTRODUCTION

According to the International Diabetes Federation the number of people with diabetes in Romania is 1,351,400 (IDF Diabetes Atlas 4th ed, 2009). The estimated number of adults living with diabetes worldwide has soared to 366 million, representing 8.3% of the global adult population. This number is projected to increase to 552 million people, or 9.9% of adults, by 2030 which equates to approximately three more people with diabetes every 10 seconds. (IDF Diabetes Atlas 5th ed., 2011). The incidence of Type1 diabetes in children aged less than 14 years has also increased over the years. Between 1990 and 1994 this increase was 2.4% and between 1995 and 1999 it was slightly higher at 3.4% (DIAMOND Project Group, 2006).

The economic impact of diabetes is very strong. Only In 2007, U.S. diabetes treatment alone cost 174 billion dollars (Pazdro, Burgess, 2010). In European countries estimates of the costs caused by diabetes range between 6 and 14% of the total allocated health budget. This includes both direct costs (expenses resulting from screening, diagnosis, care, prevention, research) and indirect costs (decreased productivity as a consequence of sick leave, disability or death before retirement) (Triplit, Charles, Reasmer and Isley, 2005).

Diabetes is a typical example of a chronic disease that the whole family must learn to live with, since it affects the lifestyle of each family member and the family organization. Everyday life, eating habits and even holiday planning must be changed and rearranged depending on patient treatment especially when the patient is a child. Professional and social issues must also take into account the limitations imposed by diabetes.

Many studies have tried to identify parental behaviour relating to dietary adherence and metabolic control in young children and adolescents with insulin-dependent diabetes mellitus, and to understand the interrelationships among the variables of parental behaviour, adherence to blood glucose monitoring, and glycaemic control. Such variables as parental involvement (Anderson B, Ho J, Brackett J, Finkelstein D, Laffel L., 1997), authoritative nonhelpless parenting style (Davis et al., 2001 and Shorer et all., 2011), family communication and conflict resolution (Wysocki, 1993) supportive parental style and parental coping (Graca Pereira et al., 2011), family structure (one- vs. two-parent household) (Grabill et al, 2010) have been found to predict better glycaemic control and adherence in the child. The interest regarding educating parents to support and care for their children when they are diagnosed with diabetes mellitus is also illustrated by the initiative of American Diabetes Association to publish a book designed specifically to help parents deal with these additional responsibilities.

Guide to Raising a Child with Diabetes, by Jean Betschart Roemer (2011), now in its third edition, which teaches parents about adjusting insulin dosage so that kids can still eat their favourite foods, how to help the child to accept insulin injections, developing a meal plan for the whole family and transitioning to adult care. This research on the family's role in diabetes management examines the problem in terms of the effects of parental attitudes toward the disease and treatment plan on the child. This involves a linear model of family functioning where influences are described in only one direction: from the parents to the child. Systemic Family theory considers the family as a system of interdependent parts in which each member of the family is seen as influencing and being influenced by other members. So the parents are also influenced by their children's' illness. When a child is diagnosed with Type 1 Diabetes Mellitus it is the parents who will have to take care of the treatment to a great extent. This new parental responsibility can lead to stress and changes in the family structure for many years that are not decreasing even when the child grows up and the parents must gradually hand over the responsibility to the child. There is limited knowledge of how parents are influenced over time.

The parents of children diagnosed with diabetes not only have to cope with the fact that their children have been diagnosed with a chronic lifelong illness, but also have to overcome their sense of grief (Bowes, Lowes, Warner, Gregory, 2008). Parents feel sad and guilty, helpless facing the disease and unconfident of their ability to cope with the situation (Lowes, Gregory, Lyne, 2005), they have significantly poorer quality of life in respect of their physical health, psychological health and general well-being (Bhadada, Grover, Kumar, Bhansali, Jaggi, 2011).

Currently, in Romania, the only treatment provided for people with diabetes is the basic one, that includes medication, diet, physical exercises and medical advice, with the patient's mental quality of life and especially the influence of the disease on their family being neglected. Due to the increased incidence of this disease, we believe it important to identify the most appropriate therapy methods, both medical and psychological, that can optimize the physical and mental health status, disease management and not least the life quality of patients with diabetes and of their families as a whole.

While there is a growing interest in psychological issues in diabetes, it is important to focus also on parents and caregivers, to identify the changes and problems they are passing through in terms of stress, health perception and couple satisfaction. This objective is important especially in such countries as Romania where there is a low general level of interest in the psychological wellbeing of the parents of children diagnosed with diabetes. In Romania there are no especially designed services to help them and the educational programs developed by doctors are focused simply on treatment and metabolic control.

Aims and objectives

The aim of this study was to identify the changes that mothers of children with diabetes pass through in terms of parental stress, couple satisfaction and health perception by comparing them with mothers of healthy children.

The specific objectives were:

- To examine whether there are differences regarding health perceptions between mothers of children diagnosed with diabetes and those of healthy children.
- To explore the differences between mothers of diabetic children and those of healthy children regarding couple satisfaction.
- To look for any evidence that mothers of diabetic children have higher levels of parenting stress than mothers of healthy children.

DESIGN AND METHODS

Patients diagnosed with lung cancer at Constanta Clinical Pneumology Hospital between January 2009 and December 2013 and who had undergone spirometry prior treatment, were included in the study. These patients were >40 yrs of age, Caucasians, in which histologic or cytologic proof of primary lung cancer was confirmed in 85% of cases. Tobacco smoke exposure was evaluated as current smoking status, number of cigarettes smoked per day, years of tobacco smoking, and age that started to smoke. Nonsmokers with lung cancer were excluded from this study.

A quantitative study was carried out at a Paediatric Hospital providing services to a major area of Western Romania.

The following instruments were used:

1. Parenting Stress Index – the 3^{ed} edition (Abidin, 1995)

The questionnaire was developed by Richard R. Abidin. The purpose of the 120-item PSI is to produce a diagnostic profile of perceived child and parent stress. The PSI was developed based on the theory that total parental stress is a function of child and parent

characteristics, as well as situational variables. It contains 13 sub-scales within major domains: total stress, child domain, parent domain. The total stress domain, which measures the level of stress in the parent-child relationship, is comprised of the child and parent domains. The child domain has six subscales that measure the child's distractibility/hyperactivity, adaptability, reinforcement of the parenting experience, demandingness, mood, and acceptability. The remaining seven subscales make up the parent domain and measures: competence, isolation, attachment, health, feeling of role restriction, depression, and spousal support. Internal consistency (Cronbach's alpha) for the PSI sub-scales ranged from.70 to.83 in the Child Domain,.70 to.84 in the Parent Domain, and was greater than.90 for the two domains and the Total Stress scale.

2. Dyadic Adjustment Scale, developed by Graham B. Spanier.

The instrument includes 32 items and was designed to assess relationship quality as perceived by married couple, is also a general measure of satisfaction in the couple's intimate relationship by using total scores. This instrument measures four aspects of relationship: dyadic satisfaction (DS), dyadic cohesion (DC), dyadic consensus (DCON) and emotional expression (EE). The scale has good internal consistency with alpha of.96. Subscales have the following consistency: SD =.94, DC =.81, DCON =.90, and.73, EE =.73.

3. The Multidimensional Health Questionnaire (MHQ) developed by W. E. Snell and G. Johnson in 1997 which consists of 20 health-oriented subscales, each containing five items (Health Anxiety, Health-Efficacy, Health Consciousness, Motivation to Avoid Unhealthiness, Chance-Luck Health Control, Health Preoccupation, Health Assertiveness, Health Expectations-Optimism, Health Illness Self-Blame, Health Monitoring, Motivation for Healthiness, Health Illness Management, Health Esteem, Health Satisfaction, Powerful-Other Health Control, Health Self-Schemata, Health Status, Health Illness Prevention, Health Depression, Internal Health Control). Good reliability in the.7 to.8 range has been established for this measure (Snell & Johnson, 1997).

Participants

The participants were:

- a group of 31 mothers of children diagnosed with type 1 diabetes for more than 1 year, under treatment and with a good glycaemic control. Children of these women are aged between 3 and 12. This group represents the study group. Participants in the current study were recruited from two outpatient paediatric specialty clinics in Timisoara, Romania. Eligibility requirements were: (1) parent of a young child (age 3–12) with Type 1 Diabetes; (2) child's diagnosis > 12 months; (3) absence of any co-morbid medical or developmental condition.
- a group of 31 mothers whose children are physically healthy and are also aged between 3 and 12. This was the control group.

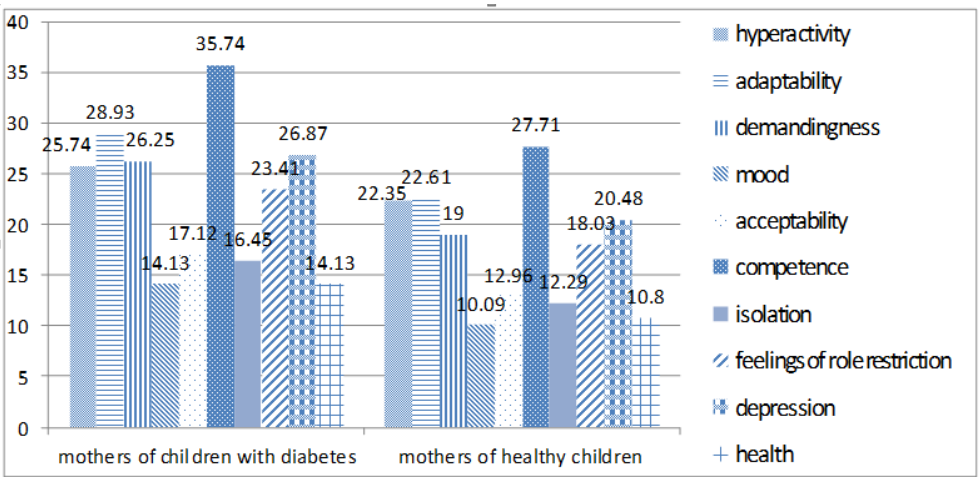
RESULTS

Group comparisons were made using independent t test to compare differences between means on the total stress scores, health perception and couple satisfaction. Differences were also evaluated regarding the subscales of each dimension. The level of parenting stress, couple satisfaction and health perception reported by mothers of healthy children and those with diabetes were compared using the above mentioned analysis methods.

Parenting stress and diabetes

The differences between mothers of children with diabetes and those of healthy children regarding parenting stress proved to be significant and are manifest in both children and parent domains.

Results revealed significant differences between the groups regarding parental stress.



Graph 1. Difference between samples regarding parental stress

As shown in the graph significant statistical differences between mothers of children with diabetes and those of healthy children were recorded in parental stress level, t (60) = 4.87, p <.01. These results were also supported by the effect size indicating a big effect r2 =.28 of the difference statistically in the favour of mothers of children with diabetes. Differences were also identified in 10 of the 13th subscales of child and parent domains. This means that mothers of children with diabetes compared with those of healthy children have higher levels of parental stress generated by

- children characterized with higher level of hyperactivity t(49.94) = 3.66, p<.01, r2 =.21, adaptability t(60) = 3.84, p<.01, r2 =.196, demandingness t(53,745) = 5.11, p<.01, r2 =.32, mood t(47,672) = 4,39, p<.01, r2 =.28 and acceptability t(52,290) = 2,752, p<.01, r2 =.12.
- parent characteristics such as competence (60) = 4,120, p<.01, r2 =.22, isolation t(54,215) = 3,27, p<.02, r2 =.16, feelings of role restriction t(60) = 4,44, p<.01, r2 =.24, depression t(60) = 3,94, p<.01, r2 =.20 and health t(60) = 3,98, p<.01, r2 =.20.

It is important to note that the observed effect size for the difference in parenting stress among these parents is a large effect except for the subscale of child acceptability where the observed effect size is small, although the difference is still statistically significant.

Subscales with no significant statistical differences are parent reinforcement, attachment and husband/wife.

Table 1. Parental Stress Index stress data

	Mothers of children with diabetes				Mothers of healthy children			
	min	max	mean	Standard deviation	min	Max	mean	Standard deviation
Parental stress	189	367	273,13	50,97	148	314	217	44,34
Hyperactivity	19	37	25,74	4,38	15	28	22,35	2,70
Adaptability	16	43	28,93	7,01	13	33	22,61	5,91
Demandingness	17	36	26,25	6,46	11	28	19,00	4,53
Mood	7	24	14,13	4,44	5	15	10,09	2,53
Acceptability	8	31	17,12	7,00	7	24	12,96	4,67
Competence	17	52	35,74	8,82	17	38	27,71	6,32

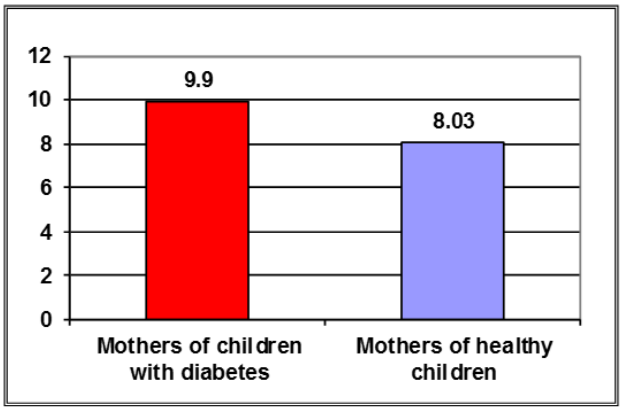
	Mothers of children with diabetes				Mothers of healthy children			
Isolation	6	28	16,45	5,77	6	22	12,29	4,11
Feelings of role restriction	13	32	23.41	4.51	7	28	18.03	5.02
Depression	12	43	26,87	6,55	9	36	20,48	6,19
Health	7	21	14,13	3,60	6	16	10,80	2,94

Health perception and diabetes

Regarding health perception of mothers we found statistically significant differences only regarding the Chance-Luck Health Control subscale. Mothers of children with diabetes consider to a greater extent than do those of healthy children that health can be controlled by luck or chance ($t(60) = 2.03$, $p < .05$, $r2 = .06$). Although statistically significant this difference is small according to the effect size.

Table 2. Multidimensional Health Questionnaire health control by chance or luck data

	Mothers of children with diabetes				Mothers of healthy children			
	min	max	mean	Standard deviation	min	max	mean	Standard deviation
Parental stress	2	16	9,90	3,94	1	15	8,03	3,29



Graph 2. Difference between samples regarding health perception

Regarding the other Multidimensional Health Questionnaire scales results did not show statistically significant differences, there were no clear differences between mothers whose children are suffering from diabetes and those whose children are physically healthy. Moreover there are scales with statistically similar results; the significance of the independent t test was very low. These are related to health consciousness, self-blame for health and health monitoring. For the last of these the similarity of the results of the two groups is very high, $t(48,662) = .06$, where $p > .90$ ($p = .95$), and the magnitude of the difference is practically non-existent $r^2 = 0.00$, so 0%.

Couple satisfaction and diabetes

Results show that there are no statistically significant differences between the two samples either regarding couple satisfaction or the in the four subscales of the Dyadic Adjustment Scale. Mothers of children with diabetes have a similar perception on couple satisfaction compared with mothers of healthy children.

Table 3. Couple satisfaction data

	Min		*Max*		*Mean*		*Standard Deviation*		*t*	*Sig(1 tailed)*
	with diabetes	*healthy*	*with diabetes*	*healthy*	*with diabetes*	*healthy*	*with diabetes*	*healthy*		
Dyadic satisfaction	25	24	49	48	41.81	41.42	5.78	5.53	.27	.79
Cohesion	10	8	23	23	18.74	17.84	3.57	3.32	1.03	.31
Consensus	41	36	63	62	53.64	52.26	5.92	5.48	.96	.34
Affective expression	6	6	10	10	8.10	8.06	1.07	1.18	.11	.91

DISCUSSIONS

The information obtained regarding parental stress in mothers of children with diabetes is significant and important.

A study regarding family roles in the treatment of a child with diabetes were carried out by Etzwiler and Sines (1962) involving 72 children, aged between 6 and 15, and their parents. The study reported that mothers and fathers assumed very different roles in the care of their child's diabetes. In most of the families studied, mothers were primarily responsible for communicating with physicians, supervising all aspects of the treatment regimen at home, and handling diabetes-related emergencies. This is a common situation for Romania, where mothers quit their jobs to stay home and take care of the child's condition. Not surprisingly, mothers score high on parenting stress.

Normal duties and responsibilities of a parent are doubled in the cases of mothers of children with diabetes because of the burdens of treatment. Thus mothers find themselves with very little time for personal needs or for their husbands; they can no longer relax or do pleasant activities whenever they feel the need. Thus they experience a state of strain and stress. This condition may be exacerbated for Romanian mothers because of the low level of information they receive, the limited support and especially because of the weaknesses of the health system.

It is also important to underline that the parenting stress the mothers experience is generated in the same time both by children's behavioural and mood characteristics that may be exacerbated by the disease, such as hyperactivity, lessened adaptability, demandingness, mood and acceptability and also by such parent characteristics as competence, feelings of role restriction, depression and health.

The results obtained in this study are consistent with other studies regarding parental stress when there is a diabetic child in the family.

A study by S.M. Seppänen, H.A.Kyngäs, M. J. Nikkonen (1999) regarding the process of coping in parents of children with diabetes identified six stages that parents pass through: distrust, lack of information and guilt, learning about care, normalization, uncertainty and reorganization. In each of these periods, parental stress is felt differently. A chronic illness of a child is always a shock for parents who often lose control and tend to deny their feelings or the diagnosis. This can also be a manifestation of stress. In Seppänen, Kyngäs and Nikkonen's study issues shown to be stressful for parents include those arising from perceived lack of skills and knowledge regarding taking care of a diabetic, and the responsibility and changes in the daily routine of the family.

In a study of parenting stress involving 52 mothers of children with diabetes, Hauenstein, Scarr and Abidin (1987) showed those mothers to have high scores on mood and demandingness scales and low scores on such scales as acceptance and parent reinforcement in the child domain. In the parent domain low scores were obtained in competence, health, partner and attachment. The researchers found that in families with a diabetic child mothers may need help in identifying the positive attributes of the child and to be reassured of their maternal skills (R. Abidin, 1995).

Auslander, Miller-Johnson, Weist and Jacobson studied the factors that may be correlated with decreased metabolic control and showed a close relationship with high levels of family stress, low family resources, increased conflict between parents and children, low levels of parental involvement and of the ability of families to express their feelings openly (Court & Lamb, 1997).

Interesting results were obtained regarding health perception. Mothers of children with diabetes think to a greater extent that health is controlled by chance or luck than do mothers of healthy children. This effect can be the effect of the diabetes diagnosis received by the child. Most of the time, diabetes has an insidious onset and the diagnosis is made quickly by a doctor who does give clear explanations about the causes of the disease. It is known that type 1 diabetes is an autoimmune disease with a multi-factorial mechanism. These are the reasons why a parent's question"why especially my child?"remains unanswered. It is hard for some parents to understand why type 1 diabetes is also named"destiny disease". In Romania this lack of control over health can also be the result of lack of trust in the medical system and the lack of preventive health behaviour.

Recent studies have reported contradictory psychological findings regarding couple satisfaction. Some suggest that mothers of children with a diabetes diagnosis receive less spousal support than mothers of healthy children and lack of paternal involvement has important implications for a mother coping with her child, (Hauenstein, E., Marvin, R., Snyder, A., Clarke, W., 1989) while other studies reported no significant differences between parents caring for a child with chronic disease or impacts on married parents with healthy children affecting marital quality or perceived marital stability (Eddy, L., Walker, A., 1999).

This study has revealed no difference between mothers of children with diabetes and mothers of healthy children regarding couple satisfaction as defined by dyadic satisfaction, cohesion, consensus and affective expression responses. These results may reflect the fact that the study group was formed by mothers of children with a good glycaemic control. The importance of good psychological adjustment in families has been highlighted in several studies. Dumont investigated psychological factors associated with acute complications in children with DID and drew attention to the part played by family conflict, low levels of cohesion, family organization and expressiveness in the presentation of low levels of social skills by children, behavioural problems and recurrences of diabetic ketoacidosis (Court & Lamb, 1997). Also Ryden, comparing families of children with optimal metabolic control in infants with those with poor physiological adjustment, showed that the latter have parents who appreciate each other less, do not agree on child care and do not encourage independence and integrity in their child. He showed that family therapy is more effective than conventional therapy in improving diabetes control (Court & Lamb, 1997).

CONCLUSIONS

Diabetes, together with myocardial infarction and cancer, ranks at the top of the hierarchy of medical conditions from the point of view of epidemiological prevalence. This condition affects the psycho-somatic-relational balance of both patients and their family members through a number of factors such as the acceptance of the diagnosis, adapting to a strict diet consistent with a constant medication and adjustments of lifestyle.

This paper has aimed to highlight changes in maternal psychological profile of children with type 1 diabetes. Results have shown differences between the mothers of children with diabetes and mothers of healthy children in some psychological dimensions such as parental stress and health perception. No differences were demonstrable regarding maternal self-perception on martial satisfaction.

These results show some changes in the psycho-socio-relational registry of mothers of children with diabetes, changes that need to be known to be taken into account whenever a child is newly diagnosed with type 1 Diabetes. That information is very useful to initiate

support and interventions programs for disease acceptance and adaptation to new conditions of life imposed on the family by the child's condition. Such programs for the children themselves, and for the parents and siblings of those diagnosed, should be used to complement treatment schemes established by the attending physician to improve quality of life for families who have a child with diabetes and to minimize the negative effects of the diagnosis.

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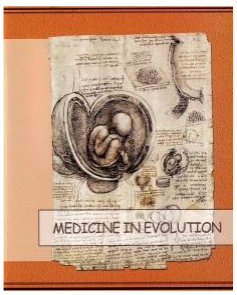
The influence of negative affectivity to coronary revascularization cardiovascular events on the rate fatal/non-fatal



Cosor O.-C., Baibata D.-E.-S., Mosteoru S., Gaita D., Mancas S.

"Victor Babes"University of Medicine and Pharmacy, Timisoara

Correspondence to:
Name: Asist. Univ. Dr. Oana Catalina Cosor
Address: Str. C.D Loga,Nr.49, Timisoara
Phone: +40 724036836
E-mail address: oanacatalinaiancu@yahoo.com

Abstract

Background: Depression become an psychosocial indicator that relate with evolutivity of atheroma plaque, independently of coronary dezobstruction process.

Aim: To analyze Kaplan Meier survival curve linking the degree of depression severity in coronary revascularized.

Material and methods: We included 6 months- 3 years coronary postrevasculated and have watched rate of events (MACE) on the entire sample selected. Scores HAS, DASI and maximum metabolic equivalent have defined 4 categories of analysis.

Results: 341 patients; mean age 64.22 ± 8.9 years; B / F 278/63. MACE median time was 4.33 years. There were significant differences of Kaplan Meier curve between categories of coronary depression ($p = 0.005$; 95% CI, Log Rank test).The average of metabolic equivalent was low: 6.09 ± 1.5 METs. There were significant correlations between METS and DASI score ($r = 0.968$; $p < 0.001$).

Conclusions: Our study demonstrates component negative influence of afectivity on the rate of MACE in coronary regardless of dezobstruction process. Those with average / high depression score had an obvious limitation on exercise capacity.

Keywords: myocardial revascularization, depression, MACE.

INTRODUCTION

Depression increases risk for coronary heart disease independently and the rate of cardiovascular events fatal / non-fatal myocardial infarction. [1]

A review of the literature including studies on coronary patients revascularized reveals that depression increases of 3 to 4 times the risk of recurrent cardiac events and death in patients after myocardial infarction rate of myocardial infarction. (Frasure- Nancy Smith and collaborators, Ingrid Connerney Louis Borowicz Jr., James A. Blumenthal) [2,3,4]

Depression has a clear impact on quality of life. [4] It should be seen as an psychosocial indicator that relate with evolutivity of atherom plaque, independent of coronary dezobstruction process. [5]

Our study was designed to test the hypothesis that long-term rate of cardiovascular events fatal / non-fatal could be influenced by negative affectivity component coronary revascularization remote > 3 years and <5 years dezobstruction process.Recrudescent of depression may or may not impact on the prognosis of these patients?

MATERIAL AND METHODS

Study design

The group of 375 hospitalized pacients in Timisoara Institute of Cardiovascular Diseases, based on criteria for inclusion / exclusion set forth below, we selected a total of 341 patients revascularized interventional- PCI (percutaneous transluminal angioplasty with vascular prosthesis placement) and surgical revascularization - CABG (coronary artery bypass grafting). Evaluation of patients was done in two different times:

T1 - baseline or initial assessment, about 6 months to 3 years postrevascularization

T2 - the final moment or reassessment, quantifying and analyzing survival MACE prevalence of depression categories at > 3 - <5 years from the baseline.

Our study was conducted in accordance with the principles of the Declaration of Helsinki and the study population was informed about the risks and benefits of each procedure of the study, it was signed a consent form approved by the Ethics Committee of the Institute of Cardiovascular Diseases Timisoara.

Criteria of inclusion and exclusion

The study population was represented by revascularized patients with acute coronary syndrome and select subsequent from database Timisoara Institute of Cardiovascular Diseases. The group of patients was eligible for the following inclusion criteria:

Inclusion criteria: - the inclusion 6 months- 3 years, bypass surgery indication or emergency coronary angioplasty or percutaneous transluminal coronary indication in the emergency, acute myocardial infarction, acute myocardial ischemia.

Exclusion criteria: - anxiety / depression and / or specific treatment prior revascularization, kidney failure; respiratory; liver, cardiogenic shock, stroke prior revascularization).

The population sample was analyzed at (T1) through data collected from observation sheet General Clinical when revascularization, which included both demographic data relating to: (age, sex, rural / urban) and Psychological related data measurement tools used to determine the severity of each patient affective disorder. Severity for depression and anxiety questionnaire was analyzed by HAS / HAD (Hospital Anxiety and Depression Scale) [6]. Were defined four categories of patients depression with anxiety that depending on their score (0-7 = normal score, score 8-10 = mild depression, scoring 11-14 = moderate depression and severe depression score = 15-20) and analyzed.We also analised DASI score (Duke

Activity Status Index) [7] representing the functional capability of the subject self-assessment then calculated by mathematical relationships maximum permitted O2 consumption and maximum metabolic equivalent. [8].

Revascularization procedures was mentioned in the note of discharge and the rate of cardiovascular events occurred at (T2) > 3 years and <5 procedure was examined by determining the survival curves, according to results from rehospitalization patients at acute event. TIME variable was defined as the time from the date of coronary revascularization untill January 2015 and the event being analyzed included in MACE variable. We defined major cardiovascular events fatal / non-fatal occurred - (Major Adverse Cardiovascular Events - MACE) coronary angioplasty (PTCA), bypass grafting (CABG), acute coronary syndrome (ACS), stroke, transient ischemic / stroke, heart failure (IC), newly diagnosed diabetes (diabetes), cardiovascular death or death from any cause.

The primary endpoint: survival curve achieved by Kaplan Meier method - relate or not, severity level of anxiety / depression postrevascularization artery.

Secondary endpoints included:

- A) defining variable MACE (Major Adverse Cardiovascular Events) and determining the median time to occurrence of MACE events (period under review: the > 3 years and <5 years) in the event of dezobstruction process.

- B) Establishing relationships possible association between self-assessment score (DASI) and exercise capacity (VO2 and METS) of the subject, based on estimates resulted on mathematical relationships supported (DASI score, maximum O2 consumption and maximum metabolic equivalent).

The estimation of the maximum oxygen consumption was carried out according to the formula:

0.43x (DASI) + 9.6 = x (ml / min) Interpretation: - wave mx = 58.2 mL / min
(NOTE: 1 MET = 3.5ml / kg / min) - wave. min. = 0

Consumption / metabolic equivalent was calculated using the formula:

Y METS = $\frac{x\ ml/min}{3.5}$ (1 MET = 3.5 ml/kg/min)

Follow –Up

Patients in the study were followed for at > 3 years and <5 years from the moment of dezobstruction assessment. We filled a chart tracking evolution in which we noted the fatal event rate / non-fatal cardiovascular or other mortality due date from coronary revascularization patients and by the time the event has been detected as present or absent. All data from the study were statistically.

Statistical analysis

Statistical analysis was performed with SPSS Statistics 17.0, statistical significance was taken to a value of p less than 0.05 for the 95% range. To test differences between means and the environment variables were used Kruskal-Wallis test and Mann- Whitney. Analysis of the survival data was performed by means of Kaplan Meier that suppliers probability of survival for a period of 3 years > and <5 years of dezobstruction process.

For the analysis of survival was generated a Kaplan-Meier graph using the median survival time. To evaluate the relationship between survival and time variable and if there were differences between survival group and the other group we used log-rank test.

RESULTS

The study group consisted of a total of 341 coronary revascularization who meet the eligibility criteria.

In Table 1 we show the percentage basal characteristics of the sample analyzed:

Table 1. The weight of basal characteristics of the sample examined

Variable	Study group n = 341
B/F	278/63
Age (years) *	64.22 ± 8.90
Afectivity Anxiety score * Depression score *	 7.33 ± 4.35 6.68 ± 3.77
Depressive categories ** Normal (0-7) Low (8-10) Moderate (11-14) Severe (15-20)	 51.6 34.9 11.1 2.3
Revascularization process ** PTCA CABG PTCA + CABG	 42.8 51.9 5.3

* average ± DS
** % group

Revascularized patients with depression prevalence was 48.4% with predominant forms of mild and moderate depression. DASI score histogram frequency is represented in Figure 1:

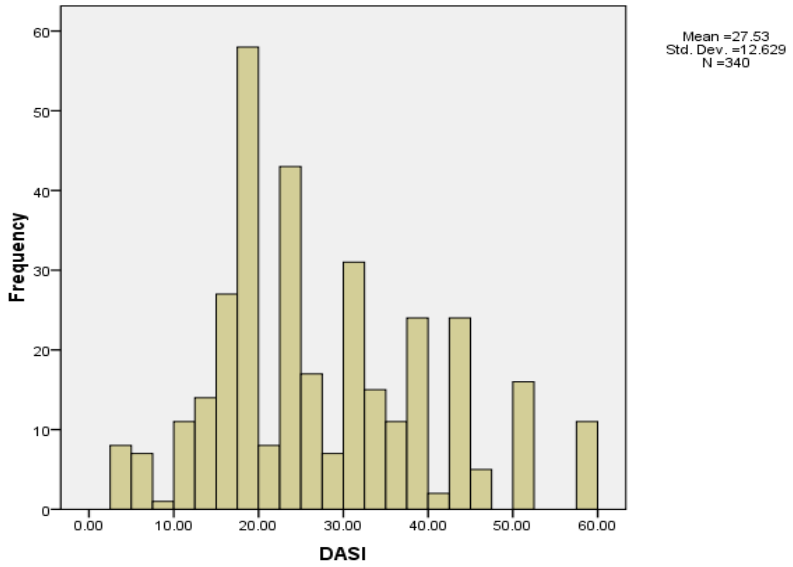


Figure 1. DASI score histogram on studied sample

The definition of MACE events and their analysis reveals the prevalence of rehospitalization for heart failure in 21.7% to 10.9% in pacemaker implantation and coronary revascularization in other territory in 26% of cases. Cerebrovascular event rate was 6.5% of non-fatal. Please note that during assessments was not registered cardiovascular death. But it is true that we recorded death from another cause in 17.4% of cases.

Probability analysis Kaplan Meier survival method is shown in Figure 2:

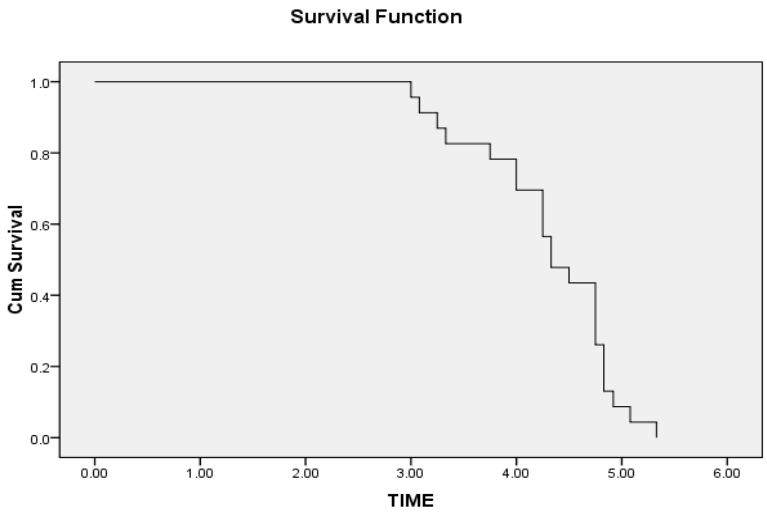


Figure 2. Rate of major cardiovascular events

Median time to occurrence of MACE events was estimated at 4.33 years (3.93 - 4.72 years). We found statistically significant differences Kaplan Meier curve between patients with depression categories (Figure 3):

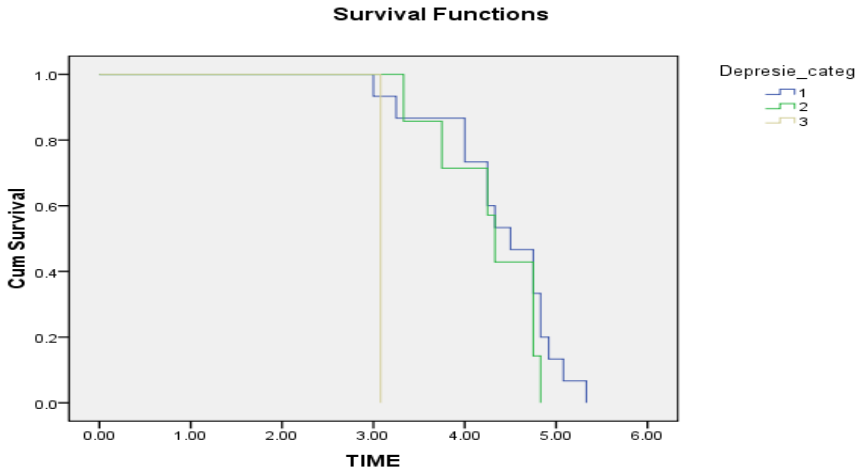


Figure 3. Kaplan Meier survival on analised categories

Less depressed coronaries (mild and moderate category) had the highest proportion of non-occurrence of MACE events (p = 0.005; 95% CI, log rank test). The relationship between negative component association affection and exercise capacity determined by patient self-assessment method is real. Metabolic average of these pacients clearly highlights limitation of exercise capacity (6.09 ± 1.5 METS).

We found highly significant statistical correlation between DASI and METS score (r = 0.968; p <0.001) (Figure 4).

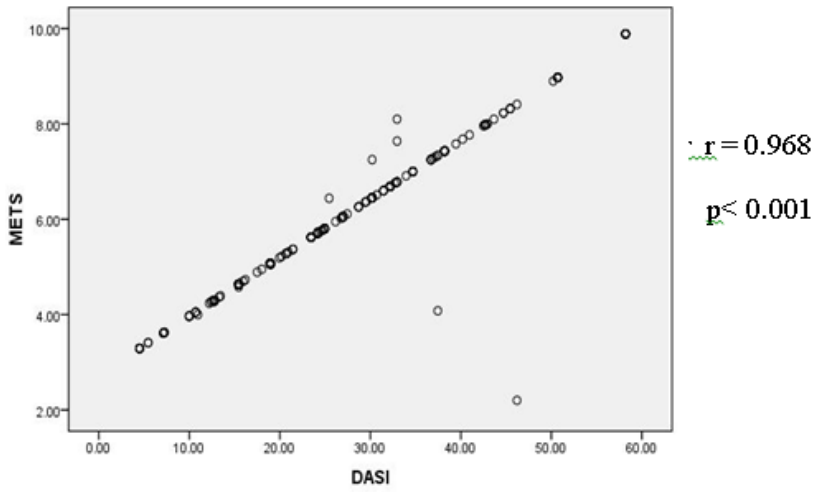


Figure 4. Correlation between DASI score and methabolic equivalent METS

Also, there were significant differences between the average VO2 DASI and 4 categories depressed patients (p <0.001; 95% CI) (Figure 5):

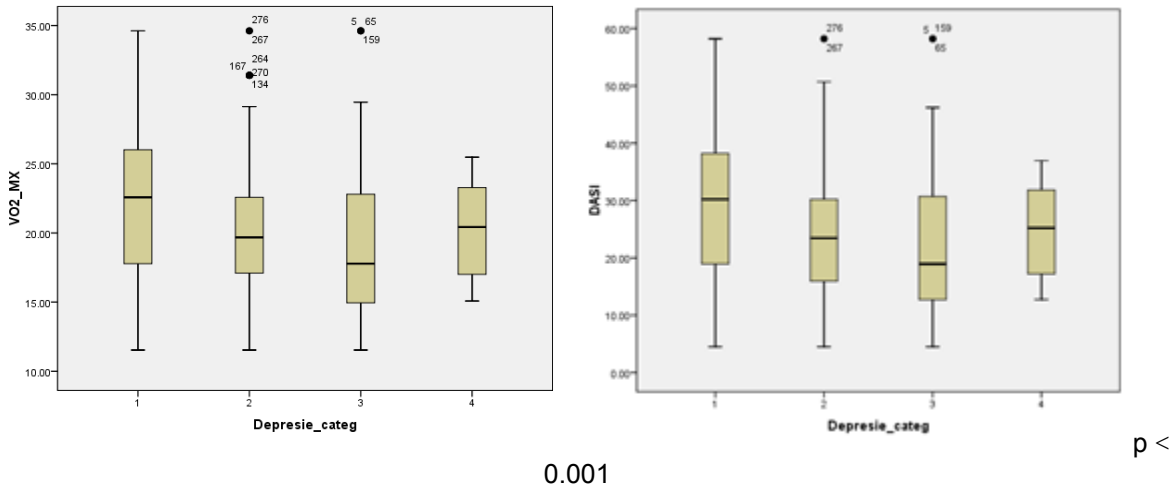


Figure 5.. Relationship between categories of depressed pacients and DASI average and VO2 max.

Our research results are validated in a sample of coronary revascularization, limited criteria for inclusion / exclusion formulated to the study design.

DISCUSSIONS

The present study started from the premise that presence and / or recrudescence of depression could have an impact on the prognosis of coronary postrevascularization. Our study confirms that between categories depressed patients reviewed had no statistically significant differences Kaplan-Meier curve. Our results were based on the analysis of cardiovascular events included: MACE variable and TIME variable determination. Our results argues that depression is an independent and important contributor to morbidity by any cause and psychosocial up to 5 years after revascularization. These evidences with statistical significance on postrevascularization pacient justify assessing for controlling depressive patient quality of life. It is estimated that this score of depression one month after coronary dezobstuction is an important indicator of cardiac morbidity medium and long term. [9]

Other prospective studies assessing depression symptoms in postrevascularized patients and the effects on long-term. [10]

Stringent references regarding prevalence of depression at coronary revascularization groups and the relationship between medical and psychosocial depression and morbidity clearly justify the place of psychologist in comprehensive cardiovascular rehabilitation team.

Current cardiac postrevascularized rehabilitation programs emphasize the importance of justified sedentary intervention. In our study, patients with higher depression score consistently reported fewer physical activities, appreciated by us through transformation in metabolic equivalent and maximum consumption of O2.

The relationship between depression and physical activity is an obvious limitation already demonstrated. Capacity of effort and relation of association with cardiovascular events rate analyzed with MACE is interested on coronary depressive pacient by correct autoevaluation.

Our study confirms that among the 4 categories of patients analyzed there is a clear limitation of physical activity.

Given the importance of physical activity in this population, our findings regarding independent association of depressive symptoms with low physical activity has important significance on quality of life.

For example, Milani and Lavie reports that regular exercise reduces depressive symptoms in postrevascularized patients. In addition they say that cardiac rehabilitation is associated with a reduction in depressive symptoms and mortality [11].

It is a reason to believe based on the results of the new study sample that depression may occur anytime in the coronary patient and therefore should conduct a screening ongoing depression in this subset of patients, especially during aggravation of cardiac symptoms.

CONCLUSIONS

1. The rate of cardiovascular events fatal / non-fatal coronary revascularization among component was significantly influenced its negative affectivity.

2. Regardless of coronary dezobstruction process, the median time to occurrence of events was analyzed over 4 years and did not influence the prognosis of these patients.

3. In contrast, our study supports and demonstrates limiting exercise capacity among revascularized coronary score and medium / high depression.

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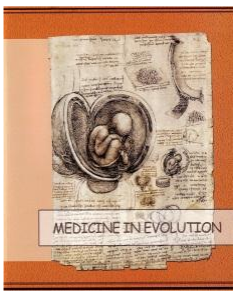
Charcot- Marie- tooth disease in a 60-year-old man - Case report



Chirileanu R.D.[1,2], Simu M.[1,2], Tudor R.[1,2], Cecilia R.[1,2], Jurca P.[2]

[1]*University of Medicine and Pharmacy"Victor Babes"Timisoara*
[2]*Department of Neurology, Emergency County Hospital of Timisoara*

Correspondence to:
Name: Assoc. Prof. Ruxanda Dana Chirileanu
MD, PhD, Senior neurologist
Address: Emergency Clinic Hospital 2nd Department of Neurology, I Bulbuca Street, Number 10 Timisoara, code 300736
Phone: +40 722743356
Fax: +40 256487890
E-mail address: dana.chirileanu@gmail.com

Abstract

Charcot-Marie-Tooth disease is a genetically determined neuropathy, inherited or caused by de novo mutations, characterized by distal predominant motor and sensory loss, muscle wasting and pes cavus. Differential diagnosis especially with spinal diseases is important in cases of painless bilateral foot drop with numbness. The treatment is only supportive at this point. We present the case of a 60-year-old male who presented with paraparesis accompanied by numbness and moderate pain, which started 2 years before he underwent surgery for a schwannoma at T8-T9 spinal level in 2011; although the tumor wasn't relapsing, his symptoms were progressing, he had bilateral foot drop, bilateral muscle wasting of the anterior leg, foot and thenar eminence, bilateral pes cavus and hammer toes, fasciculations and seemed to have had functional limitations- like playing sports, when he was in his teen years, although he didn't remember any pain or sensory loss back then.

Keywords: Charcot-Marie-Tooth, hereditary neuropathy, pes cavus, bilateral foot drop.

INTRODUCTION

Charcot-Marie-Tooth(CMT) disease is the most common inherited neuropathy, representing a genetically and phenotypically heterogeneous group of disorders. CMT disease includes hereditary motor and sensory neuropathies, hereditary sensory and autonomic neuropathy and hereditary distal spinal muscular atrophy; most types are autosomal dominant, but there are also X-linked, autosomal recessive and de novo mutations[1]. The most frequent ones are: CMT1A linked to PMP22 duplication, CMT1X linked to GJB1 mutation, CMT2A linked to MFN2 mutation, CMT1B linked to MPZ mutation, and hereditary neuropathy with liability to pressure palsy linked to PMP22 deletion[2]. Symptoms usually occur in the first to second decade, the onset is insidious and most of the patients have slowly progressive muscle weakness and wasting-especially of the muscles innervated by the peroneal nerve, decreased reflexes, vibratory and other sensory loss, pes cavus, hammer toes and scoliosis. Electrodiagnostic studies are very important for clinical diagnosis, but genetic diagnosis is important for prognostication[1]. Other causes of bilateral foot drop need to be considered in the differential diagnosis, especially spinal diseases[3]. Treatment for CMT patients is only supportive, although clinical trials are ongoing and the combination of baclofen, naltrexone and sorbitol has recently proved some efficiency[2].

CASE PRESENTATION

I. Anamnesis

A 60-year-old-man presents to our clinic for diagnosis and treatment with paraparesis, accompanied by numbness and moderate pain. From the patient's history we found out that the symptoms started 5 years ago with difficulty in walking and paresthesia in both of his legs; the onset was insidious and the symptoms progressed slowly for a period of 2 years to paraparesis with numbness. Magnetic resonance imaging (MRI) of the spinal column performed 3 years ago showed the presence of a tumor at T8-T9 level suggestive for a schwannoma, which compressed the spinal cord causing edema at T6-T9 level, discal protrusion at L5-S1 level with stenosis of both foraminal canals, and discal protrusion at C4-C5 level without spinal cord compression. The patient underwent surgery, the histopathological exam confirmed the schwannoma and the symptoms seemed to be regressing when the patient was discharged. He was admitted to our clinic with the suspicion of a tumoral relapse, although he reported no amelioration of the symptoms after the surgery, furthermore he accused a progression of the symptoms since onset, with short periods of mild amelioration after intravenous treatment with neurotrophics. He also reported difficulties in playing soccer when he was a teenager and started developing pes cavus and hammer toes when he was about 20 years old and was suspected of Friedreich's ataxia- but since he didn't develop anymore symptoms characteristic for ataxia, the diagnosis was invalidated among the years. He had no other comorbidities and no family history of neuropaties. At admission he was on oral treatment with muscle relaxers and peripheral vasodilators.

II. Clinical examination data

At neurological examination the patient was conscious, cooperative, and temporo-spatial oriented, he had muscle wasting of both of his anterior legs, feet and thenar eminences, bilateral pes cavus and hammer toes, fasciculations in his calf on both sides, bilateral foot drop, bilateral steppage gait with unilateral support, Romberg test was positive of the mioartrokinetic type, he had paraparesis 4/5 bilateral, hypotonia in both of his legs, normotonia in both of his arms with no motor deficit, lower limb deep tendon reflexes were absent and a normal cutaneous plantar reflex was present, idiomuscular reflexes were

present, he had numbness and moderate pain in his legs and a perturbed vibratory sense in his lower limbs, he had mild ataxia at the finger to nose test on the left, but was able to perform rapid alternating movements, no dysarthria and swallowing disorder were present. Mini Mental Examination revealed a scor of 30. The physical examination was without abnormalities and there were no signs of neurovegetative disautonomy.

III. Laboratory data

The biological findings were all normal.

IV. Additional paraclinical investigations

Nerve conduction velocity showed unobtainable nerve action potentials at electrical stimulation at peroneal level on both sides. Electromyography showed unobtainable compound muscle action potential at rest and in medium contraction it showed normo and hypovoltage potentials which were conclusive for chronic neuropathy. MRI of the spinal column showed no relapse of the tumor and a degenerative stenosis of the spinal canal at C4-C5 level, without radicular compression and without modifications of the spinal cord. The financial possibilities did not allow genetic testing. The patient was diagnosed with CMT disease.

V. Treatment and evolution

The patient underwent treatment with iv neurotrophics and oral muscle relaxers for a period of 10 days. He was discharged without any subjective complaints; his pain was gone, he had no more paresthesia and he could walk without support, although he still had bilateral steppage gait and paraparesis (+4/5). He was recommended oral treatment with neurotrophics and baclofen.

DISCUSSIONS

The particularity of this case was the relatively late onset of the disturbing symptoms and the fact that they were initially thought to be due only to spinal disease, although the patient had typical muscle wasting and bilateral pes cavus. The majority of CMT disease patients develop the first symptoms in the first to second decade, the onset is typically insidious and moderate pain is noted by the majority of the patients. Because of the insidious onset and progression, sometimes deficits are less obvious for the patient, that is why is important to ask about functional activities at a younger age- such as difficulties in playing sports, or frequent spraining of ankles, symptoms that are suggestive for a slowly progressive hereditary etiology and that our patient started developing when he was about 20 years old, but ignored since he had no motor deficit. He had no family history of neuropaties, so he could have suffered a de novo mutation, maybe with reduced penetrance, since severe symptoms started worsening only in his 50s. Differential diagnosis was essential in this case. First with spinal tumor-the MRI showed no relapse at that level; second, the patient had bilateral foot drop and numbness with discal protrusion at L5-S1 level with stenosis of both foraminal canals, but bilateral S1 radiculopathy doesn't cause pes cavus, and our patient had no radicular pain; third with Friedreich's ataxia-even though the patient had mild ataxia at the finger to nose test on the left, CMT disease is known to affect the posterior columns, and the patient had no other ataxia symptoms, or speech disturbances. Differential diagnosis with Aran-Duchenne disease can also be considered, since the disease also manifests with muscle weakness, wasting and paralysis, but this is due to degeneration of motor neurons in the spinal cord and usually begins in the small muscles of the hands and without sensory symptoms[4], and our patient had pain and the muscle wasting started at peroneal level. In CMT disease there are genetic defects of Schwann cells and the malfunctioning cells lead to

progressive axonal and neuronal loss, resulting in neurogenic muscle atrophy[2]. Treatment with intravenous neurotrophic and baclofen was benefic for our patient, highlighting CMT disease etiology of the symptoms and the role of supportive treatment. CMT disease usually affects younger adults, but is important to be considered as cause of neuropathy when associated with muscle wasting, motor and sensory deficits and characteristic deformities, no matter the age of the patient.

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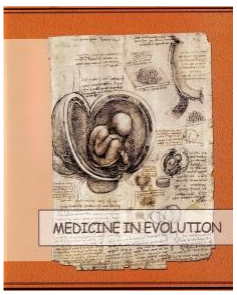
The contribution of transfontanellar ultrasonography in the diagnosis of bacterial brain infections – General review



Boia M.[1,2], Cioboata D.[2], Nicoara D.M.[2], Manea A.M.[1]

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

Correspondence to:
Name: Mariana Boia
Address: Giroc Str. Gospodarilor Nr 42,"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
Phone: +40 740137597
E-mail address: marianaboia@yahoo.com

Abstract

Acute cerebral infections in neonatal period represent a major cause of infant mortality, especially if it is grafted on a ground with immunological deficiencies due to prematurity or intrauterine growth retardation. Therefore the applicability in practice of a medical rapid diagnostic methods- cranial ultrasonography, since the first hours of life, represents a real help for neonatal intensive care units. Pathological germs involved, Group B Streptococcus and E. coli, Haemophilusinfluenzae, Streptococcus pneumoniae and Neisseria meningitis cause severe forms of the disease, usually associated with brain injury. The authors aim in this article to present the useful sonographic signs for quick diagnosis of neuropathological lesions specific for meningitis, meningoencephalitis, arachnoiditis, ventriculitis, vasculitis, cerebral edema and cerebral infarction. Also is presented a correlation between sonographic and clinical signs with the purpose of improving both immediate and late prognosis.

Keywords: cranial ultrasonography, infections.

TRANSFONTANELAR ULTRASONOGRAPHY AND BACTERIAL BRAIN INFECTIONS

In recent decades routine use of ultrasound has led to early detection of cranio-cerebral injuries, including acute ones, followed by prompt treatment and shorter hospital stays.

Neonatal sepsis with cerebral involvement represents a major emergency, therefore early recognition and dynamic sonography have considerably improved both immediate and late prognosis. The most common etiologic agents reported are Group B Streptococcus and E. coli, followed by Haemophilus influenzae, Streptococcus pneumoniae and Neisseria meningitidis.

In the acute forms of the disease, e.g. meningitis and meningoencephalitis, the neurological picture includes arachnoiditis, ventriculitis, vasculitis, cerebral edema and cerebral infarction [1, 2]. These lesions, given the involved area and associated pathology, may progress to severe encephalitis, limit themselves leading to an abscess, or may evolve to complete resolution.

Typical sonographic findings, which can lead to prompt treatment and early and late prognosis are: increased echogenicity of the cerebral parenchyma, brain abscess, subdural fluid collections and ventriculitis [2].

Increased focal or diffuse cerebral echogenicity, in the acute stages of the disease usually indicates the presence of encephalitis, cerebral edema or cerebral infarction secondary to vasculitis - fig. 1- 4. Based on the character of the echogenicity we can appreciate the severity of the disease: focal hyperechogenicity, in the gyrus area may be caused by cerebral infarction; diffuse brain echogenicity is usually associated with significant neurologic sequelae, unlike the echogenicity of the circumvolutions, which generally resolves gradually and is not associated with neurologic sequelae.

Brain abscesses, currently rare among newborns, are a complication of encephalitis, especially Gram negative ones (Proteus, Citrobacter); the most common location is in the frontal lobes of the cerebral hemispheres. Ultrasound diagnosis may be easily established in the presence of specific sonographic signs and in the context of a severe infection - fig. 5-8: hypoechoic lesions, surrounded by a hyperechoic sleeve [3]; ventricle compression on the same side; shift of midline structures. In a newborn or infant with encephalitis abscesses form within 7-14 days.

Ventriculitis, another specific sign of bacterial brain infection, occurs in 65-90% cases of neonatal meningitis, significantly increasing the morbidity and the mortality in this age category. The following are evolutionary stages of the disease: dissemination to the choroid plexus, were the bacteria multiply leading to choroid plexitis, in turn followed by ependymitis and exudative inflammation of the cerebrospinal (CSF) fluid. Later on glial protrusions into the ventricles lead to ventricular septa causing compartmentalization. All these stages may be visualized and identified by ultrasound: ventricular septa and strands as small hyperechogenic foci, echogenic ventricular CSF, inhomogeneous echogenicity of the choroid plexus - fig. 1-2 [2]. Intraventricular septations lead to multiloculated ventricles which in turn may hinder shunt placement and the intraventricular penetration of antibiotics. Ventricle septa lead to CSP obstruction, which can be present at any level: foramen of Monro, Sylvius aqueduct, IV ventricle orifice. In time, ventricular dilatation without permeabilization of these foramens leads to the development of hydrocephalus [4, 5]. Another mechanism is represented by the impossibility of CSF reabsorption from the subarachnoid space, as a result of obstructive arachnoiditis. Ultrasonographic signs of hydrocephalus are typical: first ventriculomegaly, than light intraventricular strands that lead to hyperechoic ependymal lining, intraventricular echogenic strands or inhomogeneous echogenicity of the choroid plexus [6, 7].

Subdural and/or sub-arachnoid pericerebral effusions are other specific signs of cerebral infection; they are most commonly associated with Haemophilus influenzae meningitis. Allthough frequently present, especially in young children with meningitis, they are not clinically relevant, and no drainage is required, in the absence of significant midline shifting [8] or features suggestive of cerebral empyema (prolonged fever, seizures).

Extra-axial fluid collections are usually hypoechoic, generally located in fronto-temporal region. Subdural fluid collections along the cerebral convexities widen the space between the skull and the cerebral hemispheres, and the interhemispheric collections enlarge the interhemispheric space [9].(fig.10) Subdural empyema, cannot be distinguished by means of ultrasound from a sterile collection. Differentiation can be achieved only by means of computer tomography or magnetic nuclear imaging that highlight the enhancement of the subdural membrane.

The late complications was ultrasound diagnosicated and were multicistyc encephalomalacia (fig.9), cerebral atrophy (fig.10), hidrocephaly (fig.11) and hidranencehaly and may be associated whit subdural fluid collections or whit cortical and periventricular calcifications. (9). These ultrasound sequelae are present in the severe forms of encephalitis with extensive neuropathological lesions, and some severe forms caused by invasive germs associate multiple injuries, increasing the risk of neurological sequelae.

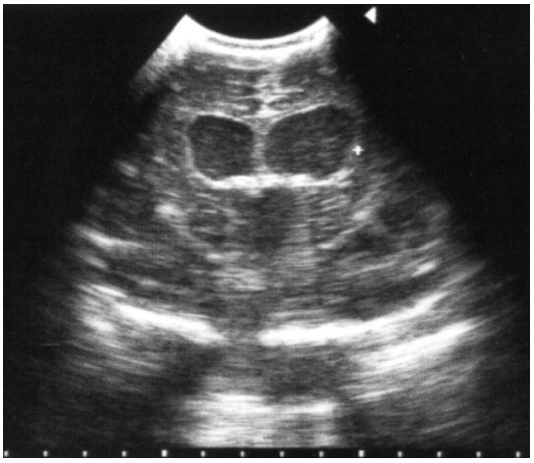


Figure 1. Medial coronal section. Ventriculitis caused by bacterial meningitis.

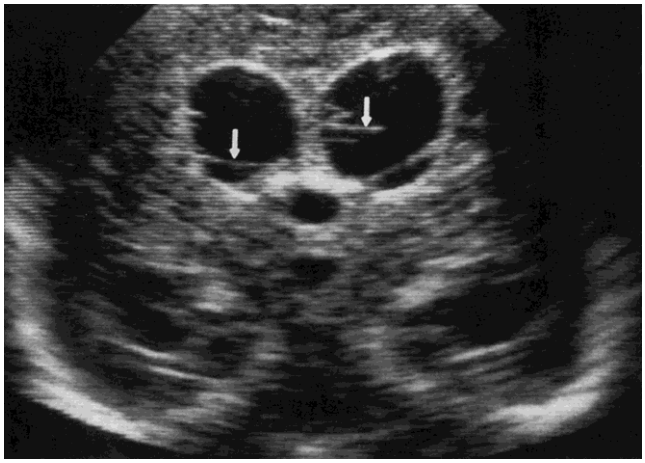
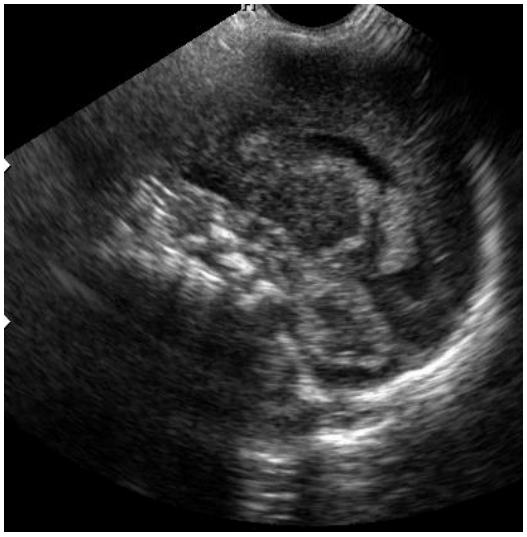


Figure 2. Medial coronal section. Ventriculitis with septs



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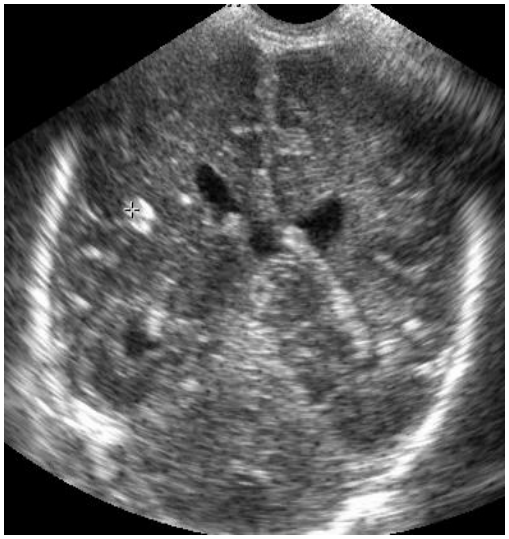


Figure 4.

Periventricular focal echogenicity secondary to cerebral infarction. Ventriculitis in a 36 weeks preterm neonate with B. Proteus meningitis.

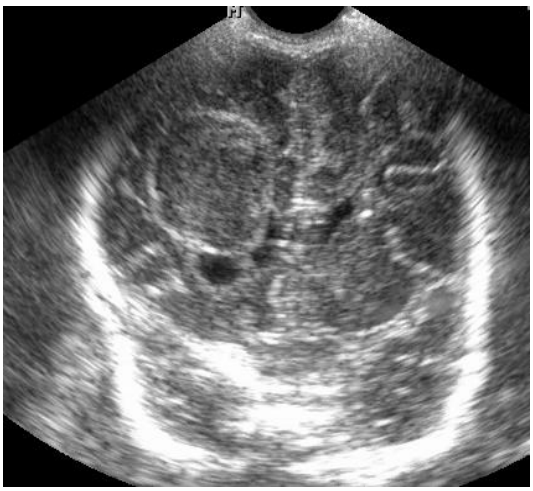
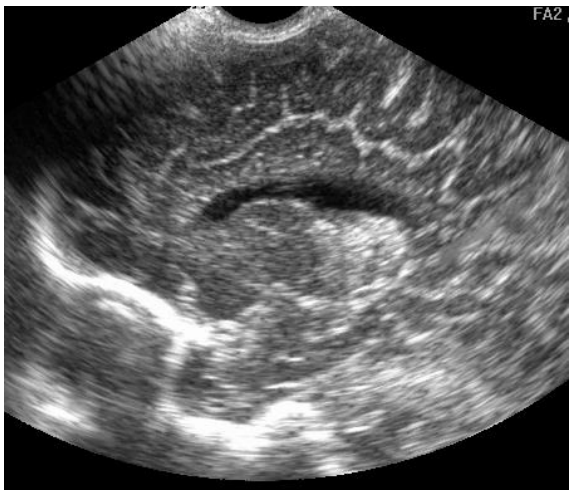


Figure 5.



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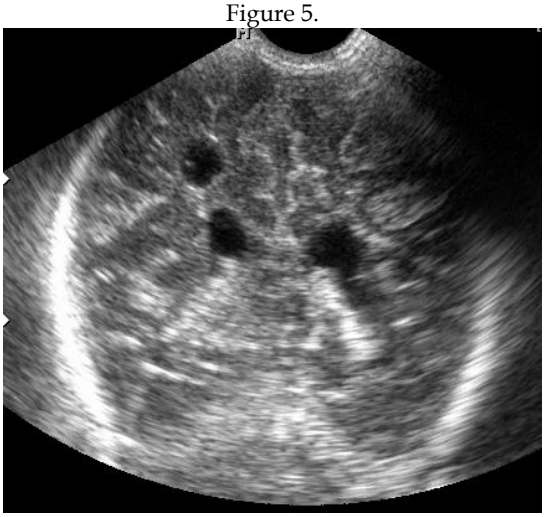

Figure 7.

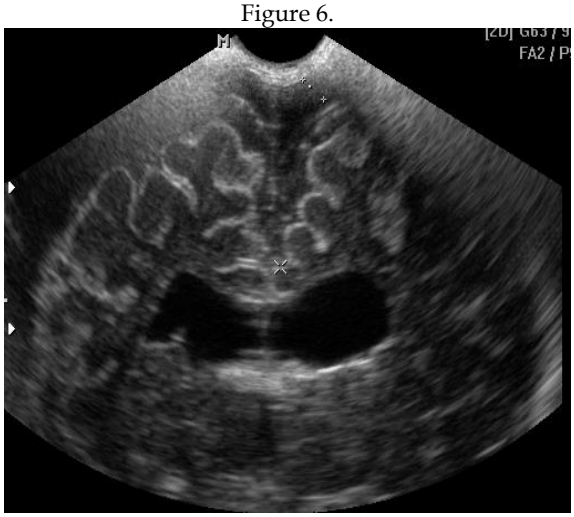

Figure 8.

Cerebral abscess characterized by a hypoechogenic area, surrounded by a hypoechoic sleeve, with same side ventricular compression and midline shifting (fig. 5 and fig. 6), periventricular cyst (fig. 7) and effusion accompanied by interhemispheric fissure enlargement and ventriculitis (fig. 8).

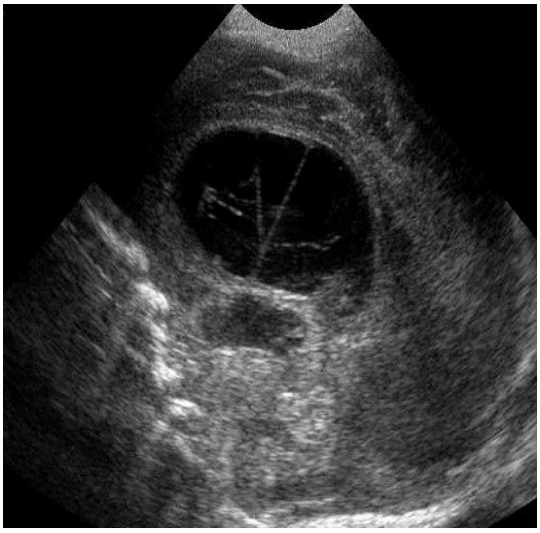

Figure 9.

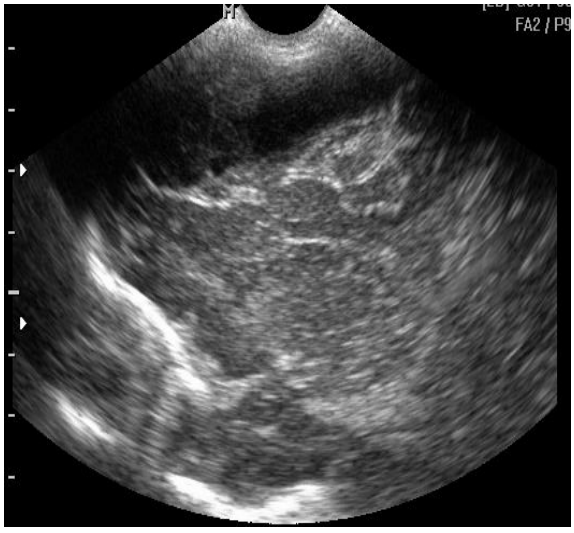

Figure 10.

Cystic stuctrure appeared in a bacterian meningitis evolution(fig.9). Transonic fluid collection in fronto-temporal region (fig 10)

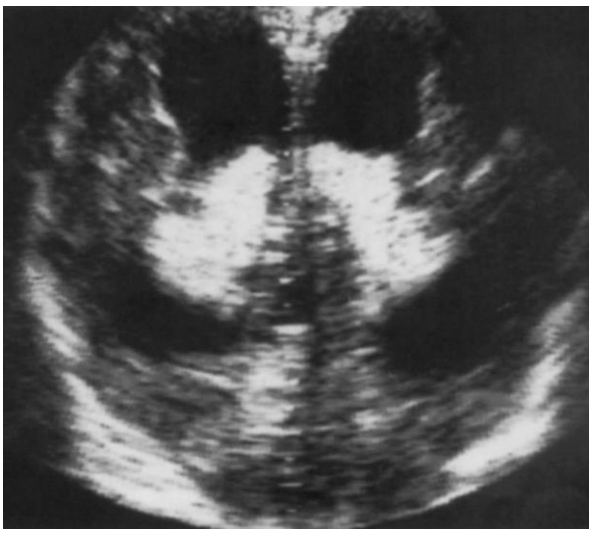

Figure 11. Evolutive hidrocephaly due to bacterian menigitis

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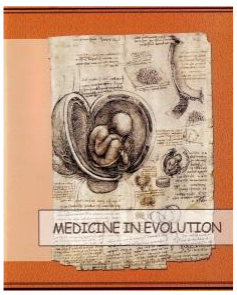
Review: Colorectal Cancer a life style problem or a genetic one



Dumitrascuta Adrian, Ana Lascu, Ramona Camelia Anculia, Iosif Adalbert Szucsik, Crinela Luminița Popa

Faculty of Medicine, „Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

Correspondence to:
Name: Crinela Luminița Popa
Address:"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
Phone: +40 723320956
E-mail address: popacrinela2004@yahoo.com

Abstract

Colorectal cancer is an important public health problem. Colorectal cancer is the third most common cancer in the world, with nearly 1.4 million new cases diagnosed in 2012 and half a million deaths from this neoplasm occurs annually worldwide.

There are several factors considered to be causally associated with the development of colorectal cancer. For instance, the risk of colorectal cancer is clearly increased by a Western diet. Genes responsible for the most common forms of inherited colorectal cancer have also been identified.

Objectives:

The reader of this article should be able to identify epidemiologic trends in the incidence, mortality, and survival rates for colorectal cancer across different patient demographics; describe familial and hereditary risk factors associated, dietary and lifestyle factors known with the development of colorectal cancer.

Keywords: colorectal cancer, lifestyle factors, public health, epidemiologic incidence.

INCIDENCE OF COLORECTAL CANCER

Colorectal cancer is an important public health problem. Colorectal cancer is the third most common cancer in the world, with nearly 1.4 million new cases diagnosed in 2012 and half a million deaths from this neoplasm occurs annually worldwide. [1-3]

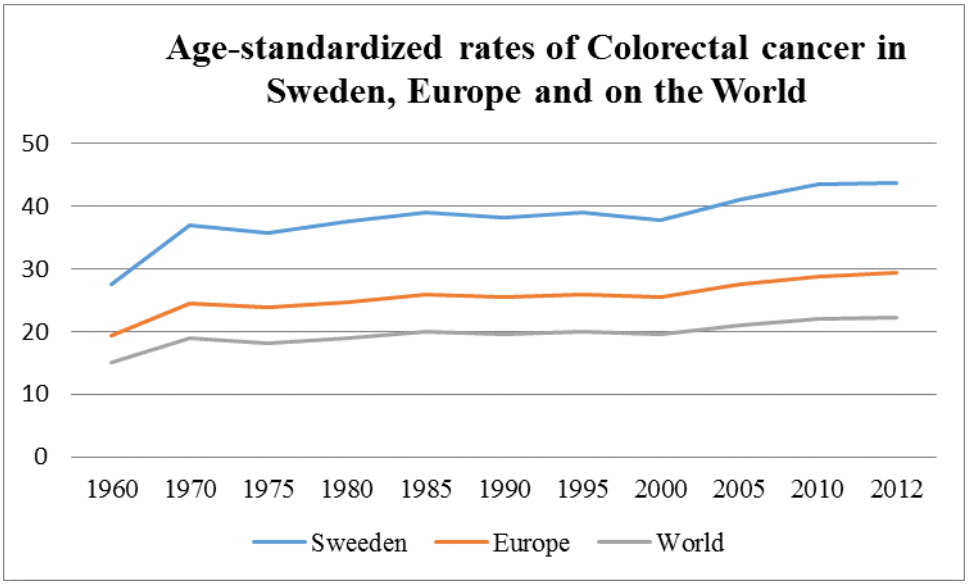


Figure 1. Age-standardized rates of colorectal cancer in Sweden, Europe and on the World[4]

About 54 per cent of colorectal cancer cases occurred in more developed countries. The highest incidence of colorectal cancer was in Oceania and Europe and the lowest incidence in Africa and Asia. It is the third most common cancer worldwide and the fourth most common cause of death.[5; 6]

In Romania the colorectal cancer is the second most frequent cancer 50, 3/100000 at man and 29.2/100000 at female, after the lung cancer.[7]

Approximately 95 per cent of colorectal cancers are adenocarcinomas. Other types of cancer that can occur here include mucinous carinomas and adenosquamous carcinomas.[8]

Table 1. Incidence rates of colorectal cancer in Europe and on the World[9,10,13]

Incidence rates	**World**			**Europe**		
	Man	Female	Persons	Man	Female	Persons
number of new cases	746,298	614,304	1,360,602	241,813	205,323	447,136
number of new cases per 100,000 population	21.0	17.6	19.3	67.6	53.5	60.3
ASR(W)	20.6	14.3	17.2	37.3	23.6	29.5
proportion of all newly diagnosed cancers (apart from skin cancers)	10.0%	9.2%	9.7%	13.2%	12.7%	13.0%
rank among all newly diagnosed cancers (apart from skin cancers)	3rd	2nd	3rd	3rd	2nd	2nd

Geographically presence of colorectal cancer: The data from table1, demonstrates a significant colorectal cancer burden in European countries, which is still associated with very high mortality rates [11, 12]. Moreover, recent statistics have indicated that the Slovakia has one of the highest rates of colorectal cancer worldwide, and this applies particularly to Slovakia males. Among European countries in 2012, Slovakia, Hungary, Denmark, the Netherlands and the Czech Republic had the highest incidence rate of colorectal cancer.[13-16].

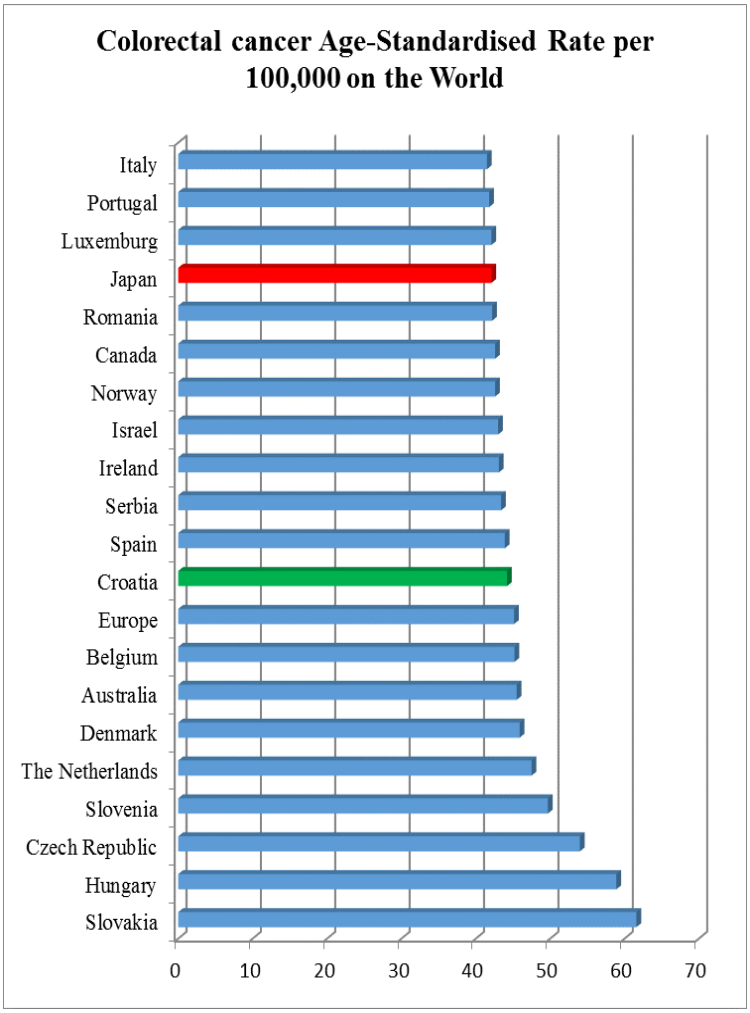


Figure 2. Colorectal cancer Age-Standardized Rate per 100,000 on the World[17]

In Romania, CRC frequency in 2000 was 17.74/ 100000 people/year which situated Romania with a medium frequency of this cancer. CRC it's the second cause of death, 19.05/100000 people, after the bronco-pulmonary neoplasm.[7]

MORTALITY OF COLORECTAL CANCER

Age-standardized rates (standards for Europe) of colorectal mortality rate in Romania is 27.5/100000 at mans and 14.5 at female. More recent data from the US on colorectal incidence and mortality rates from 1992 to 1998, age-adjusted to the 1970 US standard population, confirm the racial/ ethnic gradient of this disease. In detail, incidence rates (per 100,000) reported for Blacks, Whites, Asian/Pacific Islanders, and American Indian/Alaskan and Hispanics are 50.1, 42.9, 38.2, 28.6 and 28.4 respectively.[18]

Table 2. Mortality rates on the World and in Europe[13]

Mortality rates	World			Europe		
	Man	Female	Persons	Man	Female	Persons
number of deaths	373,639	320,294	693,933	113.246	101,620	214,866
number of deaths per 100,000 population	10.5	9.2	9.8	31.7	26.5	29.0
ASR(W)	10.0	6.9	8.4	16.2	9.9	12.5
proportion of all cancer-related deaths (apart from skin cancers)	8.0%	9.0%	8.5%	11.6%	13.0%	12.2%
rank among all cancer-related deaths (apart from skin cancers)	4th	3rd	4th	2nd	2nd	2nd

COLORECTAL CANCER PROGNOSIS AND SURVIVAL

About 50% of patients with CCR die because of this disease, which can be operated in 80% of cases, but 35% from this suffer rebound. [19]

The disease is not uniformly fatal although there are large differences in survival according to stage of disease. Five year survival in resected Dukes' A is around 80% and survival following simple resection of an adenomatous pedunculated polyp containing carcinoma in situ (or severe dysplasia) or intramucosal carcinoma is generally close to 100%. Screening research, recommendations and implementation is an obvious priority. There is also interesting evidence suggesting that specific chemo preventive strategies could prove useful in the prevention of colorectal cancer[20]. 47% of cases of colorectal cancer in the UK can be prevented by eating and drinking healthily, being physically active and maintaining a healthy weight.

Table 3. **Risk to develop colorectal cancer and the survival on the world and in Europe[13]**

Survival rates	**World**			**Europe**		
	Man	Female	Persons	Man	Female	Persons
Prevalence rates (patients still alive five years after diagnosis)						
absolute number of survivors	1,953,431	1,590,151	3,543,582	220.1	167.1	192.3
rate per 100,000 population	75.3	61.2	68.2	656,384	547,559	1,203,943
Cumulative risk of developing colorectal cancer						
from birth until the age of 75	2.36%	1.57%	1.95%	4.48%	2.73%	3.51%

RISK FACTORS

Age: The great majority of people diagnosed with colon cancer are older than 50. Colon cancer can occur in younger people, but it occurs much less frequently. Edwards et al 2 recently reported that in the USA, colorectal cancer was the most frequent form of cancer among persons aged 75 years and older.[21] Given that the majority of cancers occur in elder people and with the ageing of the population in mind, this observation gives further impetus to investigating prevention and treatment strategies among this subgroup of the population.

Sex: Colorectal cancer is present more often at males. International statistics have confirmed that men have higher colorectal cancer incidence rates than women, that is similar in Romania also. Overall the male: female ratio in the Romania population is 1.28 (Figure 2). High values of this index are typical for Central European populations like Germany, Belgium, UK, Spain and Netherlands, while Nordic countries, Norway, Sweden have reported lower ratios less than 1.35).[22]

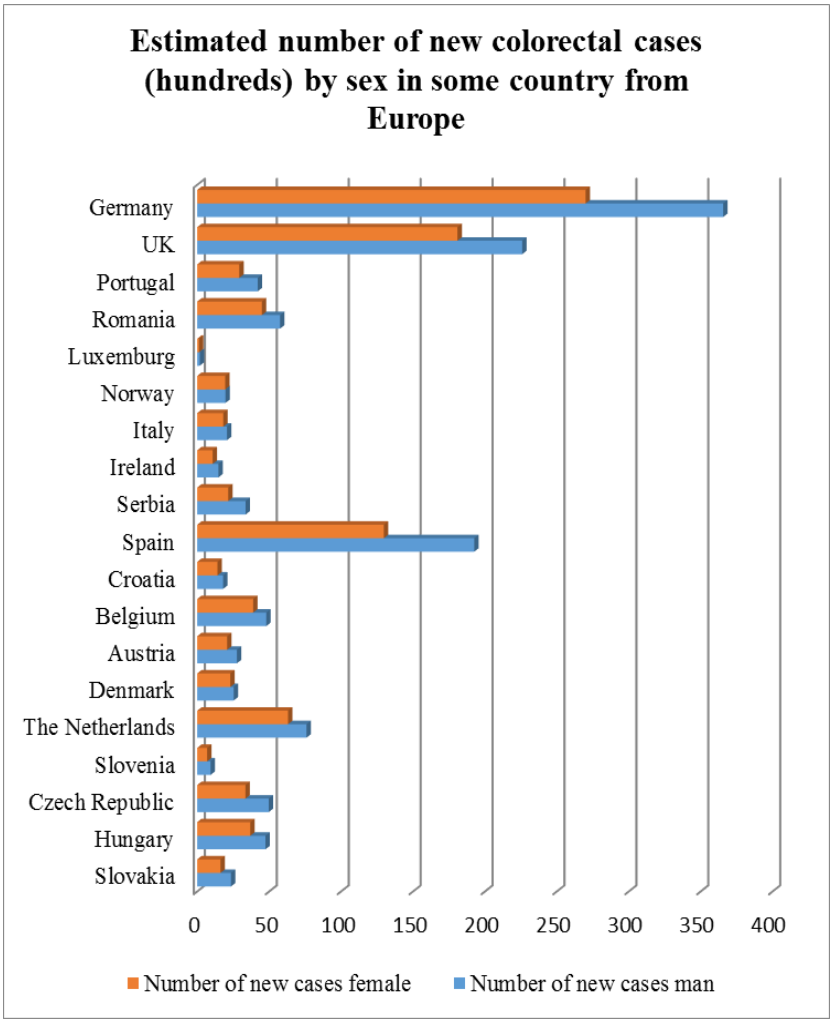


Figure 3. Estimated number of new colorectal cases (hundreds) by sex in some country from Europe

World-wide, in men the lowest incidence rates are found in a variety of population groups in the non- industrialized countries with the lowest rate reported in Algeria (0.4 per 100,000). In women, the group of highest incidence rates includes population groups in New Zealand and North America with the lowest rates recorded in Algeria and India. In each sex, a number of low rate regions are found in India[23].

Race: The incidence of this malignancy shows considerable variation among racially or ethnically defined populations in multiracial/ethnic countries. Wherever possible, the distinction between colon and rectum will be preserved. [24]

Nutrition and Lifestyle: The classical concept of risk of colorectal cancer being increased by increasing consumption of fat, protein and meat and to be reduced by increased consumption of fruits and vegetables 35 is currently being challenged as more epidemiological data become available. It has been hypothesized that alterations to serum triglycerides and/or plasma glucose could be one possible vehicle for the effects of various and etiological factors. Higher intake of folate has been relatively consistently associated with lower colon cancer risk. [25]

In a large prospective study, Murphy, et al 2000, shoved that, death rates from colon cancer increased across the entire range of BMI, with the highest rate ratio in men with BMI>32.5 and they said that., shoved that visceral abdominal fat is more associated with colorectal pathogenesis than other adipose tissue.[26]

Some studies indicates that high alcohol intake and tobacco increases risk of colorectal cancer.[27]

Family or Personal History of Adenomatous Polyps: American Cancer Society said that 1% of all colorectal cancers are due to FAP. By age 40, almost all people with this disorder will have developed cancer if preventive surgery is not done. HNPCC accounts for about 3 to 4% of all colorectal cancers. Lifetime risk of colorectal cancer with this condition may be as high as 70-80%[28]

Are more likely to develop colon cancer if in family a parent, sibling or child has the disease. If more than one family member has colon cancer or rectal cancer, your risk is even greater. In some cases, this connection may not be hereditary or genetic. Instead, cancers within the same family may result from shared exposure to an environmental carcinogen or from diet or lifestyle factors.[29,30]

Inherited genetic risk: Genetic syndromes passed through generations of your family can increase your risk of colon cancer. These syndromes include familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer, which is also known as Lynch syndrome. People with a history of colorectal cancer in one or more first degree relatives are at increased risk (approximately double with a single affected first degree relative)[29-31]

CONCLUSIONS

The transition from identification avoidable causes of colorectal cancer to implementation of preventive strategies depends on the facts associated with development of the disease. From analytical epidemiology, some clear ideas have now emerged about measures for reducing the burden of colorectal cancer. There are several factors like Western diet, gene for inherited colorectal cancer, considered to be causally associated with the development of colorectal cancer. Fortunately, the vast majority of cases and deaths from colorectal cancer can be prevented by applying existing knowledge about cancer prevention. Appropriate dietary changes, regular physical activity, and maintenance of healthy weight, together with targeted screening programs and early therapeutic intervention could, in time, substantially reduce the morbidity and mortality associated with colorectal cancer.

Future directions are to research on modifiable hormonal pathways associated with greater risk, the role of micronutrients such as calcium and folate and other agents and to identification of genetic susceptibility.

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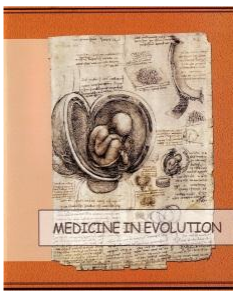
Sneddon wilkinson disease: case report and review of the literature



Tampa M.[1,2], Sârbu M.I.[1], Mitran C.I.[2], Mitran M.I.[2], Benea V.[2], Georgescu S.R.[1,2]

[1]*"Carol Davila University of Medicine and Pharmacy", Bucharest, Romania*
[2]*Dermatology Department,"Victor Babes"Hospital of Infectious and Tropical Diseases*

Correspondence to:
Name: Isabela Sarbu
MD, PhD student
Address: 37 Dionisie Lupu Street, Bucharest, Romania
E-mail address: isabela_sarbu@yahoo.com

Abstract

Sneddon Wilkinson disease is a rare, benign, chronic, recurrent disorder with a worldwide occurrence, of unknown aetiology. It has been associated with gammopathies, myelomas, pyoderma gangrenosum, Sweet syndrome and inflammatory bowel diseases. We report the case of a 47 year old male Caucasian patient from the urban area who addressed the dermatology department for a skin eruption consisting of erythematous, scaly plaques with multiple flaccid pustules distributed on the trunk, the axillary and inguinal regions, arms and palms. Multiple tests are often required to establish the diagnosis in rare cases, such as the one we are presenting, but the clinical examination still plays a central role in diagnosing dermatological disorders.

Keywords: Sneddon-Wilkinson disease, sub-corneal pustulosis, AGEP.

INTRODUCTION

Sneddon Wilkinson disease, also known as sub-corneal pustulosis or sub-corneal pustular dermatosis, is a rare, benign, chronic, recurrent disorder with a worldwide occurrence. Adult and elderly females are more frequently affected, but it has also been reported in children and adolescents. (1, 2) Clinically, it is characterized by the occurrence of erythematous patches with flaccid pustules and crusting usually distributed in the flexural areas and trunk. The histopathological hallmark of this affliction is the presence of sub-corneal sterile pustules. The aetiology of the disease is still unknown. It has been associated with IgA and IgG gammopathies, myelomas, pyoderma gangrenosum, Sweet syndrome and inflammatory bowel diseases, among others (3, 4).

CASE REPORT

We report the case of a 47 year old male Caucasian patient from the urban area who addressed the dermatology department of our hospital for a skin eruption consisting of erythematous, scaly plaques with multiple flaccid pustules distributed on the trunk, the axillary and inguinal regions and arms. Few pustules are also present on the palms. The lesions were intensely pruritic and had occurred five days before presentation. The anamnesis revealed that the patient had had a dental infection two weeks before and had been treated with amoxicillin, cephalexin and clarithromycin. The skin eruption had occurred three days after stopping the antibiotic treatment. The personal and family history were otherwise unremarkable. The physical examination showed a healthy appearing patient, with a blood pressure of 115/70 mmHg, a heart rate of 72 bpm and afebrile. The dermatological examination revealed a skin eruption consisting in multiple erythematous, scaly, well demarcated plaques, with a diameter ranging from 3 cm to 20 cm, disseminated on the trunk, axillary and inguinal folds. Several flaccid pustules were noticed in the periphery but also in the centre of the lesions. Some of the pustules were broken and covered by crusts. Few pustules were also present on the palms. The scalp, mucous membranes, nails and soles were not affected. The whole body area was intensely xerotic.

A complete blood count was performed and showed mild leucocytosis, neutrophilia and thrombocytosis. The erythrocyte sedimentation rate (ESR) was within normal range, as was the C-reactive protein (CRP). The biochemical testing showed no alterations. The patient also tested negative for hepatitis B, hepatitis C and HIV. The total protein count was within normal range, as was the albumin/globulin ratio. Serum protein electrophoresis was performed and showed no alterations. The lymphoblastic transformation test (LTT) was performed for amoxicillin, cephalexin and clarithromycin and was positive for amoxicillin.

Two biopsies were taken, one from the axillary region and one from the trunk. The histopathological examination showed ortokeratosis; sub-corneal pustules with neutrophils and some eosinophils, acanthosis, papillomatosis; dermal oedema with dilated capillaries and inflammatory infiltrate with lymphocytes, monocytes and some eosinophils (*Fig. 1*, *Fig. 2*). The direct immunofluorescence showed no antibody reactivity for IgA.

Based on the clinical examination, the laboratory findings and the histopathological examination the patient was diagnosed with Sneddon-Wilkinson disease. Since dapsone treatment was unavailable, he was treated with local corticosteroids and systemic antihistamines. The evolution was favourable, with almost immediate relief of the pruritus. The skin lesions cleared after approximately four weeks. To this moment, the patient presented no reoccurrences. He remains under the supervision of the dermatology department.

Figure 1. Histopathological aspect. Hematoxylin and eosin stain, 4X. Sub-corneal pustules, acanthosis, papillomatosis; inflammatory infiltrate

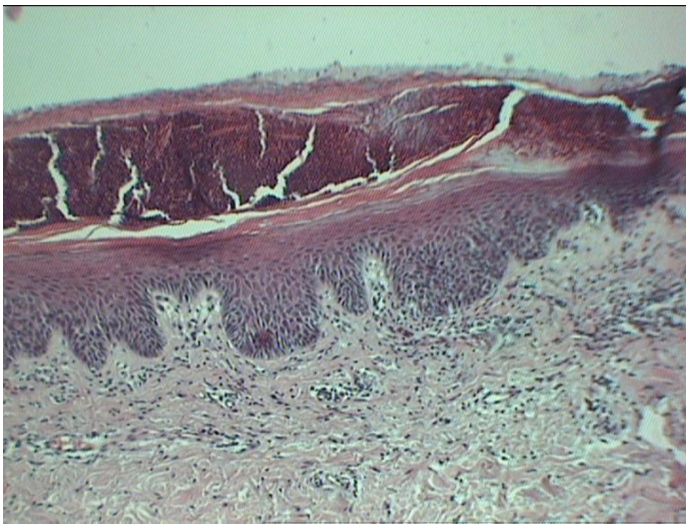


Figure 2. Histopathological aspect. Hematoxylin and eosin stain, 10X. Ortokeratosis; sub-corneal pustules with neutrophils and some eosinophils, acanthosis, papillomatosis; dermal oedema with dilated capillaries and inflammatory infiltrate with lymphocytes, monocytes and some eosinophils.

DISCUSSIONS

Sub-corneal pustular dermatosis was first descried by Ian Sneddon and Darrell Wilkinson in 1956, when the two authors reported six cases and categorized this affliction as a new blistering disorder, separate from dermatitis herpetiformis, psoriasis and the pemphigus group (5, 6). It is a rare, recurrent, pustular condition, most commonly affecting Caucasian patients, but which has been described in all races (1, 7). Females are more commonly affected than males, with a female to male ratio of 4:1 (2). It usually occurs in adults aged between 40 and 50 years. However, it has been described in all age groups, the youngest patient being three months old and the oldest ninety-three years old (2, 7, 8).

The aetiology and pathogenesis remain unknown. The blisters are sterile. However, concomitant or preceding infections have been described as possible trigger factors. Nevertheless, the data supporting this hypothesis is scarce and the role of infections is subject to controversy (1, 7). Some authors suggest that Sneddon-Wilkinson disease is strongly associated clinically, histopathologically and biologically to pustular psoriasis while other authors described cases where patients initially diagnosed with sub-corneal pustulosis later developed lesions that were clinically and histopathologically consistent with the diagnosis of

pustular psoriasis or psoriasis. (7, 9) A link between Sneddon-Wilkinson disease and IgA pemphigus is also widely discussed since there have been some reports of cases clinically mimicking sub-corneal pustulosis but presenting autoreactivity to desmocolin 1, intraepidermal IgA deposits and IgA antibodies. In these cases, the disease has been classified as sub-corneal pustular dermatosis type IgA pemphigus (1, 4, 7, 10, 11). Other authors include Sneddon-Wilkinson disease in the group of neutrophilic dermatoses, along with pyoderma gangrenosum, Sweet syndrome and erythema elevatum et diutinum (10, 12).

In the case we are presenting the skin eruption appeared two weeks after a dental infection treated with amoxicillin, cephalexin and clarithromycin. The LTT was positive for amoxicillin. The preceding infection might have been a trigger factor for developing the disorder. As regard to the positive LTT to amoxicillin, there is no evidence supporting the hypothesis that drugs could trigger the occurrence of this disease. A differential diagnosis with acute generalized exanthematous pustulosis (AGEP) was considered and excluded based on the physical examination, clinical picture and evolution of the disease. We therefore considered positive LTT a coincidental finding.

Sneddon-Wilkinson disease has been associated with several diseases, most commonly IgA paraproteinemia and pyoderma gangrenosum, but also inflammatory bowel disease, Sweet syndrome, myeloma, lymphoma and rheumatoid arthritis, among others (1, 7, 13-15).

In the case we are presenting the patient did not associate any other conditions. The negative serum protein electrophoresis and total blood count excluded IgA paraproteinemia and myeloma. The other commonly associated disorders were excluded based on the clinical and physical examination.

Clinically, the primary lesion is a flaccid pustule with pus characteristically accumulating at the base of large pustules. The pustules appear in crops on normal or erythematous skin. These lesions coalesce, break and are covered by crusts, thus forming annular and polycyclic patterns with a scaly rim. The lesions heal with hyperpigmentation but new pustules arise on the previous affected areas. The most frequently affected regions are axillary and inguinal folds, trunk and limbs. The face, scalp and mucous membranes are almost never affected while palms and soles are rarely affected. The lesions occur symmetrically and are associated by pruritus (1, 2, 16).

Our patient presented pustules on an erythematous base located in the axillary and inguinal folds and trunk. Some pustules were also present on the palms. The lesions were extremely pruritic.

The histopathological examination has a paramount importance in establishing the diagnosis of Sneddon-Wilkinson disease. In early lesions there is a perivascular inflammatory infiltrate with neutrophils and sometimes eosinophils. The neutrophils then migrate to the stratum corneum and form sub-corneal pustules - the hallmark of this affliction. Some eosinophils can also be present. Bacteria are absent. The granular layer is not affected. Spongiosis can occur. The dermal papillae are dilated and have a perivascular infiltrate with neutrophils, eosinophils and mononuclear cells (1, 2, 17).

Direct immunofluorescence testing is characteristically negative. If intraepidermal IgA deposits are identified and circulating IgA antibodies are detected by indirect immunofluorescence, sub-corneal pustular dermatosis type IgA pemphigus is diagnosed instead (1, 17).

In the case we are presenting, two biopsies were taken and the histopathological examination showed sub-corneal pustules with neutrophils and some eosinophils. Direct immunofluorescence was negative. Therefore, the histopathological examination was consistent with the clinical suspicion of Sneddon-Wilkinson disease.

Several disorders must be excluded before establishing the diagnosis of Sneddon-Wilkinson disease. The differential diagnosis must include impetigo, dermatitis herpetiformis, generalized pustular psoriasis, acute generalized exanthematous pustulosis,

dermatophyte infection, IgA pemphigus foliaceus and sub-corneal pustular dermatosis type IgA pemphigus (1, 2, 7, 16-18).

Impetigo can de differentiated from Sneddon-Wilkinson disease by bacterial culture. Histopatholocally, the differentiation may be impossible unless the presence of bacteria is demonstrated by Gram stain because both those entities present sub-corneal pustules. The chronic course pleads for the diagnosis of Sneddon-Wilkinson disease (2, 17).

Dermatitis herpetiformis is highly pruritic but it mostly affects the extensor surfaces. Histopathologically, the pustule is sub-epidermal. Direct immunofluorescence shows IgA deposits in the dermal papillae (1, 7, 17, 19).

Generalized pustular psoriasis (von Zumbusch) may clinically resemble Sneddon-Wilkinson disease but patients are very ill, with fever and leucocytosis. The nails and scalp are commonly affected. Histopathologically, sub-corneal pustules may occur in pustular psoriasis but spongiform pustules and elongation of the rete ridges do not occur in Sneddon-Wilkinson disease (1, 17, 19).

AGEP is characterised by the sudden occurrence of a pustular eruption, usually triggered by drugs or infections. However, the lesions are usually located in the distal part of the extremities and are associated by fever and leucocytosis. The histopathological examination reveals spongiform intraepidermal pustules, leukocytoclastic vasculitis and dermal inflammatory infiltrate with neutrophils, eosinophils and lymphocytes (1, 20).

Dermatophyte infection can have similar clinical features. It can however be excluded by direct microscopic examination of fungal elements (21).

Histopathologically, pemphigus foliaceus can be difficult to differentiate from Sneddon-Wilkinson disease as they both present sub-corneal pustules. Acantholysis however is more important in pemphigus foliaceus. The clinical diagnosis along with immunofluorescence testing and histopathological examination establish the diagnosis (1, 17).

Sub-corneal pustular dermatosis type IgA pemphigus can be clinically and histopathologically identical with Sneddon-Wilkinson disease. Immunofluorescence studies settle the diagnosis (18).

In the case we are presenting differentiating Sneddon-Wilkinson disease from AGEP was the main concern because the LTT was positive for ampicillin. However, the distribution of the lesions, the absence of fever and the histopathological examination supported the diagnosis of Sneddon-Wilkinson disease.

Several treatment options are available for the management of sub-corneal pustulosis. Most cases respond to sulfones. Dapsone is most often used, in doses of 50-150 mg daily. The use of this medicine is sometimes limited by the adverse reactions, especially methaemoglobinaemia and haemolytic anemia. Colchicine, sulfapyridine and sulfamethoxypyrazine have also been used, with some good results (1, 7, 16).

Corticosteroids can also be utilised. Systemic corticosteroids can be tried in extensive forms or to control the flares of the disease but the results are usually disappointing. Topical steroids have been used alone or together with sulfones, with some good results (1, 2).

Oral retinoids like etretinate, isotretinoin and acitretin have been used but data regarding their usefulness is contradictory. PUVA, UVA, broad-band UVB and narrow-band UVB can be used alone or in combination with dapsone or retinoids (16, 18).

Biological treatments have also been tried. Berk et. al. reported two cases of Sneddon-Wilkinson disease refractory to other therapies which responded to etanercept (22). Naretto et. al. reported one case of Sneddon-Wilkinson disease associated with systemic lupus erythematosus, unresponsive to conventional therapies, successfully treated with infliximab (23). Bonifati et. al. however reported a case of sub-corneal pustulosis treated with infliximab which showed a rapid but not lasting improvement (24). Further studies are therefore needed to prove the effectiveness of biological therapies for the treatment of this disease.

Since dapsone treatment was not available in our case, we treated the patient with topical potent steroids and antihistamines. Pruritus alleviation occurred within a few days and the lesions almost completely cleared after approximately four weeks.

The prognosis of the disease is benign. It is a chronic disease and reoccurrences can appear over many years. The prognosis is worsened by the associated afflictions and therefore patients should be monitored for the occurrence of gammopathies (1, 2, 16). Our patient remains under the supervision of the dermatology department.

CONCLUSIONS

We report a rare case of Sneddon-Wilkinson disease in a male patient in which the affliction might have been triggered by a previous infection. The differential diagnosis with acute generalized exanthematous pustulosis was difficult because the lymphoblastic transformation test was positive for ampicillin. However, the physical examination, clinical examination, laboratory testing including histopathological examination and immunofluorescence tests pleaded for the diagnosis of Sneddon-Wilkinson disease. Multiple tests are often required to establish the diagnosis in rare cases, such as the one we are presenting, but the clinical examination still has a central role in diagnosing dermatological disorders.

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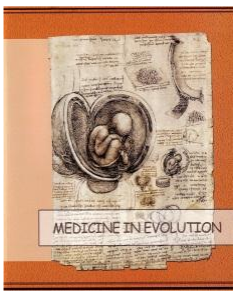
Treatment Efficiency Adjuvant Chemotherapy with Florouracil at Colorectal Cancer



Popa C.L., Szucsik I.A., Lascu A., Anculia R.C., Dumitrascuta A.

Faculty of Medicine,"Victor Babes"University of Medicine and Pharmacy Timisoara

Correspondence to:
Name: Crinela Luminița Popa
Address:"Victor Babes"University of Medicine and Pharmacy Timisoara
Phone: +40 723320956
E-mail address: popacrinela2004@yahoo.com

Abstract

Introduction: Colorectal cancer (CRC) persists as one of the most prevalent and deadly tumor types in both men and women worldwide. The primary aim of the study was to show the efficiency of the adjuvant chemotherapy and the time disease-free after the treatment.

Method: We made a study on 69 cases which received surgical and postsurgical chemotherapy, but 35 of them received also adjuvant chemotherapy with fluorouracil, they were in Group A.

Results: Subgroups used to identify prognostic factors for survival within the two groups showed that the patients which received adjuvant chemotherapy survived longer 26 months father than 17 months, the patients from group B (α= 0.396). After five years from the treatment 38 of patients died, 17 from group A and 19 from group B.

Discussion: The Adjuvant Colon Cancer Endpoints meta-analysis of adjuvant studies, which was carried out before the approval of FL for advanced disease, demonstrated that 3-year FL was an excellent predictor of 5-year.

Conclussions: With patients in Stage II or III of colonic cancer, where is possible is better to start the colonic cancer therapy with adjuvant therapy like FL, because this improving the survival, and the postsurgical complications.

Keywords: colorectal cancer, lifestyle factors, chemotherapy, metastatic disease.

INTRODUCTION

Colorectal cancer (CRC) is one of the most prevalent and deadly tumor types worldwide. More than 1.2 million patients are diagnosed every year, and more than 600,000 die from the disease. Incidence is higher in men than in women and strongly increases with age; median age at diagnosis is about 70 years in developed countries. In fact, the molecular heterogeneity of CRC is believed to be one of the factors responsible for the considerable variability in treatment response among patients with the same stage of CRC [1].

The most important risk factors are familial history of colorectal and other tumors as well as lifestyle factors such as nutrition, obesity, inactivity, and smoking. Lifestyle-related risks offer a broad area for implementing primary preventive measures, which have not yet been adequately exhausted. [2]

Metastatic disease is considered incurable, with the exception of patients presenting with oligometastatic lesions confined to the liver or lung amenable to resection. [3, 4, 5].

When treatment with curative intent is not possible, patients are typically given a combination of cytotoxic chemotherapy often in conjunction with a targeted therapy. In spite of advances in systemic therapy, the 5-year survival rate is still a mere 12.5% [6, 7], and the primary reason for treatment failure is believed to be acquired resistance to therapy which occurs in 90% of patients with metastatic cancer [8].

Non-elective colon cancer resection is associated with high mortality. In particular, right-sided resections and patients with tumor perforation are at particularly high risk. The optimization of patients prior to surgery and expeditious operation after diagnosis might prevent the need for a non-elective resection.[9] 40 to 50 percent of patients who undergo potentially curative surgery alone ultimately relapse and die of metastatic disease.[10]

The most important prognostic indicator of survival in early colon cancer is the stage of the tumor (T, according to the tumor–node–metastasis [TNM] classification), determined by the depth of penetration through the bowel wall, and the number of involved lymph nodes. [11, 12].

There are, however, discrepancies between consensus recommendations and adjuvant treatment in the community.[13-16] More effective, better tolerated, and more convenient chemotherapy is required, especially for patients older than 65 years,18 who are less likely to receive rigorous chemotherapy. [17, 18] Moreover, most patients (84 to 89 percent) with cancer would prefer oral chemotherapy, provided efficacy is not compromised.[19, 20]

As first-line treatment for metastatic colorectal cancer, Capecitabine is an established alternative to the combination of Fluorouracil and Leucovorin. It achieved response rates superior to those achieved with the Mayo Clinic regimen (26 % vs. 17 %), with equivalent progression free survival and overall survival.

The demonstration that postoperative adjuvant treatment with fluorouracil and Levamisole reduced the mortality rate by 33 percent among patients with stage III colon cancer prompted several trials, which established six months of treatment with fluorouracil plus Leucovorin as the standard adjuvant chemotherapy for stage III colon cancer.[13,14].

The primary aim of the study was to show at least equivalence in disease-free survival between patients which received adjuvant chemotherapy. Secondary end points included relapse-free survival, overall survival, and safety. Assessment of the rate of disease-free survival at three years was a prespecified secondary end point.

METHODS

We made a study on 69 cases, were considered eligible patients 18 to 75 years of age who were diagnosed with colon rectal cancer. (See Table 1).

Table 1. Demographics and Clinical characteristics of Patients

Patient Demographics and Clinical Characteristics	Frequency of patients
Median age	63 year
Age categories (years)	
20-40	8 (11.56%)
40-65	32 (46.37%)
>65	29 (42.03%)
Sex	
Masculine	33 (47.82%)
Feminine	36 (52.18%)
Disease stage	
Stage II	31 (44.92%)
Stage III	33 (47.82%)
Stage IV	5 (7.24%)
Depth of invasion	
T_2	7 (10.145%)
T_3	52 (75.36%)
T_4	10 (14.5%)
Perforation present	5 (7.25%)
Bowel obstruction present	9 (13.04%)
Histology	
Differentiated	59 (85.5%)
Poorly differentiated Unknown	8 (11.59%)
	2 (2.90%)

All the patients received surgical and postsurgical chemotherapy, but 35 of them received also adjuvant chemotherapy with fluorouracil, they were in Group A. The surgical therapy was (See Table 2.) 23.33% of the patients suffered also extern derivation of colonic surgery. They were 8 for each of group.

Patients classified as high risk for the purposes of an exploratory analysis had at least one of the following: T4, tumor perforation, bowel obstruction, poorly differentiated tumor, venous invasion, or less than 10 lymph nodes examined. Prior chemotherapy, immunotherapy, or radiotherapy was not permitted, and was necessary to be started adjuvant therapy within 7 weeks of surgery. All patients provided written informed consent, and the study was approved by the ethics committees of the participating centers.

Table 2. Type of surgical intervention

	Group A Frequecny	Group B Frequency
Segmentary colectomy	7 (10.14%)	3 (4.35%)
Right hemicolectomy	13 (18.84%)	15 (21.74%)
Left hemicolectomy	3 (4.35%)	3 (4.35%)
Sigma segmentary colectomy	6 (8.7%)	8 (11.59%)
Anterior rectosigmoid colectomy	6 (8.7%)	5 (7.25%)

Follow-Up

Patients were evaluated before ransoms segments, every 2 weeks during treatment (12 cycles in total), and then every 6 months up to 5 years after completion of treatment. In line with a post marketing commitment related to the US Food and Drug Administration approval letter for adjuvant therapy (November 2004), follow-up for OS was extended to 6 years after completion of study treatment. Assessments were made for relapse, second cancers, late toxicity, and death. The cutoff dates for final analyses were April 1, 2015 for DFS and September 15, 2015 for OS. Adverse events were graded according to National Cancer Institute's Common Toxicity Criteria, version 1.

Statistical Analysis

Random assignment was performed centrally; the minimization method was used to balance treatment allocation according to TNM stage (T2 or T3 v T4 and N0 v N1 v N2), the presence or absence of bowel obstruction or tumor perforation, and the medical center. The original planned sample size was 57 patients. After a protocol amendment (June 2010), this was increased to 73 patients, which provided more than 90% to detect a difference in DFS.

RESULTS

Comparisons of general surviving of groups according to the intent-to treat (ITT) principle were performed using a two-sided stratified log-rank test based on the primary tumor site. Analyses adjusted by disease stage were performed using Cox regression modeling. HRs with 95% CIs was calculated using the Cox proportional hazards model. Survival curves were presented according to Kaplan-Meier methods. Subgroups used to identify prognostic factors for survival within the two groups showed that the patients which received adjuvant chemotherapy survived longer 26 months father than 17 months, the patients from group B (α= 0.396). After five years from the treatment 38 of patients died, 17 from group A and 19 from group B.

Table 3. Mean (in months) of survival at boths groups

	Median			
			95% Confidence Interval	
Groups	Estimate	Std. Error	Lower Bound	Upper Bound
Group B	17.000	1.047	14.947	19.053
Group A	26.000	10.144	6.118	45.882
Overall	17.000	2.179	12.728	21.272

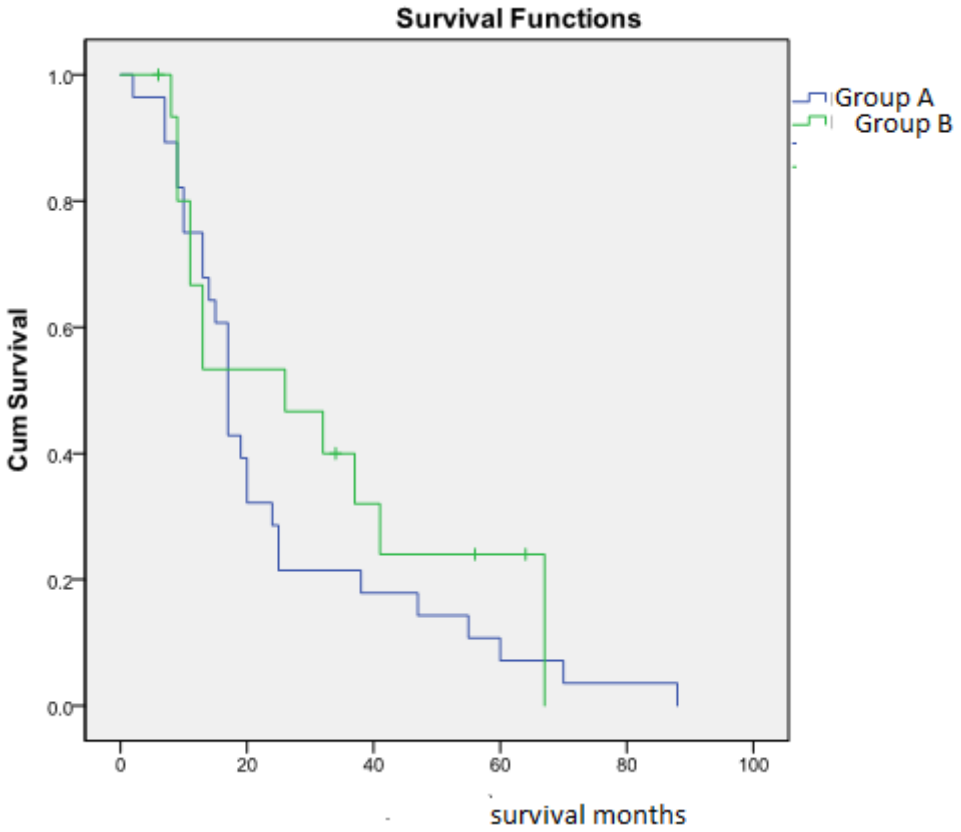


Figure 1. Kaplan-Meier estimates of overall survival at group A and group B

Postsurgical complications (See table 3) were shown at 32 patients, the most frequent was bronchopneumonia at 9 patients, and anatomic dehiscent at 10 patients. Two patients from group A, died in first 24 hours from the surgery.

Table 4. Postsurgical complication

Complications	Group A		Group B	
	Absolute frequency	% frequency	Absolute frequency	% frequency
Local:				
Plague suppuration	3	4.35%	4	5.8%
Evisceration	2	2.9%	1	1.45%
Anatomic dehiscent	5	7.25%	5	7.25%
Stercoral fistula	2	2.9%	3	4.35%
Peritonitis	1	1.45%		
General:				
Cardio circulatory	2	2.9%	3	4.35%
Deep tromboflebita	2	2.9%	1	1.45%
Pulmonary Emboli	1	1.45%	2	2.9%
Bronchopneumonia	5	7.25%	4	5.8%

DISCUSSIONS

The Adjuvant Colon Cancer Endpoints meta-analysis of adjuvant studies, which was carried out before the approval of FL for advanced disease, demonstrated that 3-year FL was an excellent predictor of 5-year. Results [22] and could be an appropriate primary end point for adjuvant studies in colon cancer. These findings led to the approval by the US Food and Drug Administration of 3-year FL as a primary endpoint for adjuvant colon cancer studies. Further analysis of Adjuvant Colon Cancer Endpoints indicated that there was no association between time to recurrence and OS in patients with stage II disease, [23] findings that may explain why, although there was a trend toward improved FL in stage II or III of the patients in this study; this was not translated into an OS benefit. With so many potential targets for therapy, personalized treatments with existing drugs would be expected to show improved results.

The improvement in disease-free survival among patients who were treated with FL plus Oxaliplatin corresponds to a relative reduction in the risk of recurrence of 23 percent. Since most relapses after curative surgery occur within the first three years, we consider our results in this respect to be complete. [17]

Although it is agreed that patients with stage III disease benefit from adjuvant treatment, whether all patients with stage II disease should receive such treatment remains debatable.

CONCLUSIONS

With patients in Stage II or III of colonic cancer, where is possible is better to start the colonic cancer therapy with adjuvant therapy like FL, because this improving the survival, and the postsurgical complications.

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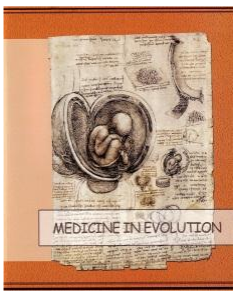
Preliminary studies in a human-murine melanoma model using A375 cell line and Balb/c nude mice



Berceanu M.[1], Popovici R.A.[2], Ceuta-Bratu L.[3], Crainiceanu Z.[1], Pinzaru I.[3], Coricovac D.[3], Bratu T.[1]

[1]*Faculty of Medicine,"Victor Babes"University of Medicine and Pharmacy Timisoara*
[2]*Faculty of Dental Medicine,"Victor Babes"University of Medicine and Pharmacy Timisoara*
[3]*Faculty of Pharmacy,"Victor Babes"University of Medicine and Pharmacy Timisoara*

Correspondence to:
Name: Ramona Amina Popovici
Address:"Victor Babes"University of Medicine and Pharmacy Timisoara
Phone: +40 762006828
E-mail address: ramona.popovici@umft.ro

Abstract

One of the most studied type of cancer is malignant melanoma due to the fact that is very aggressive and its mechanism of action is not fully understood at present. In the recent years, researchers have shown that the mechanisms of action of different types of cancer were successfully elucidated using animal models. The aim of this study was to inoculate human melanoma cells (A375) subcutaneously into Balb/c nude male mice in order to obtain a human melanoma model and to evaluate different physiological skin parameters using noninvasive measurements. For this purpose, in the study were used Balb/c mice with the age of 10 weeks. Before starting the experiment all animals were evaluated in terms of body weight and appearance. After inoculation, daily measurements of body weight, melanin and erythema were taken and the results are listed below.

Keywords: A375, Balb/c, skin parameters.

INTRODUCTION

Melanoma is known as the most aggressive type of skin cancer that develops from the malignant transformation of melanocytes. Human cutaneous malignant melanoma is responsible for the deaths of over 75% of skin cancer cases [1,2]. Only in the United States, there were estimated 76,250 new cases and 9,180 deaths in 2012 [3]. Besides these gloomy data, epidemiological studies indicate a higher incidence of melanoma compared to any other type of cancer [4-6]. Furthermore, only the primary tumors detected early are curable by means of surgical excision, whereas the patients with metastasis have a dismal prognosis with an average survival of 9 months. The low survival rate of melanoma patients could be assigned to the lack of effective treatments in evolved stages, moreover since melanoma proved an increased resistance to chemotherapy [1,7]. In order to find new perspectives, prestigious researchers studied the mechanism by which malignant cells protected themselves against agents-induced apoptosis by using animal models. There are several steps that must be fulfilled in tumor progression process, such as: a) step 1 - tumor cells from the primary tumor should develop migratory capacity and become invasive; b) step 2 – the invasive tumor cells enter into the blood circulation and attach to the capillary beds – process known as"cancer cell intravasation"; c) step 3 – once they find the suitable site, the cells leave the blood torrent – process known as"cancer cell extravasation"and d) the final step – tumor cells proliferate and form secondary tumors [8,9]. The sequence of steps aforementioned represent the epithelial-to-mesenchymal transition (EMT) type 3 which plays a major role in tumor progression and development of metastasis [8,9]. The secondary tumor formation takes place when tumor cells produce growth factors (autocrine) or respond to growth factors produced by host cells (paracrine) [10].

The aim of this study was to obtain preliminary data regarding the proper conditions and parameters for the development of a reproducible human melanoma animal model using A375 xenografts.

MATERIAL AND METHODS

Materials

Tumor cell line. In the present study, we used a human melanoma cell line – A375. According to Giard *et al.* this cell line was obtained from a 54-year-old female with malignant melanoma and was able to induce amelanotic melanomas in nude mice [11]. The cells were purchased from ECACC (European Collection of Cell Cultures, Wiltshire, United Kingdom).

Animals. The animals used in the study for the development of A375 xenograft models were 10 weeks-old Balb/c nude male mice purchased from Charles River (Budapest, Hungary).

Methods

Cell culture. The human melanoma cell line A375 (passage no.12) was cultured in Dulbecco's modified Eagle Medium (DMEM) with 4.5 g/L high glucose, 15 mM Hepes, and 2 mM L-glutamine, enriched with penicillin (100 U/Ml), streptomycin (100 µg/Ml), and 10% fetal calf serum (FCS). Cells were kept in the incubator in standard conditions (5% CO_2 and 37°C) and passaged at every two days. The preparation of the cells for the inoculation required several steps: i) the old medium was removed, ii) the cells were trypsinized, suspended in fresh medium and centrifuged, and iii) after centrifugation it was obtained a pellet of cells, that were suspended in phosphate buffer and counted using a Neubauer chamber in the presence of Trypan blue.

A375 xenograft mouse models design. During the *in vivo* experiments, the housing conditions for the animals were in accordance with the Guide for Care and Use of Laboratory Animals, as follows: a 12 hours light/12 h dark cycle, temperature of 24 °C, humidity above 55%, food *ad libitum* and free access to water. Bioethical Committee of"Victor Babes"University of Medicine and Pharmacy Timisoara approved all the procedures used in this study.

The A375 xenograft mouse model was obtained according to the following protocol: the Balb/c nude male mice were inoculated subcutaneously in two parts of the body (ventral and dorsal sides) with a suspension of A375 cells of different concentrations ($1X10^7$ A375 cells/100 µl/mouse and $8X10^6$ A375 cells/100 µl/mouse). The mice were divided in 3 groups (n=5 mice/groups): group 1 – control group – no interventions, group 2 – mice that were injected subcutaneously on the dorsal side with $1X10^7$ A375 cells and group 3 – mice that were injected subcutaneously on the ventral side with $8X10^6$ A375 cells.

The mice were monitored daily after the inoculation of the cells in terms of tumor burst, tumor volume, until the mice were sacrificed (40 days post-inoculation).

Noninvasive measurements. The physiological skin parameters, erythema and melanin were determined by noninvasive techniques using an equipment MPA5 - Courage-Khazaka, Multiprobe Adapter System, containing a Mexameter®MX 18 probe.

RESULTS AND DISCUSSIONS

Animal models always represented useful tools in the understanding of the processes associated to the development and the evolution of different diseases and were heavily applied in the field of tumorigenesis. Since melanoma is considered one of the deadliest types of cancer, it is mandatory to have a clear idea about the underlying mechanisms involved in the tumor apparition and tumor growth and the animal models can offer the missing pieces of information to understand the whole picture. Xenograft melanoma models can be obtained by orthotopic or ectopic inoculation of human melanoma cells or by transplantation of solid tumors into immunocompromised mice [12]. For the achievement of this kind of models are preferred athymic mice, the lack of a functional immune system suppresses the possible interactions between the tumor cells inoculated and the host's immune cells [12]. One of the main advantages of this animal model is represented by the capacity of the tumor cells to keep their behavior, including their metastatic potential [12].

The aim of this study was to obtain preliminary data concerning the proper number of A375 cells for the development of reproducible melanoma xenografts models. The human melanoma models that we proposed consisted in inoculation of two A375 cells suspensions of different concentrations ($1X10^7$ A375 cells/100 µl/mouse and $8X10^6$ A375 cells/100 µl/mouse) subcutaneously into the dorsal and the ventral sides of mice. The primary tumors became visible in both cases after 10-12 days post-inoculation of the cells suspensions.

According to our results the tumors observed in group 3 (mice that were injected subcutaneously on the ventral side with $8X10^6$ A375 cells) were smaller and became palpable later (day 12) as compared to the tumors from group 2 (mice that were injected subcutaneously on the dorsal side with $1X10^7$ A375 cells) which were well-defined from day 10 post-inoculation (figure 1).

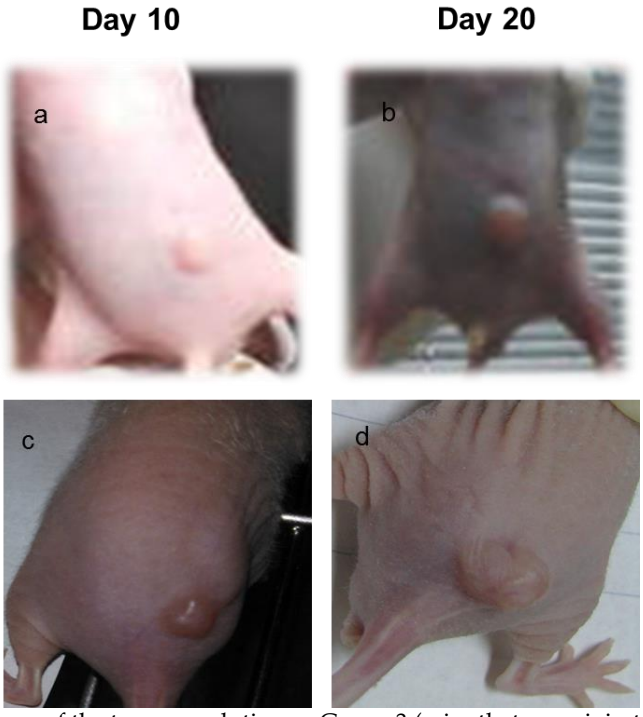


Figure 1. Macroscopic images of the tumor evolution: a. Group 3 (mice that were injected subcutaneously on the ventral side with $8X10^6$ A375 cells) – day 10; b. Group 3 – day 20; c. Group 2 (mice that were injected subcutaneously on the dorsal side with $1X10^7$ A375 cells) – day 10 and d. Group 2 – day 20

As it can be seen in the pictures, we obtained xenografts models of human melanoma in both cases, but the highest number of cells used for inoculation and the dorsal side were more appropriate (group 2). The subcutaneously inoculation on the dorsal side offered several advantages, including: an easier access to the tumor in order to measure the physiological skin parameters, surveillance of tumor growth without handling the mice.

The number of the cells that we used in the study was higher as compared to the literature [13-15] and one of the reasons that we chose those numbers was the fact that we didn't use matrigel for the inoculation.

Specific melanoma markers including melan A, S100, VEGF were positive in the tumor samples, results that confirmed the presence of melanoma. At this time point, no secondary tumors were detected.

Body weights were recorded every day and the size of the tumor was calculated using the length and the width of the tumor. In all cases was observed an increase of the body weights, increase that can be associated with the development of primary tumors. All the animals were sacrificed when the tumor size reached 10 mm^2 according to approved protocols.

Melanocytes are the cells which produce melanin, an important skin parameter that can be able to provide valuable information related to skin alterations. Melanin measurements showed a slight increase in its values in the case of mice with tumor comparative with the control group.

When there is an irritation or skin damage one of the most efficient parameters in evaluation is erythema because suffer major changes in these cases. The measurements of erythema were higher in groups 2 and 3 as compared to the control group, this effect being observed only in the tumor area.

CONCLUSIONS

Our results showed that the melanoma xenograft model that we obtained was a reproducible one. Moreover, it was observed that the number of cells used, $1X10^7$ A375 cells

and the inoculation on the ventral side of the animal were proper parameters for the development of this kind of model.

These results represent the background for our further studies regarding the assessment of the antimelanoma effects of several natural compounds.

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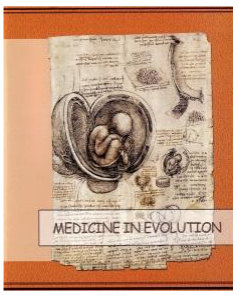
The evolution and interpretation of respiratory indices 24 hours post physical effort on a group of elite athletes



Martin Ş.A.[1], Tomescu V.[2]

[1]*University of Medicine and Pharmacy Tîrgu Mureş, Romania; Romania Rowing Federation*
[2]*Romanian Olympic Sports Committee; National University of Physical Education and Sport, Bucharest, Romania*

Correspondence to:
Name: Martin Ştefan Adrian
Address: Tîrgu Mureş, Str. Gheorghe Marinescu, nr. 38
Phone: +40 746669476
E-mail address: martinstefanadrian@gmail.com

Abstract

Aim: Respiratory indices standardization, and their adaptation, during weekly exercise practice is an important step toward programming sports training.

Material and method: An observational study was conducted among a group of 12 elite male rowers. The monitoring was conducted through Cosmed Quark CPET equipment, applying the protocol for resting metabolic rate determination.

Results: Respiratory rate (13.41±3.04 b/min) was significantly correlated (p=0.0001, CI95%=0.98-0.99), with CO_2exp value (33.32±8.35 ml) and VT (0.83±0.17 L), indicating the parameter decrease, along with the increase of RF. VE/VO2 value, has been correlated significantly (p=0.0003, CI 95%=0.95-0.56) by increasing the parameter mentioned, and a decrease in the total oxygen extracted from air (FeO2%). Action identified as well during by increasing FeO_2 value, and decreasing O2exp, CO2exp values.

Conclusions: The identification and classification of obtained values within optimal periodization will support further individual effort, characterizing the respiratory recovery stage, subsequently being able to be confirmed biochemically.

Keywords: athletes, oxygen, respiratorion, respiratory rate.

INTRODUCTION

Athletic performance is dictated by physiological, anthropometric, and psychological aspects of the individual during the work they perform. The impact that these elements have on sports performance varies depending on the effort, and work already accomplished. Among the many physiological factors, respiratory activity is one of the basic factors of performance sports activity. Cardio-Respiratory function testing, as with other tests, is an important action to identify the level of physiological preparation among athletes (1). The total volume of the lungs is estimated appropriately according to age, height and weight, the results being significantly different between performance athletes and groups of active people (2,3).

Training has the ability to increase the body's vital capacity, along with the maximum volume of oxygen that the lungs can exchange in a respiratory cycle, setting the body's total oxygen demand (4). Basically, dividing the effort areas during training microcycle/macrocycle will influence the athletes respiratory system adaptation during the performed effort (5). However, establishing the effort type that will be performed, will be done according to the period, and the level of training (6). Thereby, specific competition effort, is characterized through oxygen debt during anaerobic exercise (anaerobic alactacid/anaerobic lactacid) (7).

From this point, a series of physiological changes are involved because both cardiovascular, respiratory, and muscular system are involved in the action which could range from a few seconds, and stretch up to several hours (4). Oxygen debt, will increase the total respiratory production of CO_2, decreasing the amount of O_2 in the alveoli. Moreover, during effort, $PaCO_2$ and $PetCO_2$ are related to the respiratory rate, because expired CO_2 value will not reach a maximum stationary level (8). Action that dictates changes in arterial blood gases, involving energy metabolism. At the same time, VO_2, representing the total amount of oxygen that the body can use, among with Rf values, will influence both energy and muscle system during rest recovery periods, with possible changes in energy metabolism (9).

Aim and Objective

Establishing basic changes, and respiratory influences on the body's reaction, and how the recovery will improve the entire training program planning.

MATERIAL AND METHODS

An cross-sectional study was conducted after obtaining the aproval from the ethics committee, and informed subjects consent to participate in the study, on the basis of oxygen consumption and carbon dioxide production.

The study was conducted in November 2015 in Bucharest, by national level athletes at their training center. A total of 12 elite male rowers, with a mean age of 21.5±1.56 years, were included in the study. Through the use of Cosmed Quark CPET equipment, and by applying the protocol for the determination of resting metabolic rate, we took over the following parameters in this study: RF (b/min), VO_2 (ml/min), VCO_2 (l/min), VE/VO_2, VE/VCO_2, O_2exp (ml), CO_2exp (ml), $PetO_2$ (mmHg), $PetCO_2$ (mmHg), FeO_2 (%), $FeCO_2$ (%), Fat (%), Kcal (kcal/kg/day). In order to determine these parameters we took into consideration the resting metabolic rate specific protocol of activity: 5 hours lack of food ingestion; lack of programmed physical activity with 24 hours pre testing; no consumption of caffeine-containing supplements, along with: ephedrine, Ma Huang, presudoefedrină, and nicoteine 12-hour pre test.

Statistical evaluation was performed using GraphPad Prism 5.0 software. Statistical indicators used were standard deviation (SD), standard error (SE), and coefficient of variation (CV). For data normalization, Shapiro-Wilk (W) test, Pearson correlation index (r) and Student's t-test (pairs) were used. Level of significance, $p<0.05$ was considered statistically significant.

RESULTS

A total of 12 elite rowers were included in the study with a mean age of 21.5±1.56 years, 96.25±8.18 kg weight, and 195±4.91 cm height. Through the use of Cosmed Quark CPET equipment we determined the main respiratory parameters obtained from RMR determination at 24 hours post exercise (Table I).

Table I. Statistical data regarding the analyzed parameters

Analyzed parameters	Obtained values			CV%	Shapiro Wilk - W	Passed normality test?
	Minimum	Median	Maximum			
RF (b/min)	7.43	14.32	17.78	22.69	0.9488	YES
VO_2 (ml/min)	349.2	391.4	437.1	6.97	0.9312	YES
VCO_2 (l/min)	301.6	332.5	380.2	7.87	0.9753	YES
VE/VO_2	23.35	27	30.75	7.82	0.9753	YES
VE/VCO_2	28.37	30.92	36.15	7.32	0.9509	YES
VT (L)	0.61	0.80	0.95	21.38	0.9293	YES
O_2exp (ml)	101.4	134.8	193.7	20.2	0.9297	YES
CO_2exp (ml)	22.43	31.10	52.36	25.07	0.9297	YES
R	0.78	0.84	0.9	3.79	0.9045	YES
$PetO_2$ (mmHg)	100.8	104.2	108	2.04	0.9458	YES
$PetCo_2$ (mmHg)	35.74	37.58	39.70	3.28	0.9748	YES
FeO_2 (%)	15.89	16.47	17.11	2.10	0.9655	YES
$FeCo_2$ (%)	3.40	3.98	4.32	6.96	0.9625	YES
Fat (%)	31.78	48.23	72.3	21.91	0.9227	YES
Kcal/kg/day	24.99	28.75	33.12	7.48	0.9309	YES

Thereby, increased Rf (13.41±3.04 b/min) is associated with a descreased VT volume (0.83±0.17 L), p=0.0001, r=-0.90, CI 95%=-0.94-0.40. Also, O_2exp parameter (137.3±27.73 mL) is significantly associated through p=0.0002, r=-0.88, CI95%=-0.90-0.68, with Rf, indicating an increase oxygen volume production, and a decrease in respiratory frequency. Hypothesis confirmed as well in the case of CO_2exp value (33.32 ± 8.35 ml), p=0.0001, r -0.93, CI 95%=-0.98-0.76, which reports an increase in value, and a decrease in Rf (Fig. 1). Additionally, low respiratory frequency was associated with FeO_2 (16.42 ± 0.34%), p=0.0382, r=-0.60, CI 95%=-0.87-0.04, and $FeCO_2$ values (3.93±0.27%) p=0.0284, r=-0.62, CI 95%=-0.88-0.08, significant statistically, highlighting an increasing amount of oxygen, and carbon dioxide taken up trough lungs, along with a decrease in Rf.

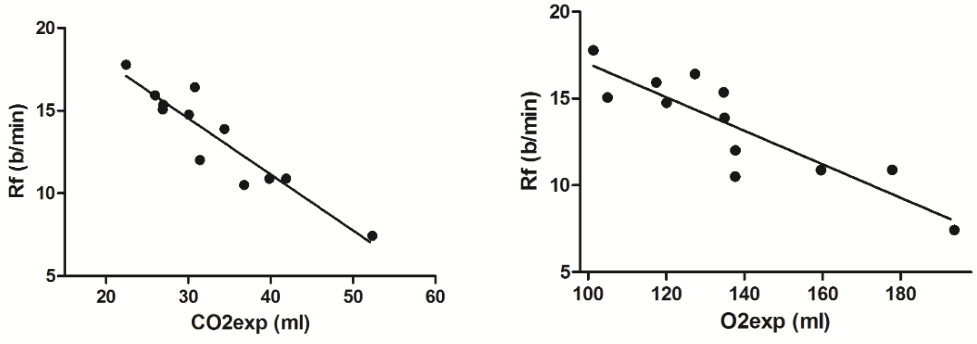


Figure 1. Relationships between Rf, CO_2exp (p=0.0001), O_2exp (p=0.0002)

VE (10.64±1.05 L) is statistically significant with the main respiratory parameters. Thus, the total volume of exhaled air is related significantly to VCO_2 value (338.9±26.66 ml/min) p=0.0086, r=0.71, CI 95%=0.24-0.91, meeting directly proportional increases in values. Within the study group, VE≤10 (l/min) (reference value 6 to 10 l/min), was related to VCO_2≤320.96 ml/min value, while an amount of ≥10 l/min VE, was associated with >320 ml/min VCO_2. Following the determinations we identified a relationship between VT (0.83±0.17 L), the amount of oxygen (p=0.0001, r=0.99, CI 95%=0.98-0.76 95%), and carbon dioxide which is produced by the body (p=0.0001, r=0.94, CI 95%=0.89-0.99). Thus, within the studied group, we highlighted a proportional increase of O2exp, and CO2exp values by increasing the total value of VT, among athletes. The oxygen volume expired, is statistically significant to the amount of carbon dioxide taken up and used by the lungs ($FeCO_2$). Information confirmed through p=0.027, r=0.63, CI 95%=0.09-0.88, meeting a normal increased amount of exhaled (CO_2exp), and inhaled carbon dioxide ($FeCO_2$). Additionally, VE/VO_2 parameter (26.89±2.10 l/min), which is associated with hyperventilation/ hypoventilation, is correlated with VE volume (p=0.0114, r=0.69, CI 95%=0.20-0.90), being reported an increase between VE/VO_2 value, VE, and $PetO_2$ parameter (p=0.0001, r=0.91, CI 95%=0.70-0.97).

VE/VCO_2 representing the ventilation equivalent of carbon dioxide, is associated with VE (p=0.0306, r=0.62, CI 95%=0.07-0.88), and Rf (p=0.0377, r=0.60, CI 95%=0.04-0.87), the increasing value of the detemined parameters being directly proportional to the parameters identified in the studied group. Moreover, $PetO_2$ (104.6 ± 2.13) registered significant increases along with increases of VE/VCO_2 parameter (p=0.242, r=0.64, CI 95%=0.10-0.88) (Fig.2). Moreover $PetCO_2$ parameter (37.60±1.23 mmHg), increases by decreasing VE/VCO_2 (Fig. 2), in the studied group (p=0.0002, r=-0.86, CI 95%=-0.96-0.58). This action is associated, in the case of VE/VCO2, with changes in energy consumption at rest (28.85±2.15 kcal/kg/day), thus increasing the energy needs in the studied group was associated with a decrease in VE/VCO2 value (p=0.0346, r=0.61, CI 95%=-0.87-0.05).

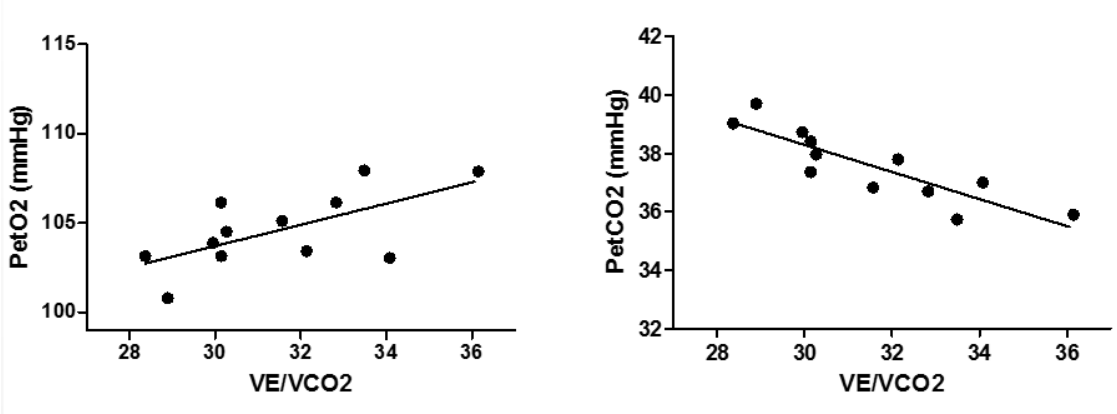


Figure 2. Relationships between VE/VCO_2, $PetO_2$ (p=0.0242), $PetCO_2$ (p=0.0002)

Partial pressure of oxygen ($PetO_2$), through its importance within the respiratory system, reveals correlations with R value (respiratory exchange ratio), identifying an increase in $PetO_2$, along with the increase of R value (p=0.0142, r=0.68, CI95%=0.18-0.90). Hypothesis confirmed through $PetCO_2$ equivalence, and fat consumption at rest (49.23±10.79%), according to which, a drop in $PetO_2$ is associated with an increase in fat consumption at rest (p=0.0191, r=-0.66, CI95=-0.89-0.14). $PetO_2$ alongside $PetCO_2$ parameter, established a correlation whose result expresses that $PetO_2$ growth, will reduce the amount of $PetCO_2$ during recovery periods (p=0.0002, r=-0.87, CI95%=-0.96-0.60). Furthermore, meeting a directly proportional increase of $PetCO_2$ value, and CO_2exp (p=0.0319, r=0.61, CI=0.06-0.88). In practical terms, a strong association was identified with macronutrients consumption at rest.

DISCUSSIONS

The ventilatory system was not seen as a limiting factor in the activity performed by athletes (10). However, the correlation of respiratory parameters with physical efficiency offers new indices of sports performance. In practical terms, parameters such as respiratory frequency, whose values may reach 40-60 breaths/min, and a maximum tidal volume of 1.5-4 liters/minute during exercise, could confirm such hypotheses (11). The values determined at rest will indicate the efficiency of the recovery process, and respiratory adaptation of the athletes (12).

Moreover, it is confirmed that respiratory muscle performance is low after completing an endurance effort, being able to restrict the activity, and performance, through different mechanisms (13). These include: inadequate hyperventilation response during effort, tachypnea, increased sensation of dyspnea, and increased sympathetic effect on the membranes of skeletal muscle vasoconstriction (14,15). Many papers have shown that the effectiveness of the respiratory system is attested trough ventilation reported in minutes, and carbon dioxide production (VE/VCO_2) (16). Moreover, skeletal muscle metabolism will increase CO_2 production intramuscularly, while $PetCO_2$ in the blood is kept constant to increase ventilatory efficiency (17). During distinct periods, when VE does not have the capacity to meet the demands imposed through effort, $PetO_2$ will drop (17).

The normal value for tidal volume is estimated between 300-800 ml per breath, when Rf is within the range of 12 to 20 breaths per minute, and VE is between 4 to 16 liters/minute. Moreover, the respiratory rate is a direct indicator of intense effort, and the reaction that the body holds during physical activity (18). Highlighting an increased respiratory rate among athletes, along with an elevated tidal volume through Rf, it can impose a maximum VE value, during effort, which exceeds 250 liters/minute (19). During rest periods, in numerous cases it is highlighted an increase in FeO_2, due to low oxygen demand, but with the beginning of effort, increasing O_2 extraction may establish decreases in FeO_2 value due to increased alveolar ventilation (20).

During an effort that exceeds the ventilatory anaerobic threshold, CO_2 production in excess will support VE, versus VCO_2 in a linear form, along with $PetCO_2$ as a constant value (21,22). A change of connections between VE and VO_2 can be seen above the ventilatory anaerobic threshold (23). Action that will increase VE/VO_2 value, along with $PetO_2$ in the presence of a decrease, or a constant value of VE/VCO_2, and $PetCO_2$ (24). During recovery period, after sustaining a moderate intensity effort, O_2 deficiency acquired during the effort, is restored through excess VO_2 value compared to the initial period of rest (24). An increased intake of O_2 is necessary to initiate the process of creatine phosphorylation in skeletal muscle, and thereafter to convert lactate into pyruvate, to its use as an energy source (25). Also, during recovery periods $PetCO_2$ value is slightly lower than blood PaCO2 at rest, but will increase during effort compared to blood $PaCO_2$ value (26).

Thus, decreased respiratory frequency (Rf) will be associated with reduced tidal volume (VT). O_2exp alongside CO_2exp will report elevated levels, by decreasing Rf. At the same time, the amount of oxygen (FeO_2), or carbon dioxide ($FeCO_2$) taken from the lung, increases with the decrease in Rf. VE parameter growth will be associated to an increase VCO_2 and VE/VO_2, whereas VT will highlight a directly proportional increases with O_2, CO_2exp. $PetO_2$ growth will be correlated with decreased $PetCO_2$ value, association performed as well with CO_2exp value.

CONCLUSIONS

Evaluating the main respiratory parameters will associate the recovery stage, and therefore the athlete adaptation to the performed exercise. Early adaptation will be achieved through proper effort periodization, taking into account a decrease in the frequency of high

intensity efforts. From a practical standpoint, endurance effort will affect the respiratory muscles, increasing the importance of the recovery process. Thus, measurement of basic cardiovascular indices (HR, Rf), together with the association of respiratory parameters (VCO_2, VE/VCO_2, VE/VO_2, O_2exp, CO_2exp, R) will indicate the recovery state of the individual after the performed effort, and therefore, the respiratory adaptation to the imposed effort intensity.

Abbreviations.
RF (b/min) – respiratory frequency
VO2 (ml/min) - maximal oxygen uptake
VCO2 (l/min) - dioxide output per unit of time
VE/VO2 - oxygen dioxide output
VE/VCO2 - carbon dioxide output
O2exp (ml) - expired oxygen volume
CO2exp (ml) - exhaled carbon dioxide volume
PetO2 (mmHg) - end-tidal oxygen tension
PetCO2 (mmHg) - end-tidal carbon dioxide tension
FeO2 (%) - the amount of O2 extracted from the air by the lungs
FeCO2 (%) - the amount of CO2 extracted from the air by the lungs
Fat (%) – Lipid consumption at rest
Kcal (kcal/kg/day) – Energy consumption during rest periods (kg/day)

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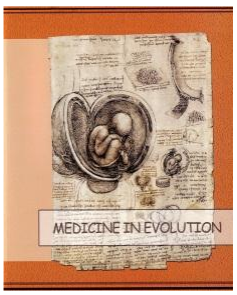
Medical assistants and the Burnout syndrome



Hogea L.[1], Nussbaum L.[2]

[1]Psychology Discipline, Neurosciences Department, University of Medicine and Pharmacy"Victor Babeş"Timişoara
[2]Pedopsychiatry Discipline, Neurosciences Department, University of Medicine and Pharmacy"Victor Babeş"Timişoara, Clinic of Child and Adolescent Psychiatry, Timisoara

Correspondence to:
Name: Laura Nussbaum
PhD
Address: Neuroscience Department, „Victor Babes"University of Medicine and Pharmacy, 2 Eftimie Murgu Sqr., Timisoara, Romania; Psychiatry and Neurology Pediatric Clinic, Timisoara, Romania
E-mail address: nussbaumlaura@yahoo.com

Abstract

Burnout syndrome is considered to be a matter of public health, reaching this stage due to a continuous frequency increase, but mainly due to the multitude of negative consequences for the health system.

The purpose of this paper is to draw a wake-up call about the presence of this syndrome among nurses, to present its prevalence and to make known methods of prevention, thereby helping in the recovery of persons who fall into this impasse.

Keywords: burnout syndrome, medical assistant.

INTRODUCTION

In Romania, the medical system is often described by his staff as being suffocated and suffering, the only culture that dominates is of helplessness, discontents, fierceness and the intertwined mistrust among them and the patients.

The Romanian healthcare system has one of the lowest rates of density in Europe regarding the distribution of medical personnel per capita.

This rate is in a continuous increase, leading to undue medical personnel already surpassed by the sheer volume of work creating serious consequences on both the hospital and the quality of the medical act.

The negative effects of this disease placed among the medical personnel are felt on the individual, the institution and the patients. According to some studies, physicians assistants, nurses and residents suffering from this syndrome are much more inclined to substance consumption, depression, insomnia, or showing an increasingly rate of suicidal ideation [1].

MATERIAL AND METHODS

The batch of subjects is made of 103 nurses coming from County emergency Clinical Hospital"Pius Brînzeu ', Timisoara; Emergency military hospital"Dr. Victor Popescu", Timişoara; Municipal Clinical Hospital of emergency, and in the floreasca emergency hospital for children"Louis Turcanu"Timişoara. Of these, 93 are female, and 10 are male.

For the data collection the questionnaire used was built on the basis of Maslach and Jackson theory, which measures the level of professional exhaustion within this profession.

This questionnaire includes 25 questions that are arranged in 3 dimensions as follows: emotional exhaustion (comprising 9 items), depersonalization (comprising 6 items) and reduction of personal achievements (comprising 10 items). As a Response method, the Likert scale has been used because it confers the advantage of a larger variety of responses, thereby reducing the risk of obtaining the same response from the subjects.

RESULTS

Results of the study show that 42% of all subjects fall into the medium level of the burnout syndrome.

An explanation for this medium level of burnout syndrome present among nurses could be that they are the ones who must continually meet both emotional stimuli from their relationship with patients and physical stimuli through the tiring work that they need to exercise in order to fill the lack of medical personnel. All this affects performance, leading to exhaustion, stress, and finally giving up their current job [Fig. 1].

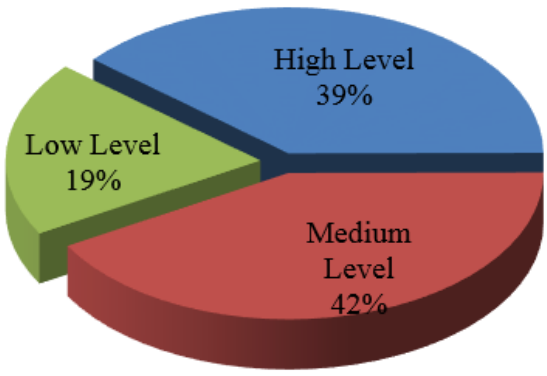


Figure 1. The total score distribution

Emotional exhaustion means that emotional energy wastage caused by excessive psychological requirements of various tasks within the workplace.

That is why the most important aspect of the burnout syndrome is the one linked to emotional exhaustion and the results of the study showed that from this point of view 45.6% of the total number of subjects, have a high stress level.

One reason for the high level is that personal relationships with patients can be very demanding because it requires empathy and emotional involvement, and over time these things have led to vulnerability to stress factors [Fig. 2].

The second dimension represented in the figure below is depersonalization. This refers to the people's attempts to detach from others by associating and treating them as objects. Depersonalization aspects are reflected either through language, through the use of labels to describe their disease or patients, either by negativism or cynicism.

Voluntarily or not, each of us have witnessed, at some point in life, treatments of this kind on the part of nurses, and we have not tried to think that it is possible for them to suffer from the syndrome of depersonalization. As we can observe, about 26% of medical assistants subjected to this questionnaire are presenting the symptoms of a depersonalization syndrome [Fig. 2].

The last major component of the burnout syndrome is represented by the reduction of personal achievements and is characterized by the tendency of negative self-evaluation capacity, professional achievements or success (35.9%) [Fig. 2]

These phenomena are initiated much faster to people who chose this profession because they considered that they had a vocation for it, and at the time of the occurrence of the failure he will regard himself as incompetent and unable to achieve his goals.

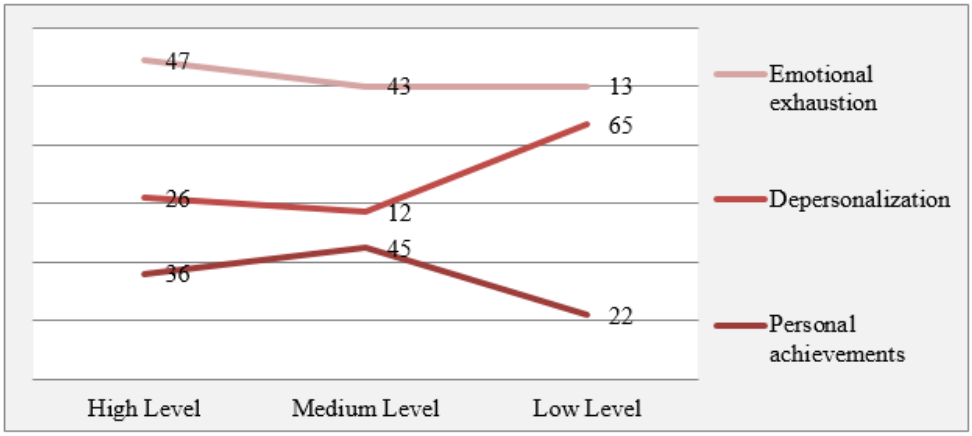


Figure 2. Distribution by emotional exhaustion, depersonalization, reduced personal achievements

Emotional exhaustion, one of the most important dimensions of the burnout syndrome makes its presence felt among its individuals with a job seniority between 5-10 years and 20 years.

An explanation for the fact that people with a low level of experience have a high degree of emotional exhaustion may be due to a lack of experience or because they have not yet developed their own means of self-protection.

People with a seniority of more than 20 years experience this syndrome due to the accumulation of a huge number of losses that they did not know how or they did not have the opportunity to express or process them [Fig. 3].

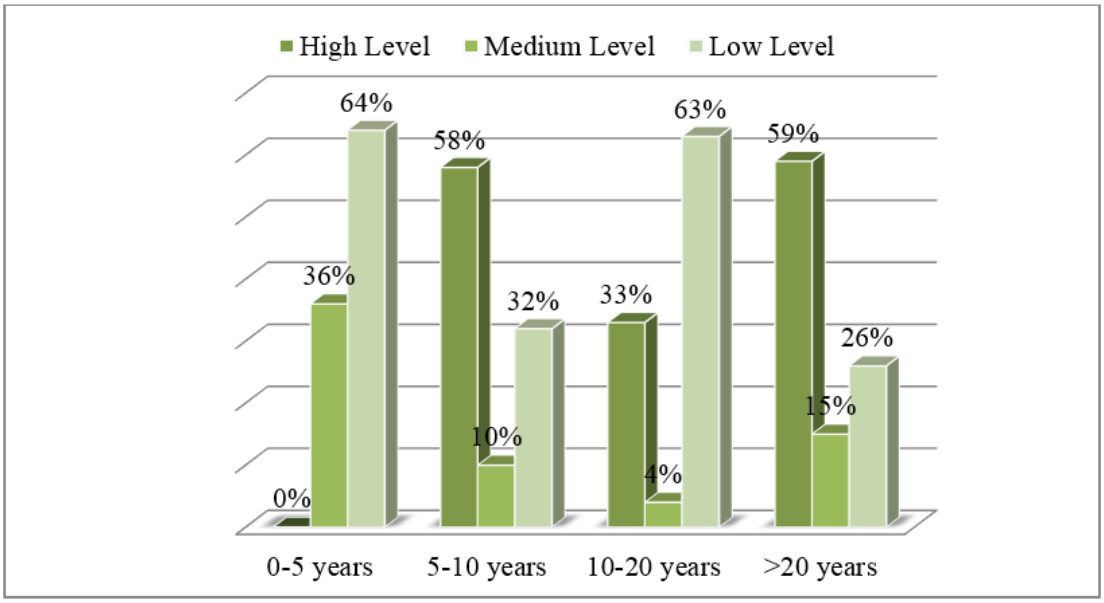


Figure 3. Professional experience in correlation with emotional exhaustion

In the case of the depersonalization syndrome, it can be seen in the figure below an increase in direct proportion between it and the professional experience acquired. If in the early years of experience only 1 of 11 people experience depersonalization phenomena, throughout the accumulation of experience, their number has tripled, up to 11 people from 34 to manifest this phenomenon [Fig. 4].

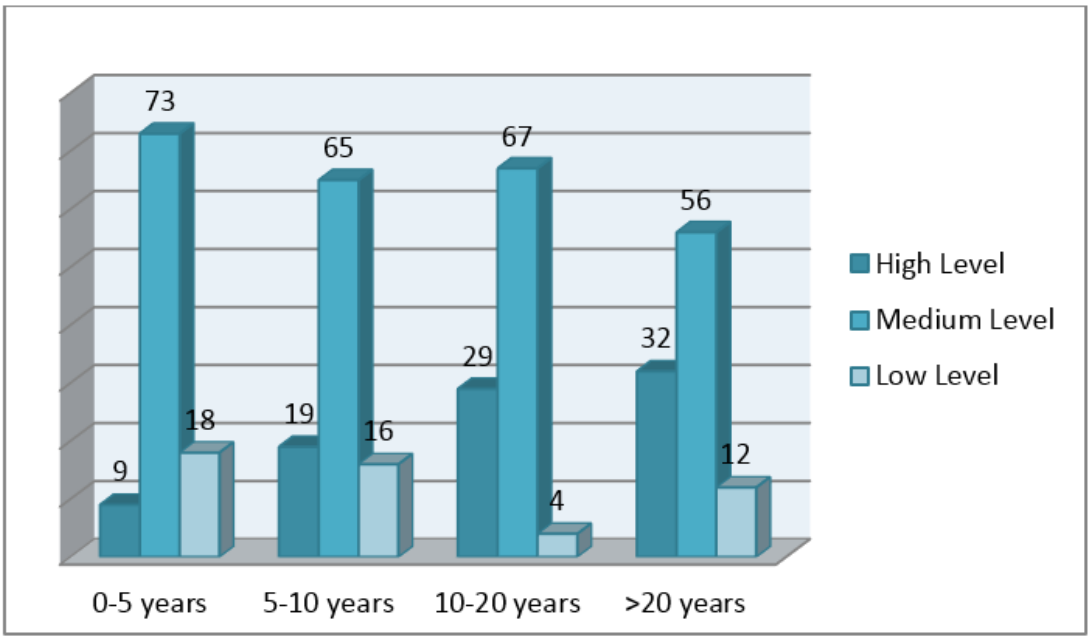


Figure 4. Professional experience in correlation with depersonalization

We can see that people with an age over 20 years are the most affected and feel the most the reduction of personal achievements phenomena, because 21 assistants from 34 state that they feel professionally unsatisfied.

A high level of user dissatisfaction in people with longstanding professional experience can lead to motivating them to quit their jobs, thus leaving gaps in the framework of the medical staff that will be filled with people lacking in experience. Thus the deficit of staff actually turns into a shortage of experienced staff.

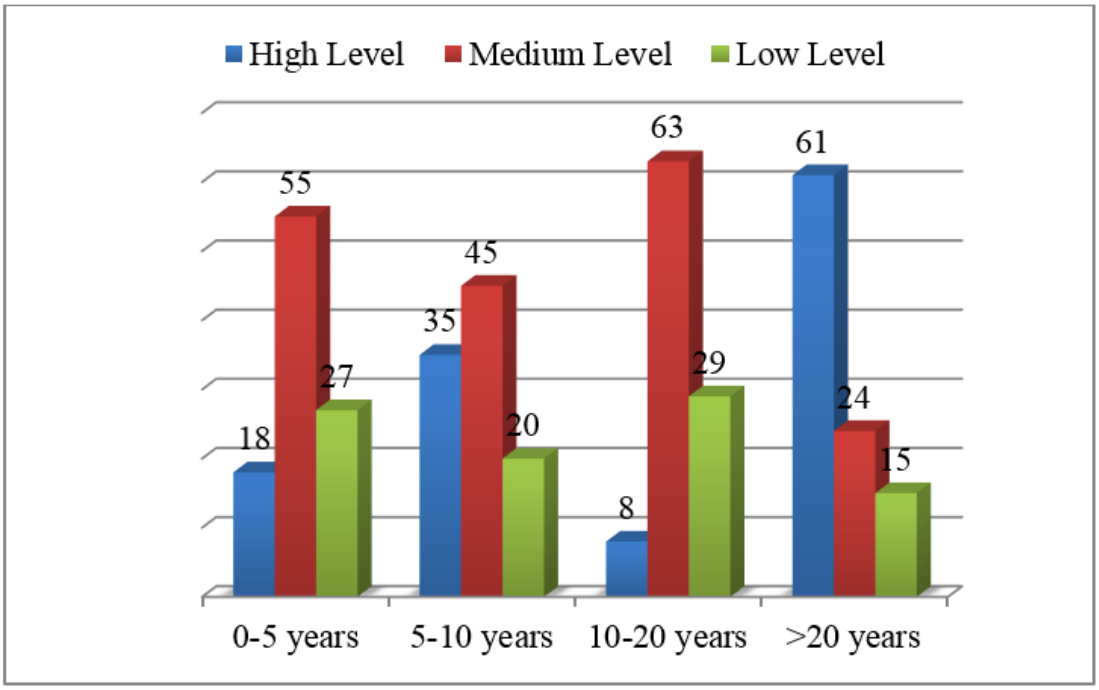


Figure 5. Professional experience in correlation with the reduction of personal achievements

Following the test, in the category of high level burnout syndrome were placed a number of 37 women, representing 39.7% of their total. The ones from the medium category are in number of 38 accounting for 41 percent, while those in the low category are in number of 18 representing 19.3%.

The results show that only 3 men, representing 30% were fitted in the category of high level burnout syndrome. In the category of medium level, there are 5 representing 50%, and in the low category there are 2 representing 20% [Fig. 6]

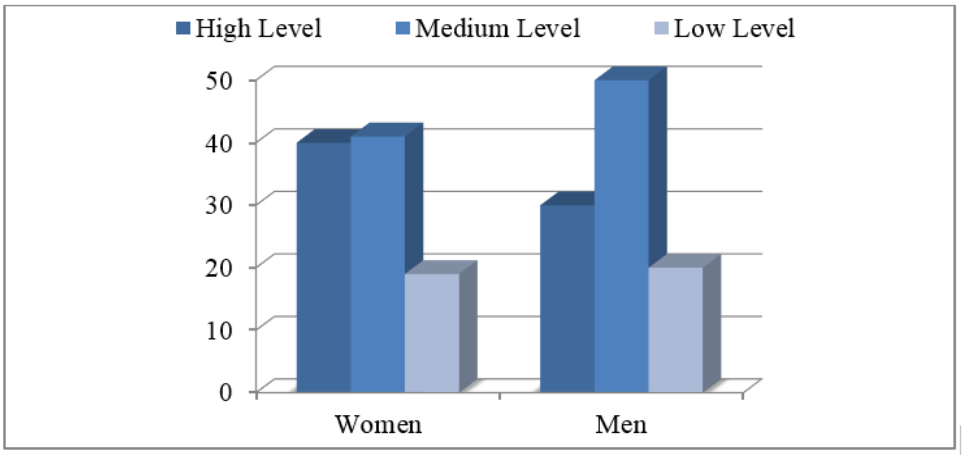


Figure 6. The relationship between gender and the total score

CONCLUSIONS

The results of this study showed that in terms of reducing personal achievements and depersonalization are average but in terms of emotional exhaustion, burnout syndrome prevalence is higher, thus confirming the first objective of this work, namely, the prevalence of burnout syndrome among nurses in Timişoara.

The feminine gender is more proned to develop this syndrome as opposed to the male sex, and an explanation for this is the influence of socio-cultural factors, whereas women are

subjected to extra work at home. Although the nurses are the ones that have higher levels of stress in the first two dimensions

A low or long professional experience is also a factor leading to the increase of the level of stress of the medical assistant and thus increase the likelihood of developing the burnout syndrome.

In conclusion we can say that both the number of years you are working in the field, as well as the feminine gender of the nurses facilitates the triggering of this syndrome.

But how can we protect ourselves? The answer is simple, through moderation. We must learn to combine some aspects of our lives so that we have an equilibrium between the careers we have chosen, our life and personal development, health, and social relations and of friendship but also our financial wishes, avoiding as much as possible imbalances between the ideal and the real.

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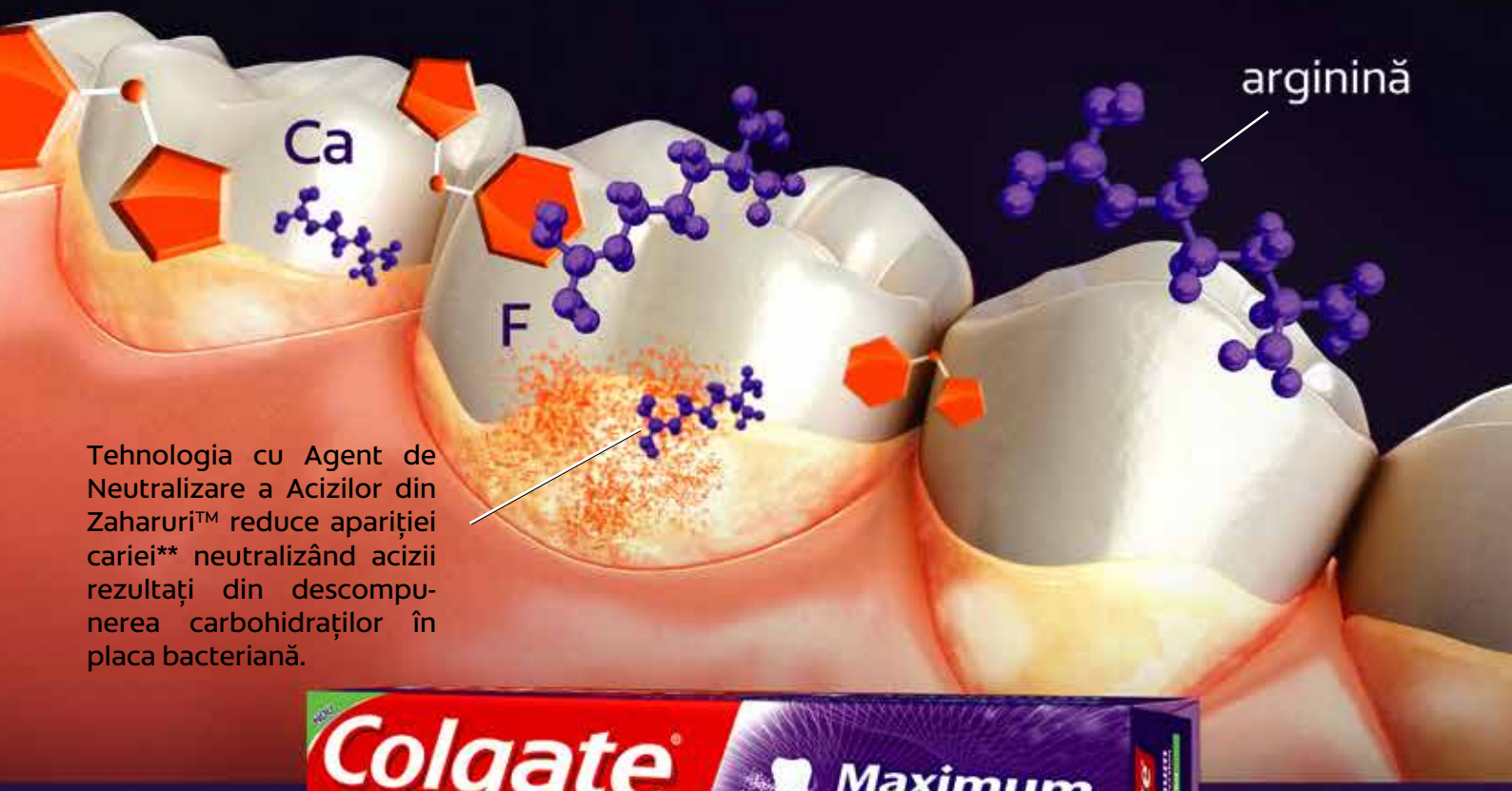

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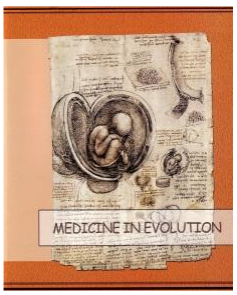
Bisphosphonate-associated osteonecrosis of the jaw. Case report



Bălean O.-I.[1], Podariu A.-C.[2], Ianeş E.[2], Borţun C.-M.[2], Doina C.[2]

[1]*PhD Student at"Victor Babeş"Universty of Medicine and Pharmacy Timişoara;*
[2]*Faculty of Dental Medicine,"Victor Babeş"Universty of Medicine and Pharmacy Timişoara*

Correspondence to:
Name: Octavia-Iulia Bălean
PhD student
Address: Str. Nicolae Iorga, Nr 4, Ap 9, Timişoara, România
Phone: +40 748677191
E-mail address: balean.octavia@yahoo.com

Abstract

Bisphosphonates have become the elective treatment for osteoporosis, both in preventing and treating bone metastasis associated with neoplasms and Paget's disease. With the increased prescription of bisphosphonates, the incidence of osteonecrosis of the maxilla and mandible has increased significantly. Seeing that these lesions are easier to prevent rather than treat, prophylaxis has become a necessity. The treatment is difficult, long lasting and sometimes unsuccessful. In this article we present a clinical case of bisphosphonate-associated osteonecrosis of the maxilla.

Keywords: *osteonecrosis, bisphosphonates, CBCT, jaw*.

INTRODUCTION

The bisphosphonates are a group of pharmacological agents used in the prophylaxis and treatment of bone metastasis associated with malignancies of the breast, prostate, lung, multiple myeloma, but also for osteoporosis and Paget's disease. Off label, they are also recommended for osteopenia, fibrous dysplasia, Gaucher's disease and osteogenesis imperfecta.[1,2,3,4,5,6]

The bisphosphonates are synthetic analogs of pyrophosphate (an endogenous regulator of bone turnover) in which the P-O-P of the pyrophosphate is replaced with P-C-P that renders stability and is responsible for their affinity to bone tissue.[4,7,8]

The Bisphosphonates are divided into 2 generations: first generation (etidronate) and second generation (alendronate, risendronate, ibandronate).[8,9]

Both generations have the same mechanism of action: the inhibition of bone resorption. The difference between these compounds is in their intensity, it is pharmacotherapeutic effect and toxicity.

The toxicity is greater for intravenous administration, compared to oral administration, therefore zolendronate is the most toxic intravenous administered bisphosphonate and alendronate is the most toxic in case of oral administration. [7,10]

The bisphosphonates can be administered both orally and intravenously. Intravenously administered bisphosphonates (pamidronate and zolendronate) have been used to stabilize osteolysis associated with bone metastasis. They are also prescribed for reducing hypercalcemia caused by various malignancies. Those administered orally are usually used in the treatment of osteoporosis (alendronate, risendronate), as well as Paget's disease (etidronate and tiludronate).[1,7]

The bisphosphonates have become the 19th most prescribed medication worldwide and alendronate (Fossamax) is the 13th most prescribed orally administered drug. After these treatments, it has been observed that any bisphosphonate taken, independent of dosage, leads to a variable degree of bone toxicity.[10] Osteonecrosis is the most common manifestation of toxicity and it can be found mostly in the maxilla due to the fact that bone turnover in the alveolar bone is 10 times higher than in the tibia. In the maxilla it is 5 times higher compared to the basal margin of the mandible and 3.5 times that of the cortex of the mandibular canal.[12,13]

Long term administration increases toxicity and can lead to serious complications that can alter the quality of live, affecting the patient functionally, physically and psychologically.

CASE PRESENTATION

A 63 years-old male patient is admitted in the Oral and Maxillofacial Surgery clinic with a primary diagnosis of bisphosphonate associated osteonecrosis of the left maxilla and a secondary diagnosis of prostate adenocarcinoma with liver and bone metastasis. The patient received zolendronic acid 4 mg, once a month, goserelin 10.8 mg, every 3 months and bicalutadium 50 mg daily. Two years ago, while under bisphosphonate treatment, the patient underwent 2 dental extraction procedures in the left maxilla, without any prophylactic measures, such as covering the wound with muco-periostal graft and antibiotic treatment. Post-extraction wounds did not heal; instead, they suffered multiple infections which were treated with antibiotics that proved ineffective. Therefore the pain and inflammatory phenomena reoccurred in a short period of time. Approximately 14 months following the extractions, due to the infectious complications, the patient noticed in the left maxilla an extending zone of denuded bone with no tendency to heal, which determined him to seek medical care.

During the endo-oral exam an atonic wound of the gingival mucosa was observed at the alveolar crest of the left maxilla, further indicating bone denudation and necrosis of approximately 6/4 cm, the bone being of a white, grey color. (Fig. 1)

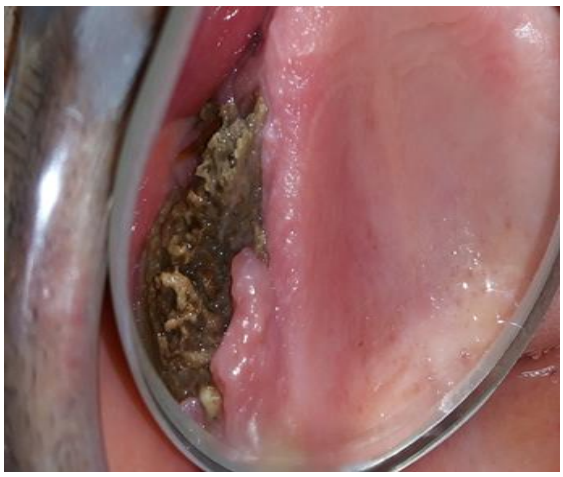


Figure 1. Initial clinical image. Necrotic bone exposed in quadrant II

Due to the extensive lesion and its proximity to the maxillary sinus, a CBCT was recommended in order to obtain a three-dimensional image of the alveolar process and the adjacent maxillary sinus.

The CBCT exam, in axial incidence, in quadrant II, in the premolar-molar zone shows a bone structure modification of 5.9 cm^2 with an increase in bone rarefaction associated with an increase in bone opacity, neatly contoured, oval in shape which suggests the presence of a bone sequestrum.(Fig.2)

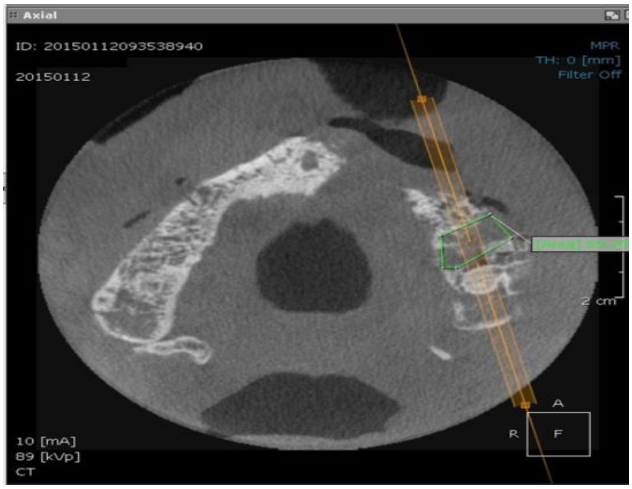


Figure 2. CBCT axial view

In sagittal incidence, we observe structure modification in the molar area of the alveolar bone and the homogenous veil-like opacification of the sinus. This bone rarefaction associated with the presence of a bone sequestrum and the discontinuity of the maxillary sinus base, suggests an oro-sinus communication.(Fig.3)

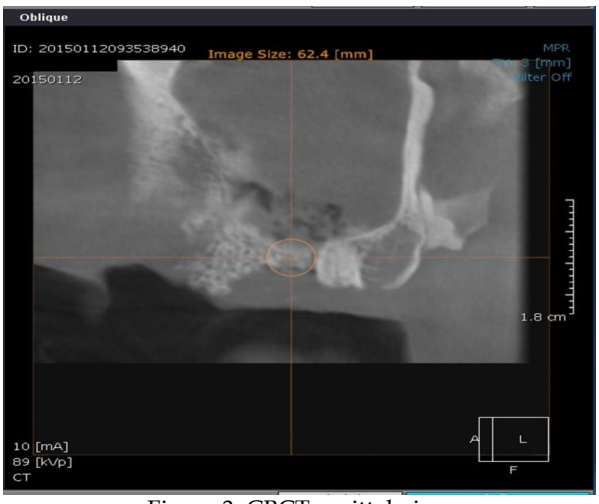


Figure 3. CBCT sagittal view

A purulent sample was taken from the wound and its microbiological test and DST showed there is Eserichia coli sensitive to, cefotaxime, ciprofloxacin, doxycycline, ampicillin, amoxicillin, clavulanic acid, cefuroxime gentamicin.

After clinical and paraclinical examinations, there was a surgical treatment, which consisted in extracting the modified area of the bone and the opening, and in exploring the maxillary sinus, followed by the repair of the oro-sinusal communication. Taking into consideration the extent of the lesion, the surgery was performed under general anesthesia.

The first surgical step involved an incision delimiting a muco-periostal trapezoidal, vestibular flap followed by its removal in order to expose the modified bone area. The bone sequestrum was removed and the necrotic bone was curetted which led to the formation of an 8/4 cm defect.(Fig.4) The procedure opened the maxillary sinus, and explored the sinus cavity in which there was found a thickened sinus mucosa that did not need removal, as it had no purulent secretions.

The final surgical step involved closing the oro-sinusal communication with a vestibular muco-periostal flap.

To protect the wound postoperatively the patient was fed through a nasogastric tube for a week.

Postoperatively the pacient underwent the following treatment: gentamicin, 80 mg, and ceftriaxone 2g once every 12 hours for 5 days, and then amoxicillin 875 mg and clavulanic acid 125mg, every 12 hours for the next 10 days. Ketoprofen 100mg/2ml every 8 hours for 10 days was administered for the pain.

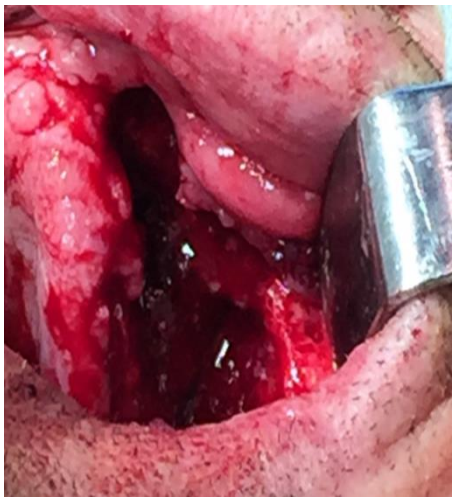


Figure 4. Intraoperative image

The surgical sample was sent for a histopathological exam. This resulted in maxillary osteonecrosis, because the examiner found a fragment of partially osteolysed spongious bone tissue, with suppurative osteomyelitic lesions, ischemic and inflammatory necrosis, with leucocyte detritus (puss) and filamentous bacteria (of the Actinomyces genus) in the areolae adjacent to the bone tissue, small oral mucosa fragments with thickened epithelium acanthosis and polymorphic inflammatory cell infiltration in the own lamina.

Postoperative evolution was favorable (Fig.5), without complications, the patient being supervised over the next 3 months. The complete recovery led to the implantation of a prosthesis.

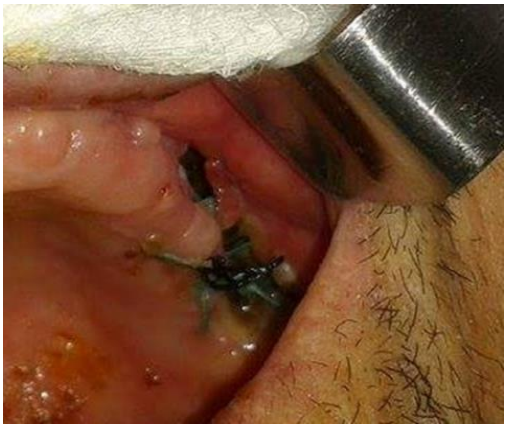


Figure 5. Postoperative image

The patient came back 6 months after the last control with an atonic wound of gingival mucosa of the alveolar maxillary ridge, highlighting the denuded and necrotic bone of about 3/2 cm, of a white grayish color, in the area of the left maxillary tuberosity(Fig.6). This confirms that this disease is not cured if the patient does not seek medical attention from the occurrence of the first symptoms.

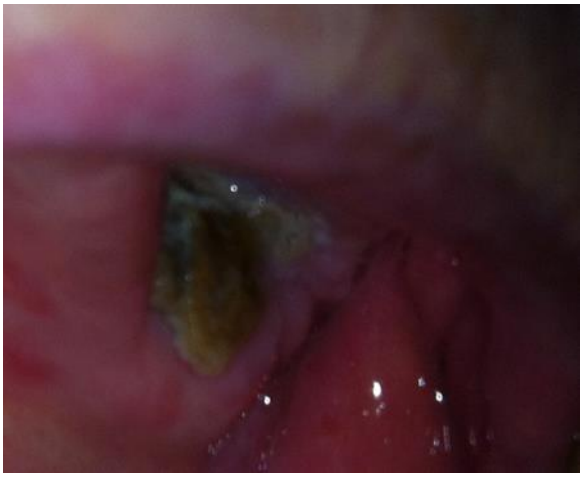


Figure 6. 9 months postoperativ intraoral aspect

DISCUSSIONS

The systematic therapy with bisphosphonates has been used since the 1990s, but only in 2003 was the first scientific reference to osteonecrosis associated with this medication published. The severity of this condition determined intense research into the action mechanism of bisphosphonates. [4,12,14]

The etiopathogenesis of maxillary osteonecrosis is not fully understood, however analysing the antiresorptive action of these substances certain conclusions can be drawn. [15,16]

In case of oral administration of bisphosphonates less than 1% is absorbed, whereas intravenous administration has a biodisposition of 50% in the bone matrix.[4]

According to current data, the incidence of osteonecrosis has a higher risk in the case of high dosage intravenous administration for a long term for malignant diseases, compared to those who undergo oral treatment. From studies, we observe that approximately 10% of patients with intravenous treatment develop osteonecrosis, whereas 1% of the pacients with intraoral treatment show necrosis.[14]

Based on these observations prophylactic strategies for patients with malignancies who require intravenous bisphosphonate treatment and for patients with osteonecrosis were devised.[2,12]

The pathological transformations are situated at the vascular level, in arteries, veins of all calibers, generating endarteritis lesions and endophlebitis, with the obstruction of the vascular lumen. The osteoblasts and osteoclasts disappear and the bone marrow is destroyed. Hypoxic phenomena facilitates infection, suggested by purulent secretion and inflammatory lesions of the surrounding soft tissue.[5,17,18,19]

All metabolic processes in the bone suffer alterations on a tissue, cellular and molecular level with the initiation of the bisphosphonate treatment.

At the tissue level there is a reduction in turnover followed by bone resorption. There is a strong connection between osteoblasts and turnover, and the bone regeneration process and its rate.

At the cellular level a reduction in the lifespan of osteoclasts is observed, inhibiting their activity and altering bone resorption.

At the molecular level an alteration in the function of osteoclasts has been noted.[4,5,20,21]

CONCLUSIONS

Bisphosphonate associated maxillary osteonecrosis is a challenge in oral and maxillofacial pathology. An interdisciplinary approach is desirable to prevent the complications of these diseases, that is, between the oncologist, endocrinologist and dentist.

The neglection of prophylaxis before initiating treatment determines an increase in the number of cases of maxillary osteonecrosis.

Emphasis must be put on prophylactic measures, that is, on the sterilization of infections before initiating bisphosphonate treatment.

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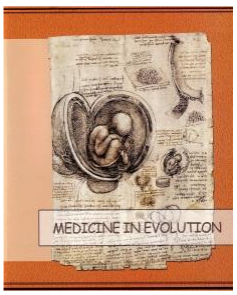
Dental anomalies in pseudohypoparathyroidism



Valea A.[1], Carsote M.[2], Ghervan C.[1], Georgescu C. E.[1]

[1]I.Hatieganu University of Medicine and Pharmacy & Clinical County Hospital, Cluj-Napoca, Romania
[2]C.Davila University of Medicine and Pharmacy & C.I.Parhon National Institute of Endocrinology, Bucharest, Romania

Correspondence to:
Name: Mara Coarsote
Address: Aviatorilor Ave, 34-38, Bucharest, Romania, sector 1, code 011683
Phone: +40 744851934
E-mail address: carsote_m@hotmail.com

Abstract

Introduction: Dental anomalies are found in genetic conditions as pseudohypoparathyroidism (PHP) which is an autosomal dominant disease involving clinical and biological hypoparathyroidism despite high levels of parathormone (PTH), dysmorphic facial features and mental retard. The main types are: type 1B which is characterized by resistance to PTH and type 1A supplementary associating bone anomalies called Albright osteodystrophy.

Cases presentation: This is the report of two type 1A cases with particular dental aspects. These are common with others conditions as idiopathic hypoparathyroidism, consistent with implantation vices, malocclusion, dental hypoplasia, multiple caries because of tooth enamel hypoplasia. Particularly, both cases associated early developed primary hypothyroidism. Therapy with vitamin D and calcium supplements were recommended as well as daily substitution with levothyroxine.

Conclusion: Long-term medical multidisciplinary follow-up is necessary. The correlation between dental anomalies of PHP and thyroid dysfunction may be incidental but a common potential genetic link is most probably involved.

Keywords: pseudohypoparathyroidism, parathormon, dental anomalies.

INTRODUCTION

The pseudohypoparathyroidism (PHP) represents a genetic condition causing a parathormone (PTH) deficiency regarding its actions associated with suggestive clinical and biological signs which are common with idiopathic hypoparathyroidism but with high levels of PTH, dysmorphic syndrome and mental retardation [1]. There are two known forms of PHP: type 1B characterized by isolated resistance at PTH action and type 2A which supplementary associates phenotype changes described as Albright osteodystrophy including nanism, round face, short neck, brahydactyly, calcification of soft tissues [2]. Rarely are seen anomalies as moderate obesity, enlargement of the skull, mental retardation, cataract and dental anomalies. The most frequent disturbances of the teeth are abnormal implantation, irregular and delayed dental eruption, enamel hypoplasia and multiple caries [3]. There is limited date in literature related to the dental anomalies from PHP but even since 1976 Gorlin et al. reported delayed dental eruption and enamel hypoplasia in PHP [4]. Later on, others anomalies have been described as dental apoplasia, malocclusion, enlargement of the dental roots and melanodontia [5]. A comparative study between PHP and idiopathic hypoparathyroidism suggested that dental anomalies are seen in all PHP cases, contrary to other recent data which suggested that only less than a half of patients with PHP have teeth disturbances [6,7].

We present dental anomalies on two cases of PHP type 1A to whom informed consent has been signed.

CASE PRESENTATION

Case 1

A 15-year old male patient is admitted for an endocrine evaluation because of multiple accuses as myoclonus, muscle contractures, epigastric pain, and asthenia. Personal medical history reveals that he has no brothers or sisters, he was born after a 39 weeks normal pregnancy, at birth the length was 55 cm and the weight was 3700 g, with an APGAR score of 10. He presented convulsive crisis since the age of 1 year and 8 months which were considered at that time an unspecific convulsive syndrome and intermittent anti-epileptic and calcium medication was offered. The first endocrine assessment was done at age of 12 and the diagnosis of PHP was established. Currently, on admission, clinical examination revealed: normal weight of 57 kg, normal height of 162 cm, dry skin, mild palpebral edemas, café au lait spots at the level of sacrum and inner corner of the right eye, dental anomalies as implant deficiencies of lateral incisors, canine teeth and first premolar at maxillary level, malocclusion. (Figure 1) The para-clinical data revealed hypocalcemia with normal levels of phosphorus with inadequately high levels of PTH; and a mild primary hypothyroidism. (Table 1) Daily therapy with thyroid substitution, vitamin D and calcium (1g/day) supplements were recommended and close follow-up.

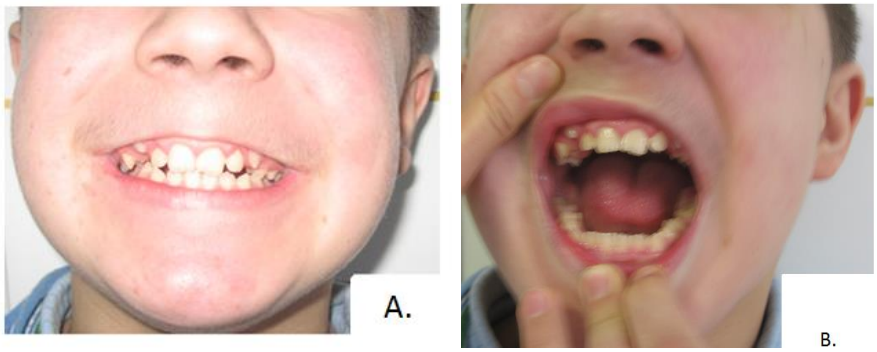


Figure 1. **A+B.** 15-year male patient with pseusohypoparathyroidism type 1A with dental implant anomalies

Table 1. The biochemical and hormonal parameters on two patients aged of 15 years (♂, case 1), respective 25 years (♀, case 2), diagnosed with pseudohypoparathyroidism type 1A

Parameter	Case 1	Caes 2	Normal values
Total calcium	7.2	9	9-10.5 mg/dl
Ionized calcium	1.56	4.68	3.5-4.5 mg/dl
Urinary calcium	26	56	100-200 mg/24- hours
Serum phosphorus	3.25	3.9	2.3-4.7 mg/dl
Alkaline phosphatase	103.7	42	40-150 U/L
PTH (parathormon)	324.7	138	15-65 pg/ml
TSH (thyreotrop hormone)	7.17	2.35	0.28-4.3 UI/ml
FT4 (Free T4)	16.73	15.4	12-22 pmol/ml

Case 2

A 25-year old female subject was diagnosed 5 years ago with primary PHP and primary hypothyroidism and therapy was started. Currently, she is re-admitted for an endocrine assessment because of Albright osteodystrophy: nanism (136 cm), body mass index of 26 kg/sqm, moon face, brachydaclyly, the brachymetacarpia (at the IIIth, IVth, and Vth finger of the left hand and Vth finger of the right hand), bilaterally brachymetatarsia of the IIIth and IVth finger. (Figure 2A+B) Oral cavity examination showed dental hypoplasia, the lack of left premolars which were extracted at age of 14. (Figure 2C) The biochemical and hormone profile revealed corrected levels of calcium under medication and mildly elevated PTH as well as thyroid correction under therapy with levothyroxine (L-T4). Further continuation of the therapy with vitamin D and calcium supplements and L-T4 treatment was recommended.

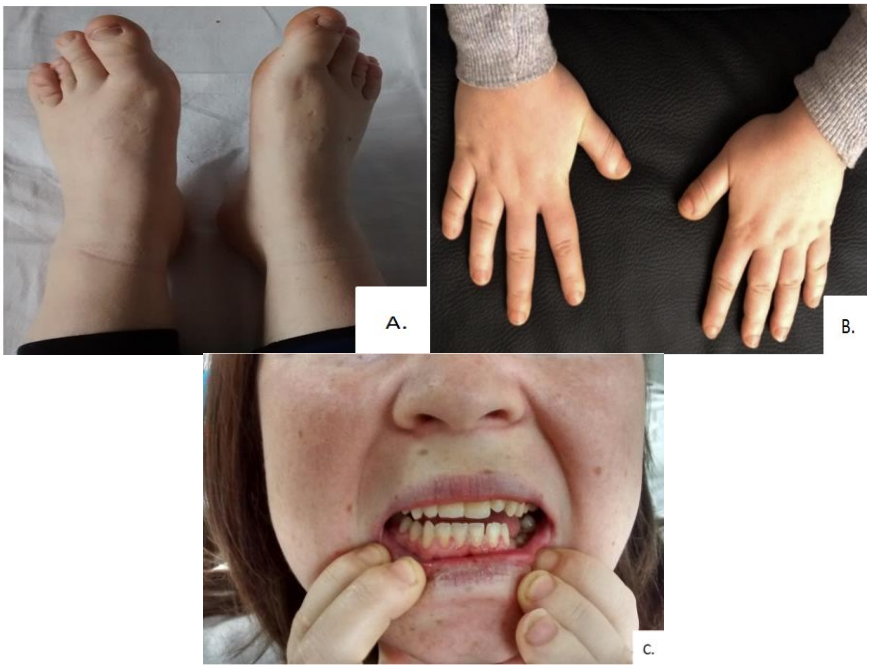


Figure 2. 25-year female patient with pseudohypoparathyroidism type 1A. A. Brachymetatarsia; B. Brachydactyly with brachymetacarpia; C. Dental anomalies like dental hypoplasia

DISCUSSIONS

Despite finding dental anomalies in PHP the murine studies did not reveal the PTH role on teeth eruption [8,9]. Opposite to the lack of evidence regarding direct connection between resistance to PTH action and delayed teeth formation the PTH is most probably involved in delayed eruption, formation and calcification of the matrix [10]. PHP also affects the dentine [11]. Our cases had early teeth anomalies since childhood but the diagnosis of PHP was established after the age of 10 years and, particularly, both cases had primary

hypothyroidism. In type 1A PTH the thyroid dysfunction mechanism involves structural anomalies of G protein [12].

The first patient had the clinical onset related to seizures and muscle cramps which were first considered a non-specific syndrome, most probably correlated to low calcium levels. The anomalies of the canines and first premolar tooth were first detected around the age of 8. The second subject had the most important elements of the clinical picture the tetany crisis associated with nanism, brachymetacarpia, brachymetatarsia and the dental anomalies were detected during a routine exam involving lateral incisors and premolars and also multiple caries were found. Overall, despite suggestive phenotype in both cases the type 1A PHP syndrome diagnosis was delayed. The early correction of hypocalcemia by prompt treatment with vitamin D and calcium supplements improves the clinical profile but not the dental anomalies which are already presented. On the other hand, if a dentistry exam accidently detects enamel hypoplasia, delayed eruption, and other anomalies it is necessary to establish the underlying cause especially if patients have a history of seizures. Sometimes orthodontic correction is necessary for malocclusion and serial dental X-Rays are useful to detect potential cysts associated with non-eruption of a tooth. Another clue is the correlation between dental changes and chronological development of teeth that allows an early diagnosis of general condition.

CONCLUSIONS

Primary pseudohypoparathyroidism associates clinical, radiological and dental anomalies as seen in idiopathic hypoparathyroidism. The multidisciplinary approach allows an early diagnosis. The early correction of hypocalcemia helps a normal development of dental tissue and limits the teeth disturbances with a better prognosis.

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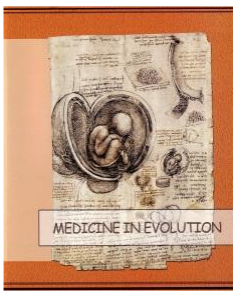
Management of pain in endodontic treatment using two types of local anesthesia



Petrescu G.[1], Iliescu A.[2], Rotariu G.[1], Spircu T.[3]

[1]*"Sc Clinica pentru zâmbetul tău med"srl, Bucharest*
[2]*Faculty of Dental Medicine, Endodontic Department,"U.M.F. Carol Davila"Bucharest*
[3]*Faculty of Medicine, Informatics and Biostatistics Department,"U.M.F. Carol Davila"*

Correspondence to:
Name: Georgiana Petrescu
DMD, PhD student
Address: Aleea Sinaia, 16, Bucharest
Phone: +40 732 092 835
E-mail address: pentruzambetultau@gmail.com

Abstract

Objectives: The study compares two types of anesthesia techniques: nerve block injection and acupuncture electro-analgesia.

Material and methods: 23 patients were selected, totalling 47 medical visits during endodontic treatment. There were also used VAS scale of pain, IEAD questionnaire, GI4 test, electro-acupuncture unit, endodontic instruments, sodium hypochlorite and other disinfection solutions, digital thermometer, voltmeter, an acupuncture analgesia technique, pulp tester, cold refrigeration spray.

There were made 32 procedures with articaine injection anesthesia and 15 procedures with electro-acupuncture analgesia during the study.

Results: Time needed for installing electro-acupuncture analgesia was longer; there were significant differences between the two groups. Acupuncture treated patients declared less anxiety referring to the waiting room, which were seeing the unit, hearing and feeling the drill.

Conclusions: Acupuncture analgesia needs a longer time to install and therefore can be used when other types of anesthesia have unsatisfactory effects. It is well received by patients with increased anxiety.

Keywords: dental anesthesia, acupuncture analgesia, electro-acupuncture, anxiety, endodontic treatment.

INTRODUCTION

Obtaining a better pain control in endodontics is a desideratum for many university research centres around the world. Our aim was to check if acupuncture analgesia could be used for patients or we need another therapeutic solution for controlling pain than dental nerve block.

About using Spix technique to anesthetize first mandibular molar, researchers have mentioned a complete anesthesia in 51% of the cases (with two negative consecutive testings in one hour) [1], there were used EPT [1], electrical and cold tests [1], [2].

In addition there were cases where nerve block anesthesia was contraindicated, restricting the ability for the dentist to intervene [3, 4].

There are many patients with dental anxiety or even more, with dental phobia. It was demonstrated by Milgrom P. et al, in 1997, that there were four dimensions of fear involving nerve block anesthesia [9]. Anxiety was shown to be a determinant factor for anesthesia failures in dentistry. [4]

Throughout time there were studies on a reduced number of patients using dental acupuncture analgesia [5, 6, and 7]. These studies could not be correlated one with another due to different points used to obtain acupuncture analgesia. The percentages for complete analgesia for the first mandibular molars were of 10%, respectively 11.3%, taking into account two respectively one molar, insufficient number of teeth for a statistical study [14, 15].

MATERIAL AND METHODS

There were included into the study only patients with first lower molars diagnosed with irreversible pulpits. Also, there were included only patients whose onset time of anesthesia by injection using the Spix technique was longer than the statistical average [1], or patients for whom for various reasons anesthesia by injection could not be used.

23 patients were selected, totalling 47 visits.

There were used questionnaires including VAS scale of pain, IEAD questionnaire, questionnaire for the method of anesthesia. Procedures included also Spix techniques, techniques for acupuncture analgesia, GI4 test, and articaine test. There were used also an electro-acupuncture unit, endodontic instruments, sodium hypochlorite and other disinfection solutions, digital thermometer and voltmeter, pulp tester, cold refrigeration spray.

The type of anesthesia was determined by the answers from the questionnaire, GI4 test results, and the discussion with the patient.

First group received nerve block anesthesia, Spix technique, using articaine. The second group received electro-acupuncture analgesia. The acupuncture points were: bilateral GI4, unilateral SI18, S5, GB2, RENMAI24, and auricular points (manual technique) SHEN MEN, and MANDIBLE.

The anesthesia was carried out, and cold tests were performed every 5 minutes [1, 2]. Time needed for the anesthesia to be effective was recorded, and then performed the endodontic treatment.

RESULTS

(Partial results after first phase of research)

There were made 32 visits with articaine injection anesthesia for a group of 16 patients, and then, 15 visits with electro-acupuncture anesthesia, for others even patients.

It has been noticed a significant correlation between articaine test results and onset time for anesthesia for both visits at the same patient.

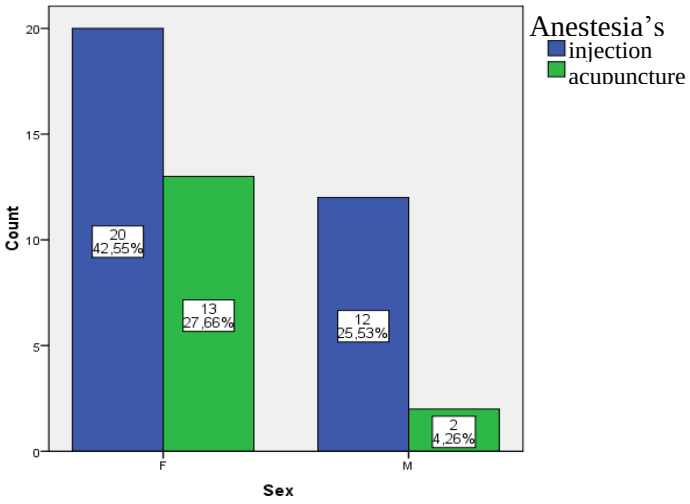


Figure 1. Patients' distribution by sex and type of anesthesia

Table 1. Correlation between articaine test and onset time for anesthesia for first visit at the same patient

Correlation first visit			Articaine test	Onset time
Spearman's rho	Articaine test	Correlation Coefficient	1.000	.801**
		Sig. (2-tailed)	.	.000
		N	23	23
	Onset time	Correlation Coefficient	.801**	1.000
		Sig. (2-tailed)	.000	.
		N	23	23

**. Correlation is significant at the 0.01 level (2-tailed).

Table 2. Correlation between articaine test and onset time for anesthesia for second visit at the same patient.

Correlation second visit			Articaine test	Onset time
Spearman's rho	Articaine test	Correlation Coefficient	1.000	.660**
		Sig. (2-tailed)	.	.001
		N	23	23
	Onset time	Correlation Coefficient	.660**	1.000
		Sig. (2-tailed)	.001	.
		N	23	23

**. Correlation is significant at the 0.01 level (2-tailed).

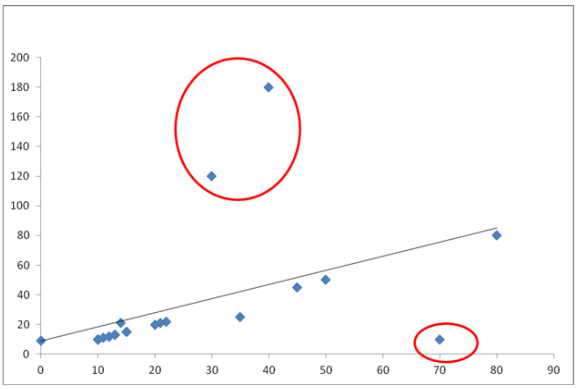


Figure 2. Time of anesthesia onset vs. the articaine test – first visit.

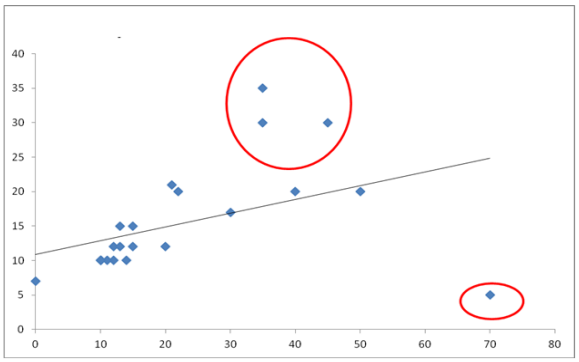


Figure 3. Time of anesthesia onset vs. the articaine test – the second visit.

It has been observed a significant correlation between seeing the needle of the syringe and feeling the needle. Somers delta index = 0.639, Kendall's tau-b index = 0.639, Gamma index = 0.755.

Table 3. Seeing the needle versus sensing the needle crosstabulation

		Sensing the needle anxiety					
		Very little	Little	So and so	Pretty much	Very much	Total
Anxietate la vederea seringii	Very little	**12**	4	0	0	0	16
		75,0%	36,4%	,0%	,0%	,0%	34,0%
	Little	0	**6**	5	0	0	11
		,0%	54,5%	38,5%	,0%	,0%	23,4%
	So and so	2	1	**7**	0	0	10
		12,5%	9,1%	53,8%	,0%	,0%	21,3%
	Pretty much	2	0	0	**3**	1	6
		12,5%	,0%	,0%	75,0%	33,3%	12,8%
	Very much	0	0	1	1	**2**	4
		,0%	,0%	7,7%	25,0%	66,7%	8,5%
	Total	16	11	13	4	3	47
		100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

Results obtained in IEAD questionnaire (situations, emotions and reactions during the dental treatment) showed no differences in replying to the first seven questions, and also a similarity of answers between groups for the questions 8-19. There were exceptions, namely the questions about feeling anxiety in the waiting room, or sitting on the unit chair, or seeing and hearing the vibration of the drill. For these, over half of the patients from the second group declared"very little anxiety", but over half of those in the first group declared"little anxiety". Overall, it appeared that there weren't major discrepancies between groups.

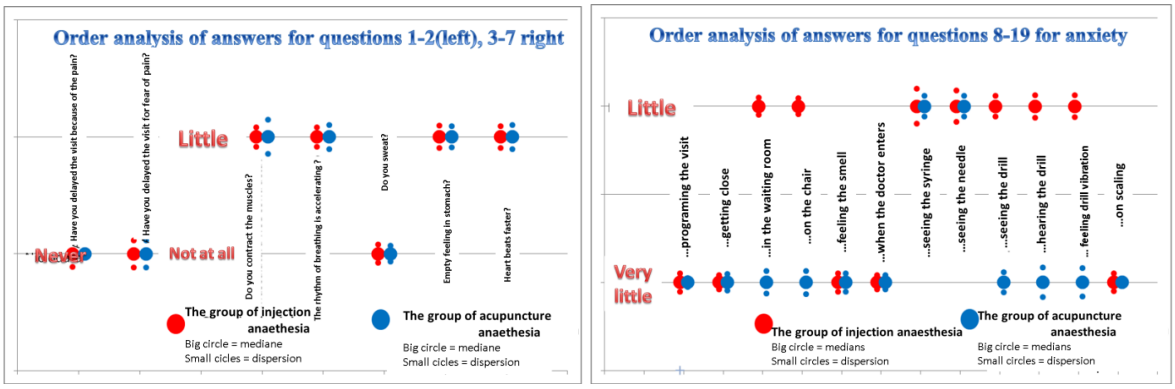


Figure 4. Analysis of answers, anxiety test

Regarding time allocated for treatment, there were significant differences between the two groups, between medians and averages. Working time for acupuncture analgesia was much longer and more convenient than the others.

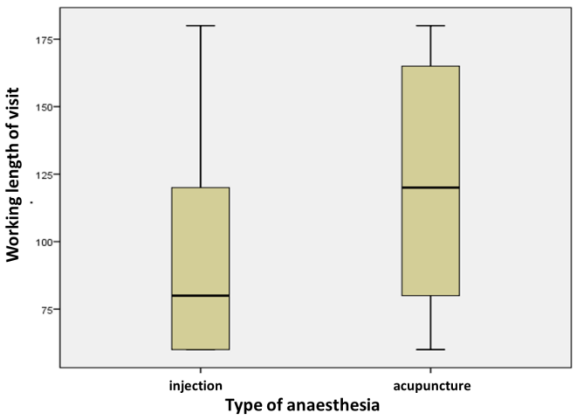


Figure 5. Working length of the visit

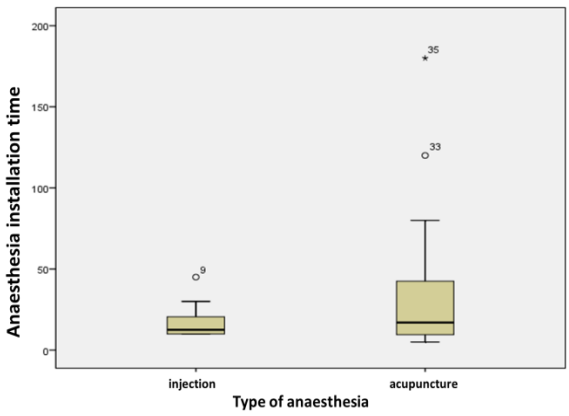


Figure 6. Anesthesia installation time

Regarding the settle time of the anesthesia, it was observed a longer time for acupuncture analgesia, on average.

CONCLUSIONS

(Partial conclusions):

Time for installing acupuncture analgesia was longer and concurrently placing the acupuncture needles and electro-acupuncture device could require a long learning curve.

Those aspects might be inconvenient for the practitioner.

There were no significant differences regarding the working method, regarding anxiety.

Using acupuncture analgesia in endodontics can be useful when the patient is allergic to any substance, or when local anesthesia presents any risks.

For the rest of the situations, nerve block anesthesia is still a better choice.

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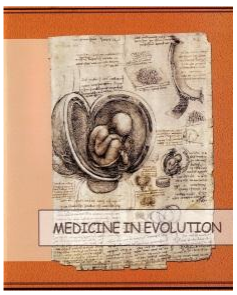
The transition from a classical dental office management to a computerized dental office management



Popovici R.A., Podariu A.C., Oancea R., Sava R.R., Jumanca D., Găluşcan A.

Department I of Dental Medicine, Faculty of Dental Medicine," Victor Babes" University of Medicine and Pharmacy Timisoara, Romania

Correspondence to:
Name: Ramona Amina Popovici
Address:" Victor Babes" University of Medicine and Pharmacy Timisoara
Phone: +40 762006828
E-mail address: ramona.popovici@umft.ro

Abstract

Medical computerization was gradually accepted as one of the important means for the institutional reform of the public health care system from the western and the developed countries.

Keywords: computerized management dental office management, oral health, public health care system.

INTRODUCTION

Most information systems are oriented to the management and decision-making, including health information system. System of health and health insurance together form one of the most important segments of society and its functioning as a compact unit. Increasing requirements for reducing health care costs while preserving or improving the quality of services provided represent a difficult task for the health system.

Dental Informatics is the branch of medical informatics oriented to dentistry [1,2, 3,4,5]. It deals with the management of information, communication and application of new technologies in clinical practice and research. Information management involves the storage and use of information generated in direct work with patients in a dental office; it includes the organization of work and arranging visits and operation of dental practice. It is therefore an information system in the dental office. Communication involves the use of electronic mail, Internet search, and promotion practices with the help of web technologies, database searching for drugs, dosages and interactions, then learning, practicing and practicing procedures in virtual reality, etc. Clinical practice and research involve the use of new technologies such as devices producing digital images based on x-ray or intraoral cameras, as well as retrieval of medical literature or publishing content on electronic media.[6,7]

World Health Organization (WHO) defines the health as a system: Complex of interrelated elements that contribute to health in the family, educational institutions and workplaces, public places and communities, as well as physical and psychological environment, health and other sectors.[8]

When it comes to the definition of health information systems (HIS), it should be noted that the World Health Organization (WHO), it is determined as part of the overall information system and includes a mechanism for collecting, processing, analysis and reception of information necessary for the organization and implementation of health care, but also research and organization of health care. Next tells that the HIS is organization of people, machines and methods which mutually act to security guards the necessary data and information about the health of the population for the purpose of planning and management in health care.[8,9]

Basic components of health information system are:

- Personnel (the organizers, planners, designers, managers, developers, users)
- Database
- Technical basis and
- Software support.

The majority of work on computer use in the dental field has focused on non-clinical practice management information needs. Very few computer-based dental information systems provide management support of the clinical care process, particularly with respect to quality management. Traditional quality assurance methods rely on the paper record and provide only retrospective analysis. Today, proactive quality management initiatives are on the rise. Computer-based dental information systems are being integrated into the care environment, actively providing decision support as patient care is being delivered. These new systems emphasize assessment and improvement of patient care at the time of treatment, thus building internal quality management into the care giving process. The integration of real time quality management and patient care will be expedited by the introduction of an information system architecture that emulates the gathering and storage of clinical care data currently provided by the paper record.

Doctors and dentists have different information needs when making diagnoses and medical decisions. While medical knowledge continues to grow at a steady pace, clinicians spend less time on clinical trial issues and develop a plan to set up clinical questions.

Numerous tests were conducted on the use of information in dentistry:

Only a very small number of studies were based on the information needs of dental research. For example, Strother, Lancaster and Gardiner interviewed 500 dentists and found that the most needed information are on new techniques in dentistry, followed by information about the products and equipment, and the practice management and medical complications.[8]

Medical computerization was gradually accepted as one of the important means for the institutional reform of the public health care system from the western and the developed countries.

In Romania the computerization of the national medical system it's started with house insurance settlement in 2007. The Unique Integrated Informatics' System (SIUI) ensures the collection, consolidation and processing of the entire health insurance system from Romania.

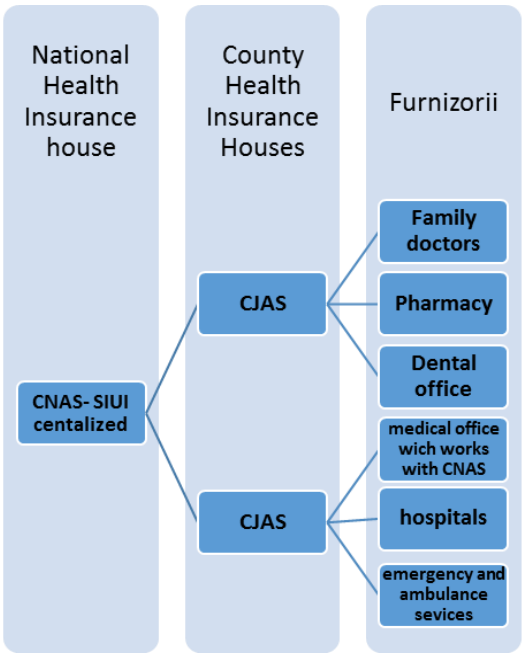


Figure 1. The area of SIUI program[10]

In 2015 in Romania it's began operating Medical Electronic Prescription and National Health Card using SIUI program. [10]

SIUI system uses three corresponding WSDL files exposed major functionalities:

Nomenclatures

- SiuiWS.wsdl services for synchronizing, file personalization, sending reports and taking over processing results reports, and other related services, described in the following sections. All these online services expose the functionality offered so far by the system offline by transfer files using removable media.
- SiuiInsuredWS.wsdl for online verification web service quality for insured a person / patient. This service is a new functionality exposed by SIUI since 2011.
- SiuiValidateWS.wsdl for web-services pre-validation of eligibility online at settlement services to suppliers. This service is a new functionality SIUI introduced in 2011 since December. National Health Insurance House in Romania Specifications interfacing with SIUI + PE + clock reporting applications the medical and pharmaceutical service providers Version: 3.7.4 of 05/27/2015
- Peter SiuiEInvoiceWS.wsdl web services using electronic bill services. This service is a new feature introduced in SIUI since July 2014.
- SiuiDrugConsumptionWS.wsdl web services for transmitting stock existing and consumption of medical supplies. This service is a new functionality SIUI brought in from December-2014.

The EP (electronic prescription) uses a single WSDL file that exposes specific functionality for prescribers, and pharmacies releases compensated and free recipes:

- EPrescriptionWS.wsdl web services processing for online eligibility to settlement services to suppliers. This service is a new functionality SIUI introduced in July 2012 since, but it's used from 2015.

The system clock (Electronic Health Insurance Card) uses a special protocol for work online with electronic cards that allow Management Unit CLOCK system through eCard.SDK to validate electronic cards, such as and for transactions activation, release or burning of these cards. This service it is a new feature introduced from December-2012, but its functional form 2015.

The computerization of dental offices started step by step since 1994. So after the medical dental services started to get private, every dental doctor organized his dental office how he wanted.

The aim of the study was to analyze the help of using the computer in dental office and in dental office management.

METHODS

For analyze the situation of dental offices in Timis County and the dental office management in this County, I applied a self answer survey with 26 questions were I asked them about using the computer, the internet connection in their dental offices and how this help them or tangle them. We took in study 116 dental doctors which work, that is 10% from all the doctors which works in Timis, County. They were representative statistic by age, sex and work are. The statistic used frequencies, and was made in SPSS.

RESULTS

Computerization in dentistry began similarly as in other human activities–recording large amounts of data on digital media, and by replacing manual data processing to machine one. But specifics of the dental profession have led to the specifics of the application of information technology (IT), and continue to require special development of dental oriented and applied IT.

Dental offices which use SIUI for reporting to Timis County Health House (CJASTM) are increase in the last five years. (see figure 2). The increase is seen better at the dental offices which are in the rural area.

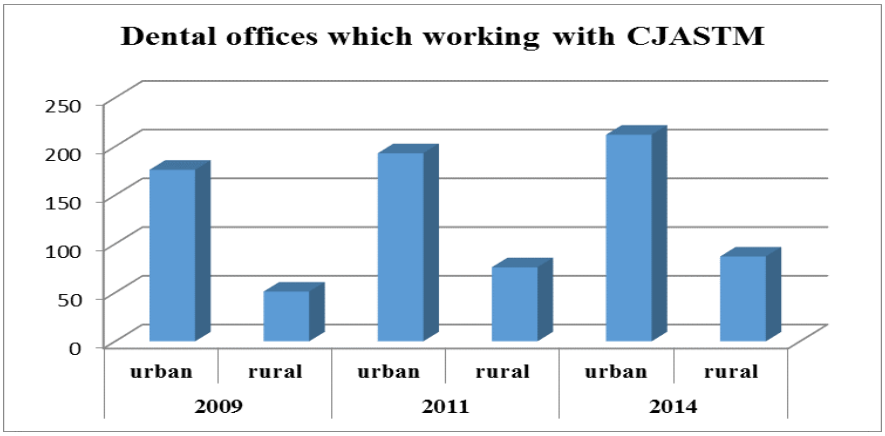


Figure 2. Dental offices which working with CJASTM- has working with SIUI program

More than 75% from the dental offices has PC, but just 58.62% has also internet connection in the dental office. 89% most of them are from poor rural area of the county. Just 6.9% from the dental offices has web page for presentations, reservations and other useful information, but 24.14% has presentation page on Facebook. (See Figure 3.)

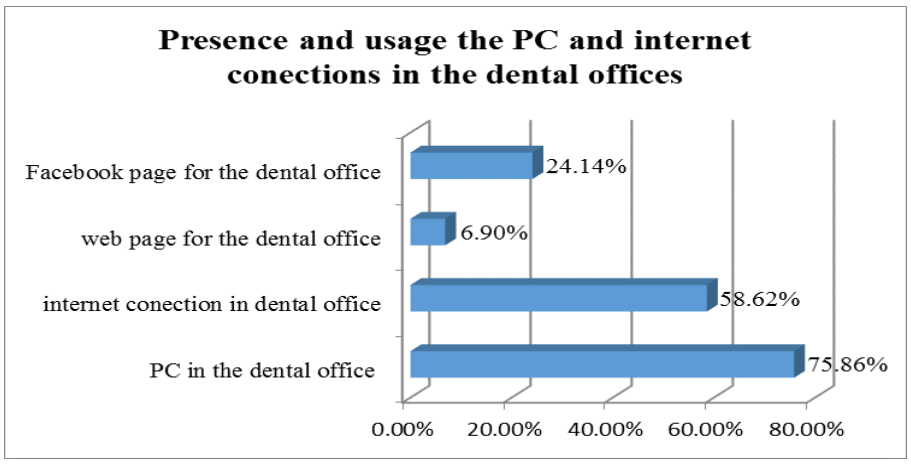


Figure 3. Presence and usage the PC and internet connections in the dental offices

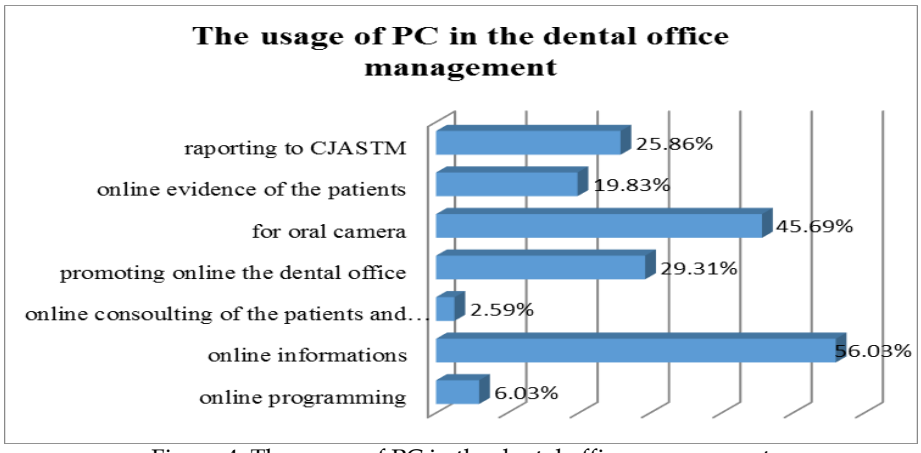


Figure 4. The usage of PC in the dental office management

The usage of PC in the dental office management is the most used for online information, for the oral camera and to promoting the dental office online. For the doctors which has is contract with the CJASTM is used for reporting data also. Just 19.83% from the doctors said that they have an evidence of the patients, and 6% for online programming. (see figure. 4)

In last 8 years the presence of the PC in the dental offices and also using them was in raise, from 3.45% in 2006 to 75% in 2014, but just 5% of them has professional tool to manage their work in the dental office.

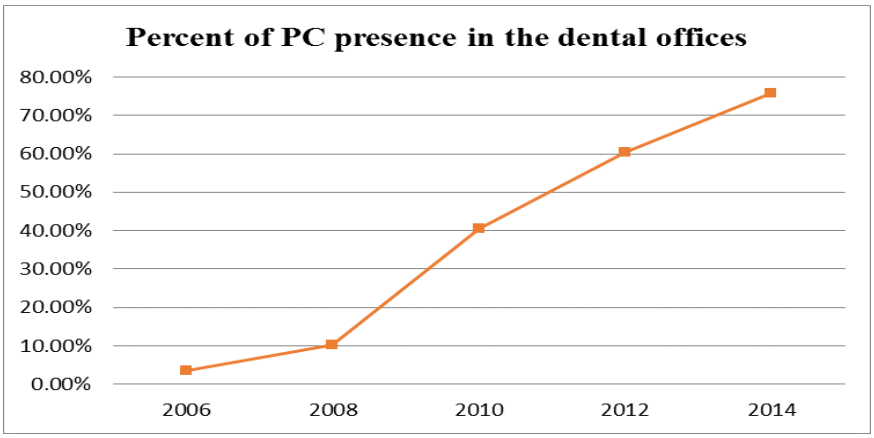


Figure 5. Percent of PC presence in the dental offices

CONCLUSIONS

In the era of paper (which is still present), patient information is stored in their medical records. Results of laboratory analysis, recording with radiological devices, findings and opinions of dentists, anamnesis data, recorded in the material (hard copy) and inserted into folders.

Distribution of these data is very poor and problematic. They must be manually transferred to any place where needed, they often lose, their value is little, if any, and many of them simply–because of the nature of such a system–must re-enter or obtain again.

Therefore, the electronic dental record is an important part of medical information system in health facilities that include a dental office.

In the future will be better for the dental office management to procure tools which help dental professionals to manage their businesses, improve their communication skills, and update their offices with new technologies. It also these tools can offer health advice, saving tips, translation aids, and CE courses specifically designed for the dental hygienist.

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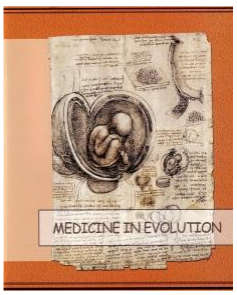
Utility of intraoral graphic CR record in full edentoulness



Muntianu L.A.S.[1], Ion V.[2], Mihai G.[1], Anghel M.[3], Circei C.[4]

[1]1st Department, Removable Prosthodontics, Faculty of Dental Medicine, Carol Davila Bucharest
[2]Dental technician demonstrator for Alligator
[3]Discipline of Oral Diagnostic and Ergonomy, Faculty of Dentistry, University of Medicine and Pharmacy"Victor Babes"Timisoara
[4]Discipline of Endodontics, Faculty of Dental Medicine, Titu Maiorescu University Bucharest

Correspondence to:
Name: Ligia Stanca Muntianu
Address: Str Aurel Vlaicu 148 sector 2 Bucureşti
Phone: +40 736 476 484
E-mail address: ligia.muntianu@gmail.com

Abstract

Aim: Evaluation of differences in centric relation (CR) record with classical method and intraoral graphic record using Centrofix system in full edentoulos arches

Material and method: CR was recorded using occlusion rims and using intraoral graphic CR record with centrofix in a pilot lot of 20 patients completely edentate in one maxillary or bimaxillary. The records were face bow transferred in articulator and the differences were analyzed.

Results:CR record coincided in 10% of the cases. CR recorded with occlusal rims was positioned anteriorly to the graphic record in a majority of cases and posteriorly in few cases.

Conclusions:

Intraoral graphic record of CR using centrofix ensures a safe registration of a habitual position.

This kind of CR record needs more working time.

The more anterior position of CR record using rims may be due to edentulous patient tendency to protrude. Thus CR record by graphic registration proves it s clinical value.

Keywords: centric relation, intraoral graphic record centrofix.

INTRODUCTION

Obtaining a proper reproductible record of centric relation (CR) was a subject of forever interest for prosthodontists, being very difficult in complete edentoulness.

The importance and necessity of proper CR record in complete edentoulness resides in the fact that this is a reference diagnostic position for a functional prosthodontic rehabilitation.

The literature suggests that in current practice, the graphic record is used mainly for verifying the centric relation position. [1]

There are also conditions and limitations for both record possibilities of centric relation record: when using wax rims, there are errors due to the wax or the record medium, when using graphic device, there are limitations due to anatomy, the bases stability, patient s ability to collaborate and patient s coordination. [2,3]

Aim

This pilot study makes a comparative analyze between centric relation record using wax rims and intraoral graphic device in unimaxillary and bimaxillary complete edentation to observe if there are differences, what causes the differences and the benefits of each method.

MATERIAL AND METHODS

It was analyzed a pilot lot of 20 patients both unimaxillary or bimaxilarry complete edentate all of them first denture wearers. The mean age has in interval between 55-75yars old. The ususalclinical and technical steps os manufacturing denture were made until the phase of centric relation record. Wax rims were made and vertical dimension (VDO) was determined, and centric relation record was performed using Repin so stabilize the position.

Data transfer was made using Amann Girbach facebow and the maxillary model was mounted on the articulator. The inferior model was then mounted too using the wax rim record of VDO and CR.

In parralel, on the models mounted at VDO, two photopolimerised bases are made for centrofix realisation. The aim ist o record centric relation using intraoral graphic record.

Centrofix belongs to the same system as the face bow and the articulator. On the mandibular model is mounted a plate and on the superior model is mounted a ball for gothic arch graphic record. The ball touches the plate at VDO predetermined with the wax rims.The plates are inserted in the mouth and VDO is verified.

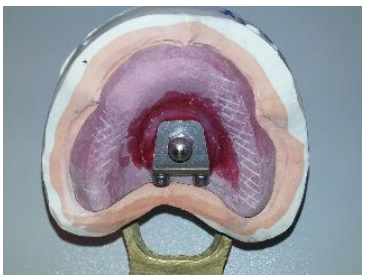


Figure 1.

Mandibular plate-centrofix | Attaching tha ball | The ball attached to the palatal base

Each patient is instructed to perform repetedly protrusions to edge to edge position and then lateralyties until edge to edge position. On the inferior plate a drawing of three lines will appear in the form of an arch having it's peak oriented extraorally.

At the intersection of the three lines there is a point corresponding to the centric position.

Figure 2. The graphic record of CR-gothic arch tracing

The bases are removed from the mouth and the retaining clip is mounted on the inferior plate looking to place it on the exact peak of the gothic arch.

The bases are inserted in the mouth again and the patient is instructed to close he mouth and the ball to be introduced into the retaining clip. Then the clip is tightened and the whole assembly can be safely removed from the mouth.

It was verified the coincidence between CR position determined using wax rims and the CR position determined using the centrofix.

RESULTS AND DISCUSSIONS

Two sets of mandibular dentures were fabricated for each patient. One using the classic CR record and the other using centrofix CR record.

Zarb-Bolender[4] says„intermaxxilary recordings are described as static, functional or graphic". In the graphic recording category stays extraoral and intraoral recordings and in the functional recordings is pantograph record.

The centric relation record on the other hand has at least 7 definitions in the „Glossary of Prosthodontic Terms". All have in common that CR position is determined by THJ structures ligamnets and muscles and not by the presence of teeth.

All mandibular movements can be generated from Cr position. Using the intraoral graphic record (centrofix) can be recorded: moderate protrusion and laterality in a horrizontal plane.

When performing a protrusion using the wax rims, posteriorly a space appears. This phenomenon is called Christensen phenomenon as is described in the literature as mandatory for a denture construction.[5]

The coincidence of CR position record with the two methods was observed was observed just in two cases aut of 20. In other cases the Cr position recorde with wax rims and centrofix did not coincide. Analyzing the variability of the graphic recordingd we observed a greater safety in gothic arch tracing in superior unimaxullary edentate patients.

The anteriorly position of CR when using wax rims may be due to a more exagerate tendency of this patients to protrusion. The differences in CR positioning both anteriorly and posteriorly tot hat determinde with the centrofix were in a range of 0,4-0,5mm. This discrepancies can be corrected at the phase of denture try in or mounting teeth presenting a moderate cuspidation.

After applying the denture in the mouth, it was observed a fewer nedd os sessions for occlusal equilibration and a better stabilty in mastication in the first months of wearing in dentures where centrofix was used, for all patients in the lot of study.

Utilyzing the graphic record with central bearing point has it's limits and can not be used in patients presenting skelatal II nd class patern subdivsion 1, or when fibrous ridges are

present, patients with parkinson disease, a big tongue volume, or lack of neurologic coordination.

CONCLUSIONS

Graphic CR recording need a good bases stability to avoid recording errors.

The wax rims are indispensable because they record valuable information for the denture fabrication and can not be eliminated from the working protocol.

The intraoral CR graphic record perfects the wax rim recording and the gothic arch tracing offers informations about TMJ.

The lack of coincidence between CR recording with wax rims and graphic record may be due to the operator experience in determining CR position with the wax rims.

Obtaining a more anteriorly position of CR when using wax rims may be due to the known protrusive tendency of edentate patients.

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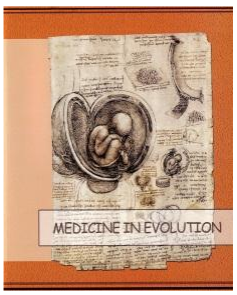
Buccal fat pad flap in management of oro-antral fistula



Nica D., Roi C., Nicoara A., Ianes E.

Department of Oral and Maxilo-Facial Surgery, University of Medicine and Pharmacy"Victor Babes"Timisoara, Romania

Correspondence to:
Name: dr. Nica Diana
Address: Department of Oral and Maxilo-Facial Surgery, University of Medicine and Pharmacy"Victor Babes"Timisoara, Romania
E-mail address: diananica27@yahoo.co.uk

Abstract

Oro-antral communication is a common occurrence following oral surgery.

Various methods have been described in literature for the oro-antral fistula closure. The most frequently flap used is the buccal flap. The main disadvantage of this flap is wound dehiscence with oro-antral communication persistence.

A double layer technique using both buccal fat pad flap and buccal advanced flap has been used for oro-antral fistula closure in 12 cases of large communication. The present study highlights the advantages and the indications of using this technique.

Keywords: Oro-antral fistula, buccal fat pad, buccal flap.

INTRODUCTION

Oro-antral communication commonly results after maxillary first and second molar extraction with the incidence ranges from 0, 31 % to 4, 7 % (1). Other causes of oro-antral communication could be benign and malignant maxillary tumors, trauma (2, 3). Left untreated, the oro-antral communication develops an oro-antral fibrous connective fistula covered by epithelium and consecutive acute or chronic sinusitis.

Two millimeter diameter oro-antral communications are likely to close spontaneously and do not need surgical procedures (4).

Numerous surgical techniques have been described in the literature, based on mobilizing a buccal flap and advancement into the defect.

The aim of the study is to present the clinical applications of the oro-antral fistulas closure using a double layer technique using the buccal fad pad and the buccal advanced flap. The technique is compared with the simple layer technique. Advantages and disadvantages of each technique are discussed.

MATERIAL AND METHODS

The 12 oro-antral communication presented cases were diagnosed in the University Oral and Maxillofacial Unit of the Municipal Emergency Hospital Timisoara between September 2015 and January 2016. All the patients were informed about the study and signed a written informed consent about the nature of the study. Data recorded included age, sex, general medical history and dental history. The etiology of the large communications were simultaneous extraction of the first and second maxillary molars in 8 cases and odontogenic cysts with complete resorption of the alveolar process in 4 cases. The average size of the oro-antral communication was 1.9 cm. The selected surgical procedure was oro-antral fistula closing using the double layer technique with buccal fat pad and the buccal advanced flap. Follow up was performed at 10 days, 21 days and 1 month after surgery. Patients with chronic general diseases and patients with acute or chronic sinus pathology were excluded were excluded from the selected cases.

Laboratory investigations were performed for all the included patients. Panoramic view radiographs were taken preoperatively for all selected patients in order to have an accurate estimation of the size of the anticipated oro-antral communication size.

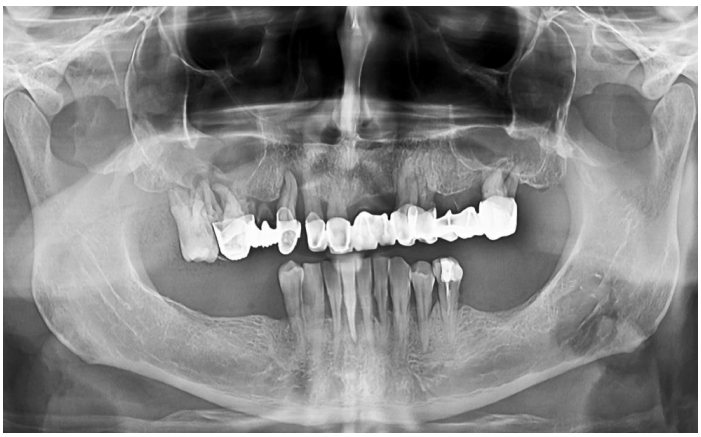


Figure 1. Panoramic radiography showing a large apical resorption at the level of the both upper right molars with the anticipated oro-antral communication

Surgical technique

An antiseptic based on chlorhexidine was used as a mouth wash before surgery. All the surgeries were performed in general anesthesia. The planned extractions and the cystectomies were performed followed by large the oro-antral communications. The diagnosis of the oro-antral communication was made by probing. The wound edges were removed for a better vascularization and the bony margins were smoothened. A buccal flap was first designed in all cases. Two vertical release incisions in the vestibulum were made. The width of the flap was 10 mm wider than the mezio-distal size of the communication. It was released using a cut in periosteum and a probe of tension-free sliding over the defect was made. A horizontal incision in the posterior mucosa in the area of the zygomatic buttress followed by a periosteal incision was made in order to release the buccal fat pad. The pedicled buccal fat was harvested and sutured with resorbable sutures over the communication. The ready-designated buccal flap was than sutured as a second layer over the buccal fad pad.

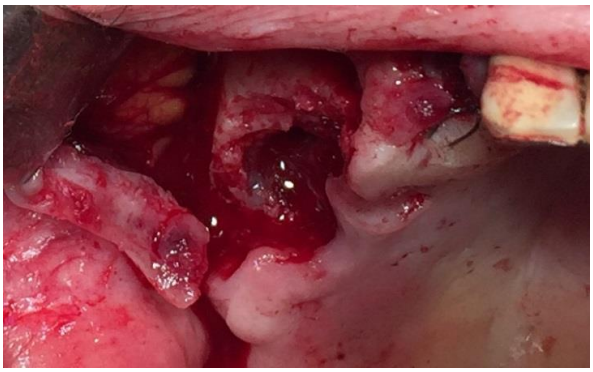


Figure 2. Large oro-antral communication after second and third upper molars extractions

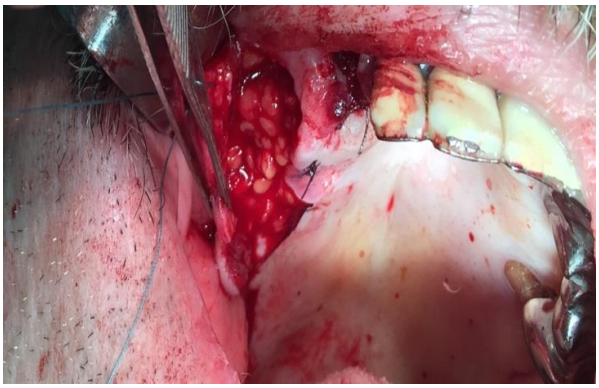


Figure 3. Pedicled buccal fat pad slipped and sutured over the defect

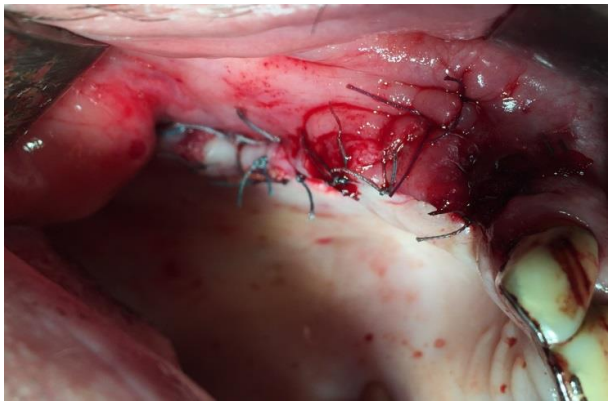


Figure 4. Oro-antral communication closure with the buccal flap sutured over the buccal fat pad

Postoperative care

Antibiotics were administered during the surgery and 10 days postoperative. Anti-inflammatory non-steroidal medication was prescribed. Patients were advised to maintain a high level of oral hygiene, to avoid chewing hard food on the operative side. Sneezing with closed mouth and nose blowing were completely prohibited for the first 3 weeks after the surgery. The patients were examined 10 days postoperative when the sutures were removed. The following examinations were made 21 days and 1 month after the surgery.

The criteria for successful surgery were complete healing without oro-antral communication recurrence.

RESULTS

All the selected patients required primary closure of the oro-antral communication at the time of extraction or cystectomy.

The selected patients included 8 males and 4 females with age range between 21 and 62 years old.

The defect size range was 1,5cm to 2,3cm. There were 8 oro-antral communications after simultaneous extractions of the first and second molars and 4 oro-antral communications after cystectomies with complete resorption of the alveolar process. Using the above described double layer technique, a complete healing without oro-antral communication recurrence were reported for all the 12 cases.

The common postoperatively complications like discomfort and edema were reported in all cases. Chewing difficulties and limited movement of cheek were also mentioned by patients.

DISCUSSIONS

The surgical approaches options in closing an oro-antral communication must take into account several factors: size of the defect, location, surrounding mucosa quality. Numerous modalities have been described for oro-antral communications closure including autogenous bone grafts, bony or soft synthetic materials, soft tissue flaps like buccal flaps, palatal flaps or a combination of these as the double layers closure techniques (5). The buccal flap closure technique is the method which is the most common used (6). The success of the buccal flap technique requires a good vascularization and a tension free closure (7). The indications for a buccal flap use are: small oro-antral communications less than 3 mm and careful manipulation of the flap in order to preserve the blood supply (8, 9).

All selected cases presented extensive oro-antral communications which required no tension flaps and also tissue bulk. We considered that the double layer technique using buccal fad pad and buccal flap is the most suitable for the large oro-antral communications. The buccal fat pad is an adipose tissue mass, very good vascularized from the buccal and deep temporal branches of the maxillary artery, the superficial temporal artery from the transverse facial artery and from the facial artery (5). The fad pad is easily dissected from the space between buccinators muscle, anterior margin of masseter muscle, mandibular ramus and zygomatic arch (10). Once dissected, it is pedicled and easily slipped over the defect. The large amount and the good vascularization of this available fad tissue allow a tension free suture which will provide an uneventful healing.

CONCLUSIONS

The ideal flap for large oro-antral communications must provide large quantity of tissue, a good vascularization, tension free suture and low morbidity at the level of donor site.

All these demands have been fulfilled by the buccal fat pad flap covered by the buccal flap for a more secured coverage.

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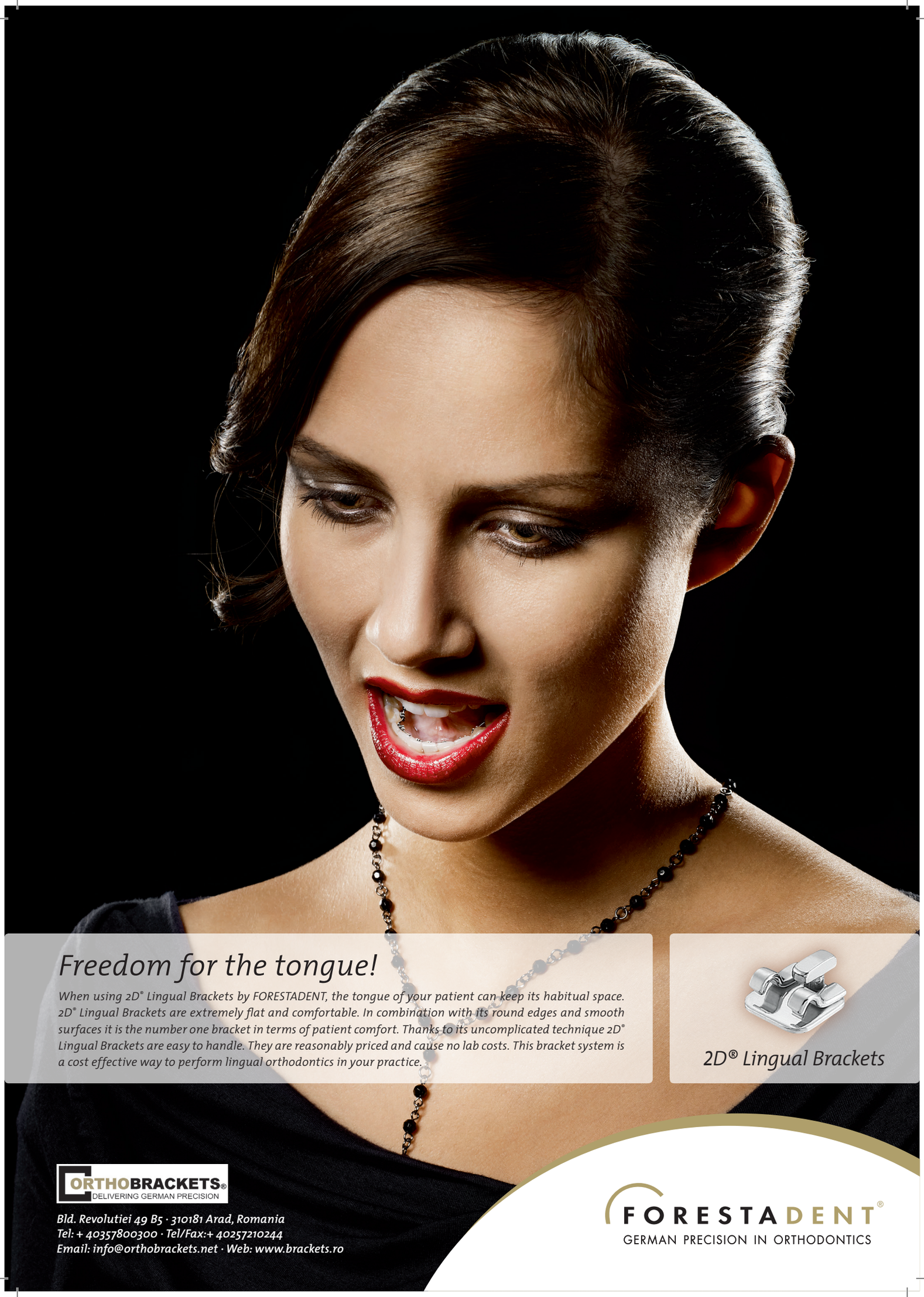
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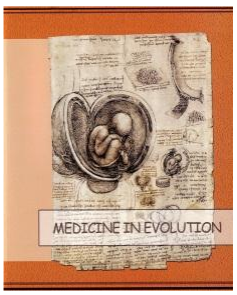
Fluoxetine, antidepressant drug with potential benefits against periodontitis – a brief Review



Bogdan M.[1], Surlin P.[2], Tica A.A.[1], Silosi I.[3], Rusu D.[4], Tica O.S.[5], Balseanu T.-A.[6], Rauten A.-M.[7], Camen A.[8]

[1]Department of Pharmacology, Faculty of Pharmacy, University of Medicine and Pharmacy of Craiova, Romania
[2]Department of Periodontology, Faculty of Dental Medicine, University of Medicine and Pharmacy of Craiova, Romania
[3]Department of Immunology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania
[4]Department of Periodontology, Faculty of Dental Medicine, University of Medicine and Pharmacy „Victor Babes" Timisoara, Romania
[5]Department of Obstetrics-Gynecology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania
[6]Department of Physiology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania
[7]Department of Orthodontics, Faculty of Dental Medicine, University of Medicine and Pharmacy of Craiova, Romania
[8]Department of Dentoalveolar Surgery, Faculty of Dental Medicine, University of Medicine and Pharmacy of Craiova, Romania

Correspondence to:
Name: Maria Bogdan
Address: University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Romania
E-mail address: bogdanfmaria81@yahoo.com

Abstract

Different studies have shown that the antidepressant drug fluoxetine has therapeutic utility in relation to inflammatory conditions. Elevated concentrations of IL-6, TNF-α and CRP have been reported to be associated with both disorders, depression and periodontitis. In several researches, both in vivo and in vitro, fluoxetine reduced levels of these cytokines, therefore it may be hypothesized that this drug would have benefit as an anti-inflammatory agent even in patients without depression but with periodontal disease.

Recent studies determining fluoxetine's effect in periodontitis recorded that it suppressed the inflammatory response, reduced alveolar bone loss, maintained the integrity of collagen fibers in the gingival tissue and it was associated with lower bleeding on probing percentages and diminished attachment loss.

Within the limits of the data available so far, fluoxetine may be considered a promising new therapeutic agent for the treatment of periodontitis which can be safely used in mentally healthy patients.

Short title: Fluoxetine and periodontitis

Keywords: fluoxetine, periodontitis, depression.

INTRODUCTION

Researches show that besides their well-known effects some drugs also demonstrate other therapeutic properties. It is the case of antidepressant fluoxetine that has been reported to have antiinflammatory effects both in experimental studies and in clinical trials [1-4].

Periodontitis is an inflammatory disease that may lead without treatment to the destruction of the sustaining tissues of the tooth with tooth loss. In time, different pro-inflammatory markers were identified in blood, gingival crevicular fluid and gingival tissue. Thus, increased levels were demonstrated for matrix-metalloproteinases (MMPs) [5-10], citokines as IL1, IL6, IL10, IL8, IFNγ, TNF, TGF [11-15], markers of osseous destruction such as OPG and RANKL [16-18], pathogen recognition receptors like TLR-2 and TLR-4 [19].

Because there is heightened interest in therapy strategies that modulate the host response to bacteria and subantimicrobial dose of doxycycline is the only host modulatory systemic treatment approved by the Food and Drug Administration (FDA) for the periodontal disease, there is a need to investigate more drugs with possible anti-inflammatory and/or immunoregulatory actions on diseased periodontal tissues [20].

The purpose of this study was to gather information about the potential benefit of fluoxetine in the treatment of periodontitis based on researches published so far.

DEPRESSION

Depression (major depressive disorder, MDD) is a mood disturbance of multifactorial origin, which determines increased morbidity and mortality, lost work productivity, adverse health behaviors and increased health care utilization. It is estimated to affect 350 million people worldwide [21]. MDD is a leading cause of suicide, and its presence affects prognosis of chronic conditions such as heart disease, diabetes and cancer, among others [22].

The relationship between proinflammatory markers and MDD has been reported in several population studies including older individuals. This relationship is bidirectional, as follows: a) chronic inflammation may impact the endocrine and nervous systems causing imbalances in critical hormones and neuroactive compounds which may ultimately lead to depression; b) depression may lead to inflammation. Psychological stress activates the sympathetic nervous system and releases stress hormones which initiate acute-phase responses causing inflammation [23, 24].

Increases in inflammatory markers levels, such as pro-inflammatory cytokines interleukin (IL)-6, tumor necrosis factor (TNF)-α, and acute phase proteins, such as C-reactive protein (CRP), were registered in depressed compared to non-depressed patients [25]. According to the meta-analysis performed by R. Haapakoski et al. there is a lack of a robust association between IL-1β and MDD, and there is no support for the involvement of other proinflammatory cytokines, like IL-10, IL-4, IL-8, IL-2, or IFN-γ, in depression [26].

Current pharmacological treatments for MDD cover multiple classes of drugs, including serotonin selective reuptake inhibitors (SSRIs). SSRIs (like fluoxetine) are commonly chosen as first-line antidepressants because of their relative safety in overdose and improved tolerability compared with earlier agents [27-29], including in elderly patients [28].

PERIODONTITIS

Periodontitis is a common inflammatory disease and is characterized by the excessive degradation of collagen-rich tissues: gingiva, periodontal ligament, and alveolar bone [30]. Clinical manifestations of periodontal disease include gingival pocket formation and clinical attachment loss, and it is considered a major cause of tooth loss among most adult populations [31] leading to loss of masticatory function and significant morbidity [30].

It was reported that periodontitis is a risk factor for different diseases, leading to higher risk for cardiovascular disease, ischemic and hemorrhagic stroke, myocardial infarction and other systemic diseases [32].

Periodontal disease has an early stage, called gingivitis which involves only superficial periodontium, and a more serious form called periodontitis affecting teeth supporting tissues [33]. Recent data indicate that at least 40% of individuals who have gingivitis do not return to biological health within 30 days after standard therapy for this condition, although clinical measures of their gingiva and periodontium suggest a return to clinical health; thus stressing the discrepancy between clinical and biological health [34]. Fast progression from gingivitis to periodontal disease emerges in about 10-15% of the individuals [35].

Evidence on the antiquity of periodontitis has been found from examinations on mummified remains in Egypt, skulls from an ancient British cohort, German skulls from the Middle Ages and writings by the Sumerians, Babylonians, Assyrians, and the early Chinese. The data suggest that the disease was much less common than today, emphasizing the importance of risk factors which contribute to severe periodontitis [36].

As periodontitis is a multifactorial disease shown to be highly prevalent in both developing and industrialized countries [32], its effective management involves a clear understanding of all the associated risk factors [37]. Risk factors may be modifiable, usually environmental or behavioral in nature, or non-modifiable, usually intrinsic to the individual. Non-modifiable risk factors are also known as determinants [38].

Modifiable risk factors linked with periodontal disease are: smoking, diabetes mellitus, microorganisms, stress [37, 38], cardiovascular disease, drug-induced disorders and obesity [37]. Non-modifiable risk factors are: genetic factors, host response, osteoporosis [37, 38], hematological disorders, pregnancy. The risk characteristics for periodontitis are: age, sex,socioeconomic status, education and race [37].

Pathogens are the primary initiator of periodontitis and activator of abnormal chronic inflammation with cytokines release [39]. Well-characterized periodontal bacteria isolated in chronic periodontitis diagnosed in patients over 35 years old are: *Porphyromonas gingivalis, Treponema denticola, Tannerealla forsythia* [40, 41] and *Fusobacterium nucleatum* [40], while in patients before the age of 35 *Aggregatibacter* (*Actinobacillus*) *actinomycetemcomitans* is the main pathogen found in the periodontal pockets. The latter bacterium has been linked with aggressive periodontitis [41].

Elevated concentrations both in serum and in saliva of IL-6 [34, 42-44], TNF-α [44-46] and CRP [47, 48] have been reported to be associated with periodontal disease. Therefore these proinflammatory cytokines show increased levels in both disorders, depression and periodontitis.

FLUOXETINE

In 1974 fluoxetine was first reported as a SSRI, and in 1978 FDA approved it as an antidepressant drug [27].

Fluoxetine is a lipophilic weak base, orally active [27], well absorbed, with a plasma half-life of 24-96h [49] that quickly diffuses through multiple body-sites [27]; norfluoxetine, the active metabolite, has a very long plasma half-life (1-2 weeks) so that few patients experience withdrawal symptoms when discontinuing fluoxetine [50]. Fluoxetine and norfluoxetine are distributed into breast milk [51].

Dosage adjustments rely on evaluation of clinical response and management of adverse effects, because there is not a strong relationship between SSRIs serum concentrations and therapeutic efficacy [50].

Fluoxetine is used not only in depression, but also in anxiety disorders and obsessive compulsive disorder. It was found to have beneficial effects in the treatment of anorexia, bulimia and bipolar depression (in combination with olanzapine) [49].

The most frequent side effects, which occurred in 10–25% of patients, were nausea (25%), anxiety, nervousness, insomnia, dry mouth, headache, tremor, drowsiness, sweating, diarrhea (10%), sexual dysfunction [52, 28] and weight loss [51]. Most of these adverse effects are met early in therapy and rarely led to drug withdrawal [52].

Drug-drug interactions may appear when fluoxetine is coadministered with another drug metabolized through the cytochrome P450system. 2D6 and 3A4, two of the isoenzymes of the cytochrome P450 system, are responsible for the metabolism of more than 80% of usually marketed drugs [53, 28]; fluoxetine presents high inhibition on 2D6 isoenzyme and low inhibition on 2C and 3A4 isoenzymes [53, 28].

Several studies have shown that this antidepressant drug has therapeutic utility in relation to allergic astma, septic shock [3], neuroinflammation [1, 2], atherosclerosis [54], rheumatoid arthritis [55]. In addition, in a previously published data analysis, Stopper H et al highlighted in 2014 that fluoxetine also revealed anticancer action against colon tumors potentially making it an interesting co-chemotherapeutic agent [27].

Baumeister D et al reviewed the in vitro studies on fluoxetine and suggested that it seems to decrease Il-6 and TNF-α [56]. Ohgi Y et al examined the effects of fluoxetine on lipopolysaccharide (LPS)-induced inflammation and found that pretreatment with fluoxetine attenuated LPS-induced increases in TNFα [57].

Given that in several other studies fluoxetine was found to reduce levels of Il-6 [55, 58], TNF-α [55] and CRP [59] it may be hypothesized that this drug would have benefit as an anti-inflammatory agent even in patients without depression but with periodontal disease.

RELATIONSHIP BETWEEN FLUOXETINE AND PERIODONTITIS

In December 2015 it was performed a literature search using PubMed with the following search terms: „fluoxetine", „periodontitis", „periodontal disease"and only 4 articles were identified, all from recent years. The subject is very topical considering the interest shown lately to establish fluoxetine's effects on inflammatoty conditions.

Branco-de-Almeida et al performed an experimental study and observed that fluoxetine reduced alveolar bone loss and maintained the integrity of collagen fibers in the gingival tissue. Administered (20 mg/kg/day) orally for 15 days after ligature-induced periodontitis in rats, fluoxetine suppressed the inflammatory response (IL-1β and COX-2 expression, total protein concentration and MMP-9 activity in gingival tissues) [60].

Aguiar JC et al tried to determine the effect of fluoxetine on bone loss in chronic periodontitis in an experimental ligature-induced periodontal disease. The drug (20 mg/kg/day) was administered for 19 days in the context of conditioned fear stress. Based on histological and immunohistochemical analyses they concluded that stress is associated with the progression of bone loss in a conditioned fear stress model in rats and that fluoxetine treatment reduces the bone loss [61].

On the other hand SSRIs are associated to increased levels of bone resorption markers and to a higher risk of fracture. As Galli et al noted, the dose of fluoxetine tested in the experimental ligature-induced periodontal disease was based on previous work highlighting its antiinflammatory properties, and was on the high end of the doses commonly used to suppress serotonin production in rats. This is approximately twice as high as the maximum recommended human dose, and this high dose of fluoxetine may be activating alternative immunomodulatory or antiinflammatory pathways that are overcoming the effects on serotonin metabolism [62].

And yet, in a cross-sectional observational study Bhatia et al. has examined the influence of fluoxetine intake on periodontal parameters in patients with periodontitis and clinical depression. The use of fluoxetine (in a frequently recommended dose of 20 mg/day) for ≥2 months was associated with significantly diminished gingival index, bleeding on probing, sulcus bleeding index, probing depth, and attachment loss [20].

The exact mechanism of fluoxetine's anti-inflammatory effect is not fully clarified, because it could appear not only due to reduced synthesis of the proinflammatory cytokines, but also to increased production of the anti-inflammatory cytokine IL-10 [20]. Other findings suggest that fluoxetine's actions might be mediated by cyclic adenosine monophosphate, and that it reduces the transcription activity of nuclear factor (NF)-κB [60].

As for findings about clinical doses of fluoxetine administered for several weeks to mentally healthy subjects, there were reported no discernible effects on psychological variables like mood, anxiety, general well being, various aspects of quality of life and personality characteristics [63].

Antidepressants appear to have a disease-specific action [64] and referring to the entire SSRIs group, limited effects were observed after administration to healthy individuals. GJH Dumont et al showed in a sistematic review that SSRIs in healthy individuals seem to cause slight stimulating effects after low single therapeutic doses, which were reported to diminish with increased doses (an inverted dose–response relation). Even fewer measurable differences from placebo were produced by multiple dosing with these antidepressants, presumably due to adaptive processes [65].

CONCLUSIONS

Within the limits of the data available so far, fluoxetine may be considered a promising new therapeutic agent for the treatment of periodontitis which can be safely used in mentally healthy patients. Further clinical studies need to confirm and clarify the benefits of fluoxetine in periodontal therapy.

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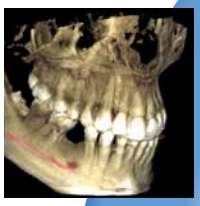

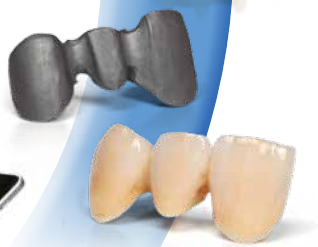

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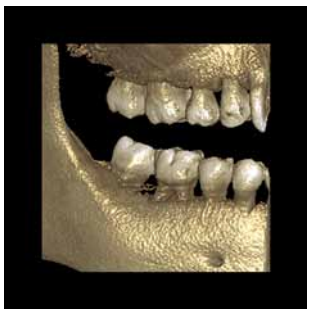

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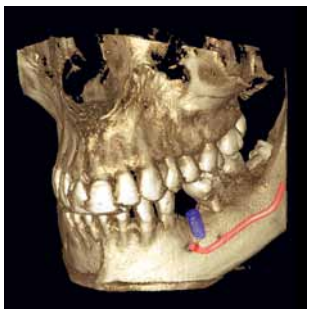

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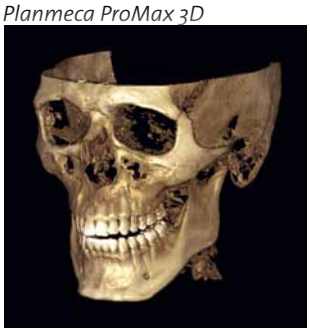

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Manuscripts will not exceed:

- general reviews: 6-8 pages
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- case presentations: 2-4 pages
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The paper will be edited according to international editing rules for manuscripts. The title will be written in capital characters and it will be followed by the name and surname of the author (authors), followed by their place of work (place where the paper has been elaborated). Studies and researches will be followed by a brief abstract, followed by 3-4 key-words.

The body of the paper will be structured on the following chapters: introduction, aim, objectives, material and method, results and discussions, conclusions. The references will be presented alphabetically and in conformity to the Vancouver Convention, including:

- for articles: name of the authors and surname initials, title of the article in the original language, title of the journal according to the international abreviation system, year of issue, volume, number, pages;
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Citation of references inside the body of the paper will be put between brackets, Harward style (author, year) or Vancouver style (number in square brackets or superscript). Cited reference titles will be selected, maximum 6 for studies and case presentations and 12 for general reviews. Acceptance, rejection or the need of alterations in sent materials, or in inconography, will be comunicated to the authors in due time. For this, the authors will indicate the person and address for corespondence (phone number, e-mail address). Given the less pleasant experience of the editorial board with some articles being rejected because they did not meet publishing criteria, we decided to support those who intend to publish in this journal by detailing the way such a paper should be elaborated, as well as our requirements.

Except some particular aspects concerning this journal, the following details are general requirements asked or imposed by other journals as well. Conditions to be met in order to propose a paper for publishing. The main author has the responsability to make sure the article has been approved by all the other authors. The journal will have copyright

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Do not use name of patients, initials or hospital observation charts numbers. If a photograph of a body part which could allow direct or deductive recognition of the patient needs publishing, then the paper must be accompanied by the written consent of the patient and clinician, as well.

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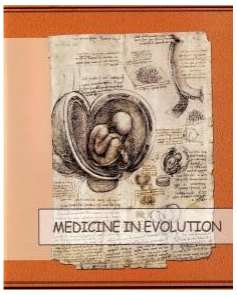

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Abstract [Book Antiqua, 12, bold, justify alignment]

Recommendations for original studies

Original studies must include a structured abstarct of maximum 150 words, containing the following titles and informations: Aim and objectives; Material and methods; Results; Conclusions; Key words: give 3-5 key words; The abstract will be translated into an international circulation language.

Keywords: Innovation, technology, research projects, etc. [Book Antiqua 9].

INTRODUCTION [Book Antiqua, 11, bold, left alignment]

Introduction presentation of general aspects, in the context of the approached theme.

Introduction include **Aim and objectives –** Define the aim of the article. Briefly expose the rationale of the presented study or observation. Make strictly pertinent referals and do not exhaustively review the subject. Do not include data or conclusions from the paper.

There is a limitation of 4/6 pages. All pages size should be A4 (21 x 29,7cm). The top margins should be 2 cm, the bottom, right, margins should be 2cm and left margins should be 2,85 cm. All the text must be in one column and Book Antiqua font, including figures and tables, with single-spaced 10-point interline spacing.

Aim and objectives **[Book Antiqua 11, bold italic, left alignment]**

The text included in the sections or subsections must begin one line after the section or subsection title. Do not use hard tabs and limit the use of hard returns to one return at the end of a paragraph. Please, do not number manually the sections and subsections; the template will do it automatically.

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MATERIAL AND METHODS [Book Antiqua, 11, bold, left alignment]

Describe the selection of observations or subjects for the experiment (including controls). Identify methods, equipments (with the name and address of the manufacturer in brackets) and give sufficient details on procedures. Give references for the selected methods, including statistical methods; offer details and brief descriptions for previously published methods which are not well known; describe new or substantially modified methods, justify their use and assess their limitations. Precisely identify all used drugs and chemicals, including generic names, dosage and administration ways. Describe statistical methods with sufficient details for reported results to be verified. Whenever possible, quantify discovered aspects and present them with appropriate measurement indicators for the uncertainty or error of measurement (such as confidence intervals). [Book Antiqua, 11 point, normal, justified alignment].

RESULTS [Book Antiqua, 11, bold, left alignment]

Present results in a logical succession as text, tables and illustrations. Emphasize or briefly describe only important observations. [Book Antiqua, 11 point, normal, justified alignment].

DISCUSSIONS [Book Antiqua, 11, bold, left alignment]

Underline new, important aspects of the study. Do not repeat in detail data which have been presented in previous sections. Include implications of revealed aspects and their limitations, including implications for future studies. Connect your observations to other relevant studies. Relate the results to the aim proposed for the study. [Book Antiqua, 11 point, normal, justified alignment].

CONCLUSIONS [Book Antiqua, 11, bold, left alignment]

Organize conclusions which emerge from the study. In the end state: a) contributions to be acknowledged but which do not justify paternity right; b) thanks for technical support;

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6.2. CONTENT OF THE PAPER - INDICATIONS FOR CASE REPORTS

Content of the paper for case report will respect indications for original articles.

Themes may be selected from all medical fields. Manuscripts which offer a special gain for daily activity will have priority. The title must be clearly, precisely stated. It may be completed by a subtitle. It is advisable to include in the key words of the title the main message, the special element which may be observed from the case evolution. The content of a case report must be divided into three parts:

Introduction – It must include a maximum of 15 typed rows (half page). Here, the main medical problem is summarized in order to place the case in a specific domain.

Case report – It contains essential specific information on the case. In order to make a logical, chronological and didactical case report the following 5 chapters are needed:

I. Anamnesis;
II. Clinical examination data;
III. Laboratory data;
IV. Additional paraclinical investigations;
V. Treatment and evolution.

Discussions – The reason for the case report must be stated. The report must be patient-centered. Occasional deviations from typical (characteristic) evolutions, nosologically important facts must be presented in such a manner to expose the clinical picture as completely as possible. The case report must not appear as an appendix of a general review. Dimensions of a case report: maximum 6-8 typed pages, 30 rows of 60 characters/page.

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All measurements must be expressed in International System (IS) units. Abreviations must be fully explained when first used.

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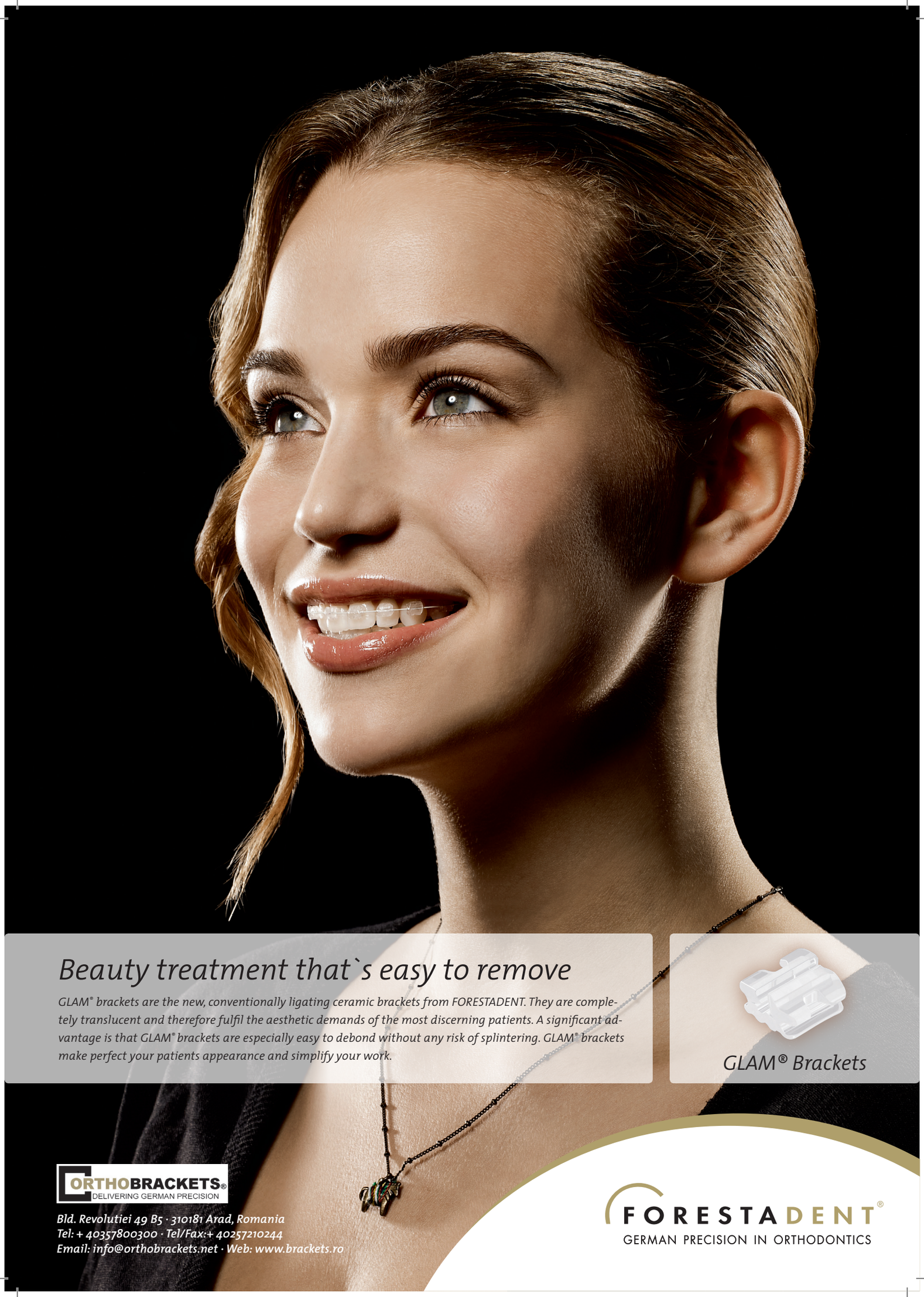
Dana Brehar-Cioflec, MD, PhD

Institute of Public Health *"Prof. Dr. Leonida Georgescu"* Timişoara
Bd. Victor Babeş no. 16
300226, Timişoara
Phone: 0256-492101
Email: danabreharcioflec@yahoo.com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