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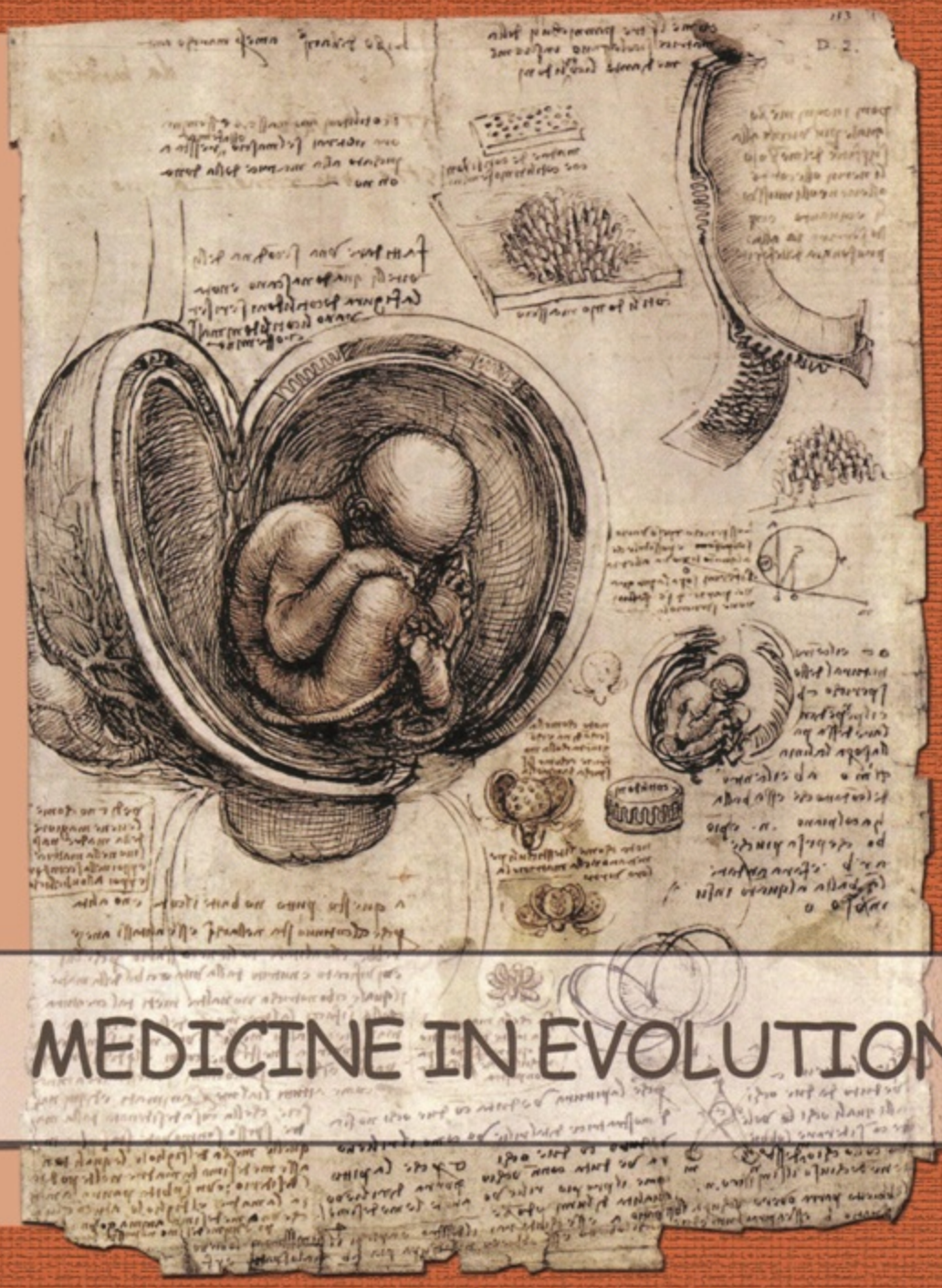

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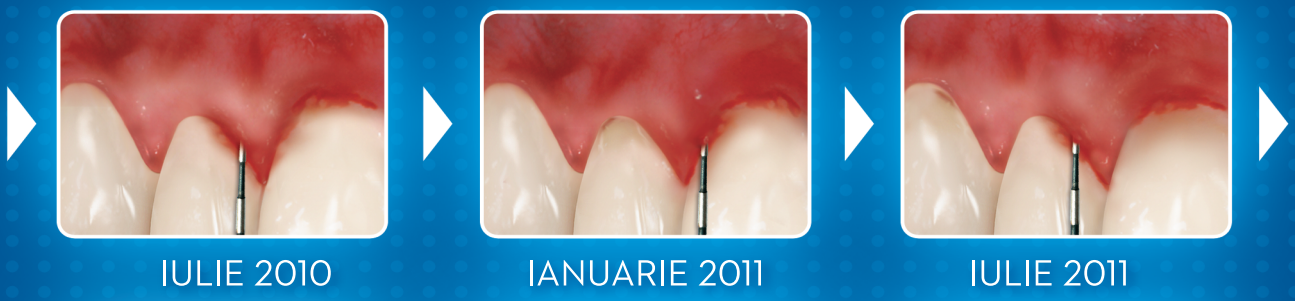

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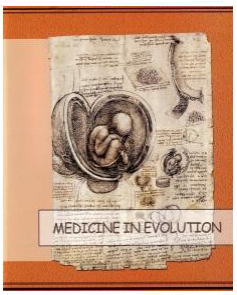
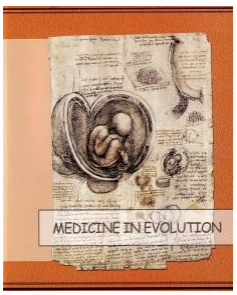


ARTICLES

The importance of fibrosis and inflammatory infiltrate in dysplastic nevi



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Abstract

Dysplastic nevi are melanocytic lesions that represent a controversial pathology due to the unclear risk for developing cutaneous melanoma. Many studies proved that dysplastic nevi constitute an independent risk factor and that dysplasia should be graded in order to better classify and understand the evolution of this lesions. Also, the grade of dermal fibrosis and inflammation could contribute to a better diagnostic. The aim of this study was to prove that fibrosis and inflammation are interconnected and that dysplasia also correlates with them.

Materials and Methods: A total of 81 nevi from 36 patients were analyzed and the grade of dysplasia, fibrosis, inflammatory infiltrate and pagetoid extension were noted on Hematoxilin-Eosin staining. Masson's Trichrome and van Gieson stains were performed in order to highlight the fibrosis.

Results: Nineteen (19%) cases presented with mild dysplasia, 64% with moderate dysplasia and 17% had severe atypia. Ninety (90%) nevi presented fibrosis. Mild inflammatory infiltrate was noted in 56% of the cases, and in 37% moderate inflammation. We demonstrated that there is a statistically significant correlation between the grade of dysplasia and the grade of fibrosis ($r(79) = 0.38$, $p<0.01$) and between the grade of dysplasia and inflammatory infiltrate ($r(79) = 0.31$, $p<0.01$). Also, significant relation was found between fibrosis and inflammation, as well as between dysplasia and pagetoid extension.

Conclusion: A statistically significant association was revealed between different characteristics of dysplastic nevi and those findings could be helpful for a correct diagnostic and classification of atypical nevi as well as a correct grading of dysplasia.

Keywords: dysplastic nevi, fibrosis, inflammation

INTRODUCTION

Dysplastic nevi represent a controversial pathology and are considered to be high risk lesions for developing melanoma. Although they are not considered precursors of melanoma [1], many studies had focused on this malignant potential [2,3]. As first described by Norris in 1820, and proved in the years to come with epidemiological, morphological, immunohistochemical and genetic evidence [1], the link between the two entities is accepted worldwide, although a clear pathophysiological pattern is not yet established. The risk for developing cutaneous malignant melanoma in patients with dysplastic nevi is considered to be as high as 10x times [3] thus the presence of a dysplastic nevi is an independent factor for the development of melanomas [4,5]. The incidence of dysplastic nevi ranges between 2% and 53 % with higher incidence in patients with history of melanoma [2, 3].

The diagnostic criteria are divided in clinical and histological subgroups. Clinically, dysplastic nevi are diagnosed by ABCD-like criteria: more than 5 mm in diameter, ill-defined border, asymmetric shape, difference in pigmentation and a red hue [3, 6, 7]. The histologic criteria resumed by WHO are divided in 2 major criteria (basilar proliferation of atypical melanocytes extending at least three rete ridges beyond dermal component and proliferation in a lentiginous or epithelioid- like pattern) and four minor criteria: lamellar/ concentric eosinophilic fibrosis, neovascularization, inflammatory infiltrate and fusion of rete ridges. [2, 7]. Many studies have raised the problem of cytological atypia and the meaning of it [3, 5, 8, 9] and most of them proved that a severe dysplasia is correlated with high risk in developing cutaneous melanoma. Nevertheless, same studies highlighted the fact that there are interobserver differences, most of them due to the lack of clear criteria for cell dysplasia. Also, a linkage was made between regression, defined as melanocyte dropout, non-lamellar fibrosis, increased dermal vascularity and lymphocytic infiltrate with melanophages and the grade of dysplasia, demonstrating a reverse correlation between them [10]. Babacan et al. demonstrated that dermal fibroplasia correlates with the degree of dysplasia, both with the cytological atypia and architectural disorganization [11].

The aim of this study is to prove the correlation between the two most common minor criteria observed in a dysplastic nevus, fibrosis and inflammatory infiltrate and the linkage between those criteria and the degree of dysplasia.

MATERIAL AND METHODS

Thirty six patients with lesions that were excised in the Plastic Surgery Department and diagnosed as dysplastic nevi in the Pathology Department at the Emergency University Hospital Bucharest between 2014 and 2015 were selected. A total of eighty one lesions were studied and gross dimensions and histological characteristics were noted. All lesions met both major criteria and at least 2 minor criteria from WHO recommendations for dysplastic nevi. The tissue samples were fixed with 10% buffered formalin and were processed by conventional histopathological method using inclusion in paraffin and Hematoxylin–Eosin (HE) staining. We noted the dimensions of the nevi after formalin fixation and graded the dysplasia in mild, moderate and severe on HE staining considering the grade of nuclear pleomorphism, the size of the nucleus and nucleoli as well as the architectural disorganization (fusion of rete ridges, shoulder phenomenon, variations in size and organization of the nevoid nests). Also, the degree of fibrosis and inflammatory infiltrate were noted as weak, moderate and strong. Special staining with van Gieson (Fig 1 and Fig 2) and Masson's Trichrome (Fig 3 and Fig 4) were made in order to highlight the grade of fibrosis. Pagetoid extension, defined by the extension of nevoid cells in the first half of the epidermis, was ensue. Statistical tests were performed using Windows Excel 2007- Data Analysis, the Pearson Correlation Coefficient and Regression formulas.

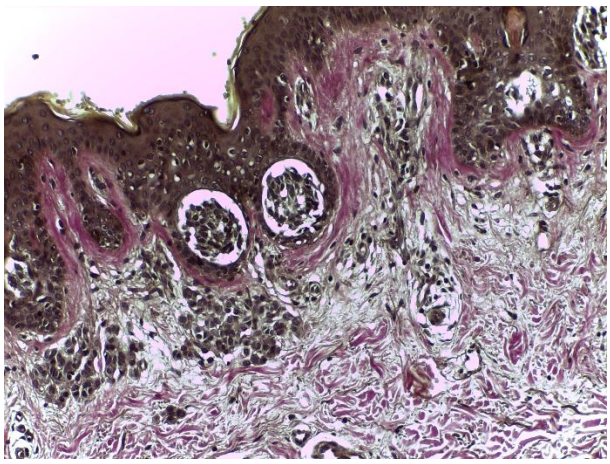

Figure 1. Dysplastic nevi with fibrosis, van Gieson, 200X

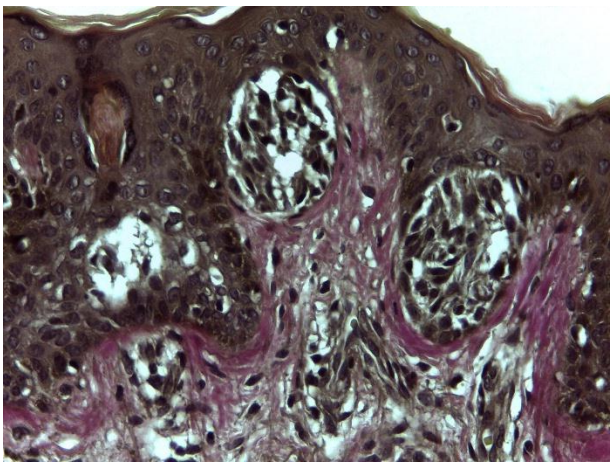

Figure 2. Dysplastic nevi with fibrosis, van Gieson, 400X

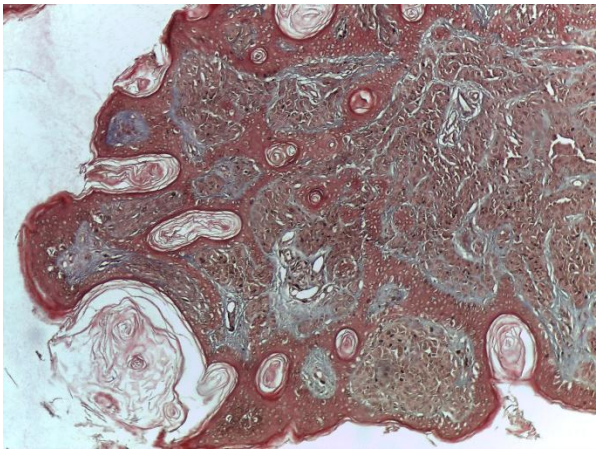

Figure 3. Dysplastic nevi with fibrosis, Masson's Trichrome, 100X

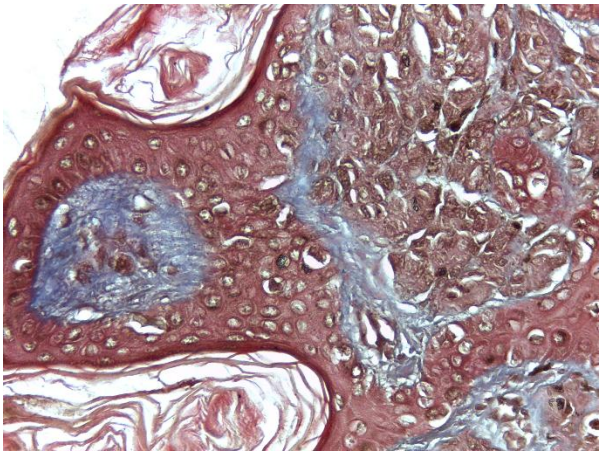

Figure 4. Dysplastic nevi with fibrosis, Masson's Trichrome, 400X

RESULTS

From thirty six patients registered, 69% were of female gender and 31% were males. The overall mean age was 32,8, with a mean age for males of 32,6 and for females of 32,8. Sixty four lesions were compound nevi (79%) and only seventeen (21%) were junctional. The mean diameter for compound nevi was 5,8 mm whereas for junctional nevi was 4,88 mm. The patients selected presented with 1 to 7 lesions diagnosed as dysplastic nevi, with an average of 2,25 nevi per patient. 81% of the patients come from urban environment and most of them had dysplastic nevi localized on the back or on special sites as mammary and axillary lines or genital sites (Table 1).

Table 1. Localization of dysplastic nevi

Head and neck	Posterior thorax	Anterior thorax	Abdomen	Arms	Legs	Special sites (acral, genital, axillary and mammary lines)
3	36	10	10	1	4	17
4%	45%	12%	12%	1%	5%	21%

Table 2. Percentage of dysplastic nevi with specific histological characteristics

	positive	negative	mild	moderate	severe
Dysplasia	-	-	15 (19%)	52(64%)	14 (17%)
Pagetoid extension	49 (60%)	32(40%)	-	-	-
Fibrosis	73 (90%)	8 (10%)	31 (43%)	39 (53%)	3 (4%)
Inflammatory infiltrate	72 (89%)	9 (11%)	40(56%)	27 (37%)	5 (7%)

Most of the clinical suspicion diagnosis were of nevi (65%), but also hemangioma (15%) and papilloma (15%) were some of the most frequently clinical diagnosis.

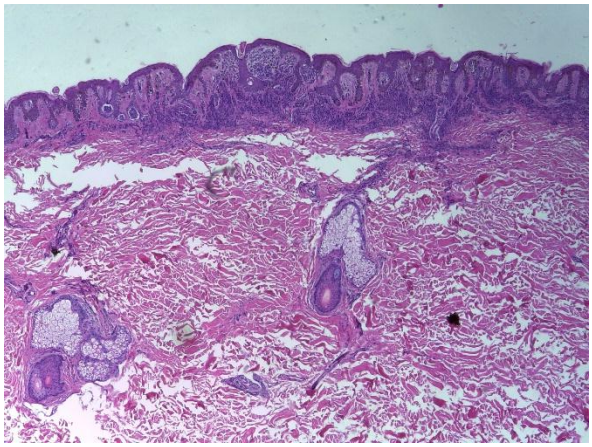

Figure 5. Dysplastic nevi with severe dysplasia, HE, 40X

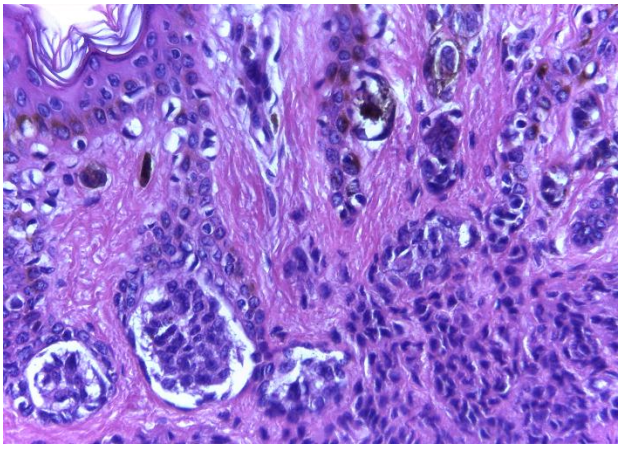

Figure 6. Dysplastic nevi with severe dysplasia, HE, 400X

All of the nevi were divided by the grade of dysplasia in mild, moderate and severe (Fig 5, Fig 6), and pagetoid extension (positive and negative), grade of fibrosis and inflammatory infiltrate (0 - negative, 1 - mild, 2 - moderate, 3 - severe) were also noted. Most of the nevi presented with moderate dysplasia, moderate fibrosis and mild inflammation (Table 2). Ninety (90%) nevi presented fibrosis with 53% presenting moderate and 43% mild fibrosis. Mild inflammatory infiltrate was noted in 56% of the cases, and in 37% moderate inflammation; only 7% of the nevi presenting with high grade inflammation. Pagetoid extension was observed in 60% of the cases.

The Pearson correlation coefficient was applied for dysplasia and the maximum size of the tumor but did not reveal a strong correlation between them ($r(79) = 0.26$, $p<0.01$). There was a moderate correlation ($r(79) = 0.38$, $p<0.01$) between the grade of dysplasia and the grade of fibrosis highlighted by specials staining (van Gieson and Masson's Trichrome) revealing, thus, that as the dysplasia is raising the grade of fibrosis increases as well. The Pearson correlation between the grade of dysplasia and inflammatory infiltrate ($r(79) = 0.31$, $p<0.01$) concludes that the inflammation is in direct association with dysplasia. Also, the grade of fibrosis changes with the level of inflammatory infiltrate ($r(79) = 0.48$, $p<0.01$). Furthermore, there was a statistically significant correlation ($r(79) = 0.40$, $p<0.01$) between pagetoid extension and dysplasia.

DISCUSSIONS

As described by Norris in 1820 and afterworlds by Clark et al. dysplastic nevi are somewhat correlated with the developing of cutaneous melanoma [1] and the risk of malignant transformation is prone to be demonstrated by newer studies nowadays. Nevertheless, the grade of dysplasia was one of the elements long studied in order to understand and correlate it with melanoma. As Arumi-Uria demonstrated, the grade of dysplasia correlates positively with the risk for developing cutaneous melanoma and with the history of family melanoma [5, 8]. But, as it is highlighted in the reminded study and in others studies [9], the interobserver agreement is not as high as expected. Although the grade of dysplasia is recommended to be noted, the difference between mild and moderate dysplasia remains a subjective issue. Many studies [5, 8, 12] tried to assess histological criteria for classifying dysplasia. On the other hand, a new perspective was raised concerning the degree of fibrosis and inflammatory infiltrate in association with dysplasia [10, 11]. Pozo and al. demonstrated a reverse correlation between the grade of regression, as defined by

inflammatory infiltrate with macrophages, increased vascularization and non-lamellar fibrosis, and the grade of dysplasia. Babacan et al. show a positive but rather moderate association between fibrosis and both cytological atipia and architectural disorders. All those characteristics could be helpful in better assessing dysplasia. In our study, we found that both fibrosis and inflammatory infiltrate correlates positively with dysplasia ($r(79) = 0.38$, $p<0.01$, respectively $r(79) = 0.31$, $p<0.01$) with a statistically significance ($p<0.05$) in both cases. The association is similar to that found in other studies [11]; still, it represents a moderate rather than a strong correlation. However, it is once again proved that as the dysplasia changes so do the dermal aspects. Also, a clear correlation was obtained between fibrosis and inflammatory infiltrate, demonstrating that this two elements are linked together in this types of lesions. As Pozo et al. noted in their study [15] there could be many explanations regarding the inflammation in interrelation with dysplasia, the former appearing as a response to neoplastic, regenerative or regression changes, as a consequence of apoptosis or as a result of a common trigger for dysplasia and inflammation. Additionally, we demonstrated a good correlation between the grade of dysplasia and the pagetoid extension ($r(79) = 0.40$, $p<0.01$), thus permitting us to postulate that if we see pagetoid extension, we can suspect a higher grade of dysplasia even if other cytological characteristics are inconspicuous. We did not manage to demonstrate a relevant correlation between the size of the nevi and the grade of dysplasia attesting the results of Braun-Falco et al regarding the necessity for applying histological criteria regardless the size of the nevi and categorize them as dysplastic / atypical nevi [13]. Our study did not show any relevant difference in the size of the tumor and the existence of compound or junctional architecture of the lesions. Most of the lesions presented on the posterior thorax but also in the special localization as acral or genital site. We emphasize that the lesions located in special sites were categorized as dysplastic nevi and not as nevi of special sites as they were meeting all the WHO histological criteria for diagnosis of atypical or B-K nevi.

CONCLUSIONS

We manage to demonstrate in our study that the degree of fibrosis, as well as the inflammatory infiltrate and pagetoid extension correlates positively and statistically significant with the grade of dysplasia and that the fibrosis is, indeed, correlated to inflammation. The explanation for this phenomenon could be that inflammatory infiltrate represents a response to the effects of dysplastic cells, as it also does in melanoma, and that the inflammation and the fibrosis are interconnected though either a common trigger or as a cause-effect relation. The pagetoid extension is a valuable sigh that a disturbance due to dysplasia is taking place and, when observed, it should at least raised the suspicion of an atypical nevi. There should be extensive studying implying a greater number of cases, with various aspects of lesions and also, more pathologists to exclude the change of bias for this observations to be fully correct and complete.

Conflict of interests

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.

Acknowledgement

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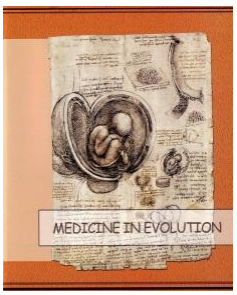
Pemphigoid gestationis – case presentation



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Abstract

Pemphigoid gestationis is a specific bullous dermatosis of pregnancy which commonly develops in the second or third trimester. Cutaneous manifestations occur mainly as a result of the formation of autoantibodies against type XVII collagen, which is encountered both in the structure of the placenta and epidermis. We present the case of a 27- year-old primigravida in her third trimester of pregnancy, who presented to our clinic for the occurrence of a polymorphous, pruritic eruption consisting of erythematous plaques and blisters, with onset on her palms and soles.

Keywords: pemphigoid gestationis, pregnancy, autoimmune disease

INTRODUCTION

Pregnancy is a condition defined by numerous immunological and hormonal changes with impact on many systems, including the skin. Several dermatological entities, which develop during pregnancy and postpartum, characterized mainly by pruritus, have been described (1). The most recent classification of specific dermatoses of pregnancy includes pemphigoid gestastionis, polymorphic eruption of pregnancy, atopic eruption of pregnancy, and intrahepatic cholestasis of pregnancy (2).

PG is thought to be the first specific dermatosis of pregnancy described, the disease being defined by Milton in 1872. Initially, given its clinical picture that includes formation of vesicles and bullaes, it was coined herpes gestationis. Subsequent studies have revealed that there is no connection between PG and herpes simplex virus. PG is a rare autoimmune disease which develops during pregnancy with an incidence ranging between 1:2000 and 1:60000 pregnancies. It may occur in any stage of pregnancy, but it is more common in the second and third trimesters (3). The diagnosis is based on the histopathological examination and direct immunofluorescence. Complement C3 deposits along basal membrane zone in the perilesional skin are characteristic (4).

CASE PRESENTATION

A 27-year-old primigravida presented to our clinic for the occurrence of a disseminated pruritic eruption which had appeared one week earlier. The onset of the lesions was on her palms and soles and progressively extended to her trunk and limbs. The patient stated that initially the eruption consisted of erythematous plaques, but after three days she noticed the appearance of blisters. She was in her 32nd week of gestation, so far the evolution had been good, she asserted a single episode of urinary infection when she was in her 24th week of gestation. The infection had been treated with azithromycin. Except for this episode her medical history was unremarkable. The patient had no history of abortions. She denied smoking.

On physical examination, she was in good condition and was afebrile. Her vital parameters were within normal range. The local examination revealed a polymorphous eruption disseminated on her trunk (Figure 1) and limbs, consisting of erythematous plaques and placards and scattered blisters. The blisters were located mainly on her palms, soles and forearms. Several erythematous plaques were noticed on her neck and face, involving the chin. There were no lesions on mucous membranes. The rest of the clinical exam was normal. Based on anamnestic and clinical findings the diagnosis of PG was suspected.

Laboratory tests revealed changes specific to pregnancy (mild leukocytosis and mild anemia), otherwise being within normal range. The histopathological examination displayed orthokeratosis, moderate acanthosis, spongiosis and vesicles with eosinophils. In addition edema in papillary dermis and a perivascular dense lymphocytic infiltrate with numerous eosinophils were identified (Figure 2). The histopathological appearance was compatible with the diagnosis of PG.

The patient underwent a fetal ultrasound which revealed normal fetal parameters. She started a treatment with 30 mg prednisone per day, which was gradually tapered with a good outcome on the cutaneous lesions.

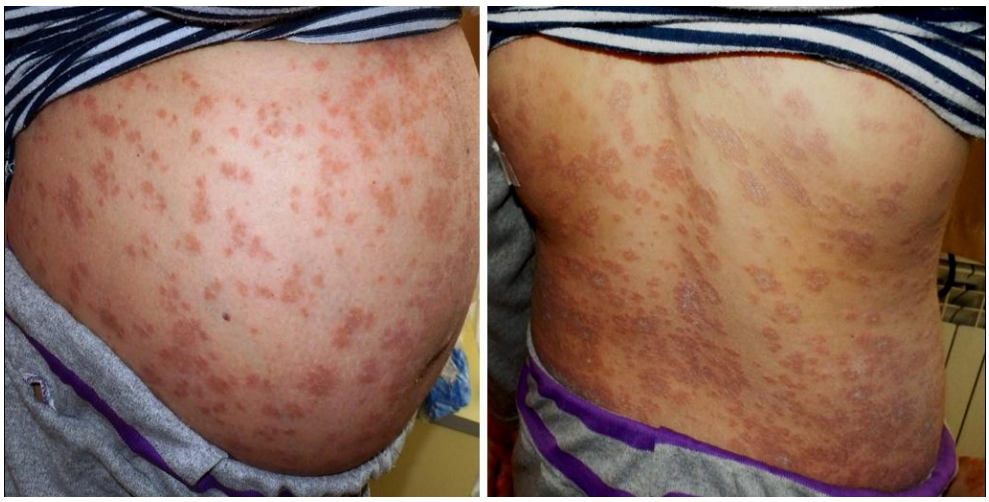

Figure 1. Well demarcated erythematous plaques and placards on the trunk

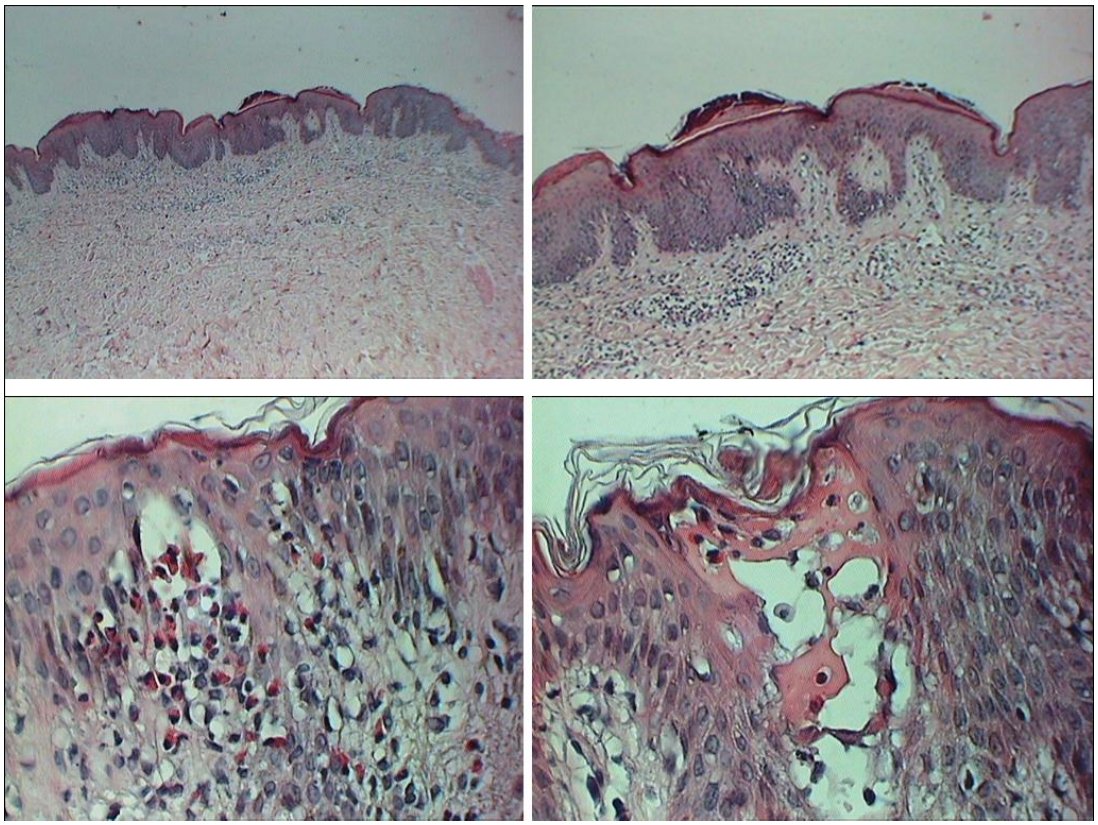

Figure 2. Orthokeratosis, moderate acanthosis, spongiosis and vesicles with eosinophils, edema in papillary dermis and a perivascular dense lymphocytic infiltrate with numerous eosinophils

DISCUSSIONS

The pathogenesis of PG is not completely known. Many studies have shown a higher incidence of PG in people presenting human leucocyte antigen (HLA) DR3 or HLA DR4. It seems that the placental major histocompatibility complex (MHC) II class antigens plays an important role in the development of the autoimmune process, resulting in a cross-reactive immune response with maternal cutaneous structures (5). Autoantibodies are directed primarily against type XVII collagen, the antigen of bullous pemphigoid (BP 180) (6). More exactly, the autoantibodies are against the extracellular noncollagenous 16A domain (NC 16A) of collagen XVII, a transmembrane glycoprotein. This glycoprotein is a component of the

placental amniotic epithelium, umbilical cord, and also of the epidermal basement membrane, which explains the appearance of skin lesions (7). Autoantibodies belong to the Ig G class (Ig G1) and once stabilized on the NC 16 A domain, attract the complement, triggering the classic pathway of complement. Eosinophils migrate to the site of antigen-antibody complex and degranulate, altering the basement membrane, which induces the formation of bullous lesions on the skin (8)

Clinically, PG is characterized by erythematous-edematous plaques and placards, mimicking urticarial lesions, followed by the appearance of bullous lesions, of varying sizes, containing a clear liquid, but in some instances they may be absent (9). In most cases, the lesions are initially located in the periumbilical area and spread on the trunk and limbs (1). The eruption may generalize. The lesions are very pruritic and sometimes may have an annular appearance, resembling those observed in erythema multiforme. The face, palms and soles are not usually affected (10). However, according to the study conducted by Rassai, facial involvement is common (11). Mucosal lesions occur in 20% of cases (12). In our case, the onset of the disease was on the palms and soles and some lesions were present in the lower third of the face. The mucous lesions were absent.

Histopathological examination displays subepidermal vesicles and dermal inflammatory infiltrate composed of lymphocytes and eosinophils. The presence of eosinophils is characteristic for the diagnosis of PG (9). Direct immunofluorescence reveals linear deposits of complement C3 arranged along the basement membrane. Deposits of Ig G may also be observed. These deposits have been also identified in samples from both placenta and fetal skin. Indirect immunofluorescence detects circulating autoantibodies, Ig G type in 20-60% of cases, in some studies the percentage reaching 100% (5,13).

Polymorphic urticarial papules and plaques of pregnancy (PUPPP) is the main differential diagnosis, which should be considered. The identification of autoantibodies using the immunofluorescence technique or ELISA is relevant, in PUPPP the result being negative. The distinction between the two diseases is important given that the therapeutic approach and their evolution are different. Thus the treatment of PUPPP consists of oral antihistamines, topical corticosteroids and emollients (14). The etiology of PUPPP remains unknown. However there is a hypothesis, which stresses the role of maternal immune response in pathogenesis (15). Clinically it is characterized by urticarial papules and plaques which are located initially on the trunk, but do not involve the periumbilical area. Sometimes the clinical picture can be completed by the appearance of small vesicles (16). Our patient presented lesions in the periumbilical area and blisters, elements which directed the diagnosis to PG.

Other differential diagnoses which should be taken into account are the atopic eruption of pregnancy (AEP) and intrahepatic cholestasis of pregnancy (ICP). In AEP, papules and eczematous lesions are observed and the disease is not related to a history of atopy (17). ICP is associated with a significant fetal risk, the cutaneous lesions are absent, but the pregnant woman complains of intense pruritus resulting in excoriations (18).

Oral corticosteroids represent the first line treatment in PG. The recommended dose is 20-40 mg per day and it can be increased to 1-2 mg/kg per day in severe cases. Intravenous Ig proved their usefulness and can be added to the treatment with corticosteroids (19). In early stages of the disease topical corticosteroids in combination with oral antihistamines can be administered. Dapsone, sulfapyridine or cyclosporine may be effective (10). In most cases, the disease worsens immediately postpartum, but then it goes into remission (15).

The main fetal risks are low weight at birth and prematurity, which are the consequences of the placental damage induced by autoantibodies, resulting in placental insufficiency. In 5-10% of cases the new born may develop an eruption consisting of subepidermal blisters. The eruption is transient and resolves without scarring, no treatment is necessary. The lesions result from the passage of maternal antibodies through placental

membrane. A correlation between antibodies levels and fetal risks has not been identified (20,21). The risk of premature birth is higher if the onset of the disease is early, in the first or second trimester or if the lesions of the mother evolve into blisters (18).

The risk of recurrence of PG in subsequent pregnancies is very high, the percentages reported in the medical literature being of up to 90%. It has been observed that in subsequent pregnancies the onset is earlier and the disease more severe (8,22).

CONCLUSIONS

PG is a rare specific dermatosis of pregnancy, whose pathogenic mechanisms are not fully understood. It is important to differentiate it from the other dermatoses of pregnancy, especially from PUPPP. Fetal risk is low but pregnant women should be informed about the increased risk of developing PG in subsequent pregnancies. In the case of our patient, the onset of the lesions was on the palms and soles, which is a localization rarely described in literature.

Acknowledgement

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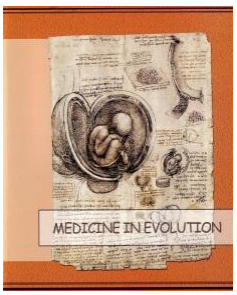
Orbital volume measurements. From past to present.



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Abstract

The orbit is one of the most complex structures of the human skull. Its anatomy and development have been studied for a long time and methods for measuring the diameters and volume of this roughly quadrilateral pyramid shaped cavity were investigated for more than a century. Measurements of the orbit are important from an academic point of view, but they are essential from a clinical point of view given the multitude of pathology involving this particular anatomic region. Traumatic orbital fractures, congenital diseases, intraorbital tumors and inflammatory diseases are frequent and this explains the multidisciplinary interest in correctly measuring and quantifying the orbital contents. The development of the CT scan and 3D technologies of volume computation represent a turning point in the study of the orbit but a clear protocol for the measurements is yet to be formulated.

Key words: orbital volume, OsiriX, history, 3D volume computation

INTRODUCTION

The human orbit is a very complex structure that protects the eyeball, optic nerve, muscles, arteries, veins and many other important tissues.

Methods to determine the volume of this very complicated entity have been studied for many decades because of its importance in multiple clinical situations. Before the 1980s there was no method of accurately measuring the orbital volume *in vivo*. Computer tomography based methods have been used since the '80s but recent improvements in CT resolution provide much more information and the 3D technologies of volume computation make this method very useful in preoperative planning [1].

The difficulty in determining the orbital volume is due to the extremely complicated anatomy. The anterior limit of the bony orbit is not in a single plane thus being a source of variability between studies using different bony landmarks. This leads to different results depending on the method. The OsiriX software was found in many studies to be reliable in determining the orbital volume and very useful for preoperative planning [2-4].

The determination of orbital volume is valuable in many situations like traumatic orbital fractures, neoplasia, inflammatory diseases (Grave's disease, sarcoidosis) congenital diseases but it was also used in studies for developing protection devices for different activities [5].

Studies have shown differences in orbital volume among ethnic groups hence it was considered important to obtain measurements from the normal population of different ethnicity before assessing pathologic orbits [6].

HISTORICAL BACKGROUND

The fascination for the orbital volume measurements has been present for more than a century. In 1873 Gayat measured the orbital volume of a skull of a 10 year old child and of an adult using lead pellets. The child skull measured 22 ml and the adult's 29 ml [7]. In 1875 Broca [8] and in 1890 Weiss [9] used the same technique and recorded an average volume of 29.74 ml. In 1904 Adachi [10] used water to measure the volume of the orbit and recorded results between 19 and 35 ml. In 1932 P'an [11] performed a study on 90 northern Chinese male skulls and used sand for the measurements. The average volume of the orbit was 29.3 ml. Whitnall [12] measured 29.5 ml in 1932. In 1933 Koch and Brunetti invented a roentgenologic technique for measuring depth and volume of the orbit in their study on anophtalmic orbits [13].

The development of the Computer Tomography was a huge step in orbital volume measurement. Many methods of quantifying the orbital content and volume were described in the literature in the attempt to standardize this very complex structure. Even though the Gold Standard of measuring the orbital volume is still the fluid displacement technique, the CT based reconstruction method is considered the most feasible for orbital volume calculation [1].

CLINICAL USE OF VOLUME MEASURING

The advancement of the imagistic technologies and the development of 3D volume computation were a turning point in the study of the orbit.

OsiriX is an open source imaging software created by Dr. Antoine Rosset and Joris Heuberger, a computer scientist from Switzerland. It is an image processing application that can only be executed on a Macintosh system, dedicated to DICOM images produced by medical equipment (MRI, CT, PET, PET-CT). It is a very user friendly software and can be easily used by non-radiologists. The method for measuring the volume of the orbit using

OsiriX is by manual selection of the ROI (Region Of Interest) with the closed polygon ROI tool on the 2D axial view (Fig. 1). After selecting the ROIs on consecutive slices the compute ROI volume tool is used and the volume of the total selected regions is calculated (Fig. 2) [6, 14].

The OsiriX software was demonstrated in many studies to be an accessible and simple tool for preoperative assessment in orbital surgery but it can also be used as a navigational tool during surgery [2-4].

Shyu et al. used the OsiriX software to compare two different methods of measuring the orbital volumes described in the literature. The difference between the two methods was the anterior limit of the orbit, one method following the gold standard of orbital volume measurement- the orbital rim (much more complex but time consuming) and the other the line that unites the bilateral lateral orbital margins (much more time efficient). Both methods demonstrated very high reproducibility and insignificant inter-rater and intra-rater variability when using the OsiriX tool [6].

Other authors [15] measured the entire globe and soft tissue and obtained a volume of 28.41 ± 2.09 ml, higher than in most studies on Asian population [16-19]. Chen et al. used 5 mm CT slices but the precision was low due to the complex anatomy of the orbit [20].

Forbes et al were the first to measure not only the bony orbit but also volumes of normal orbital soft tissue (excluding the globe), extra ocular muscle and orbital fat using the CT scan. Their aim was to calculate the normal values of the orbital structures in order to create a baseline for comparison in different pathology (endocrine, trauma and congenital). The mean volume of the bony orbit, orbital tissues, orbital neuromuscular tissue and orbital fat for female/ male patients were 23.92/23.63 cm^3, 14.83/15.99 cm^3, 4.69/4.79 cm^3 and respectively 10.10/ 11.19 cm^3 [22].

Ashley A. Weaver et al. presented a method of aligning CT images and measuring more than the bony orbit but also the soft tissue of the eye and orbit. Orbital aperture, eye protrusion, eye location and brow protrusion were measured in 39 subjects. The results suggested that the orbit widens with age and that there is a significant relationship between the height of the subject and the measurements of the orbital aperture and eye location. They suggest normalizing the measurements by height in order to reveal the effects of factors like age, sex and ethnicity on orbit anthropometry [5].

Scolozzi et al. used OsiriX to compare the accuracy of orbital volume restoration in posttraumatic blow out fractures with two techniques. They used the contralateral healthy orbits as a control group. Both techniques allowed close reproduction of the volume and shape of the healthy orbit [22].

Ozgen et al. were the first to use the CT scan to measure the diameters of extraocular muscles, the distance from the posterior margin of the globe to the interzygomatic line, the width of the optic nerve-sheath and the length of the interzygomatic line in order to establish the normal position of the globe in the general population, for future comparison to pathologies involving these structures [23].

In the past years studies on the anatomy and development of the orbit were very successful in determining the differentiation of the orbit in children. These studies were impossible until the development of the new imaging techniques and have brought essential information on orbit anatomy in children of different ages.

Tsukitome et al. studied changes with age of the angle of the optic nerve and orbit in 147 Japanese children aged between 6 months and 18 years. The opening angle of the orbit was found to decrease logarithmically with age especially in the first 2 years of life. This should be taken into account when considering surgery for strabismus in very young children [24].

Garrett et al. measured the intercanthal, bony interorbital and bony lateral orbital distances in 204 children from birth to 36 months using CT scan and established a baseline for

normal orbital measurements in children, crucial in the management of craniofacial deformities [25].

Bentley et al. measured the orbital volume of 67 children aged between 1 month and 15 years using MRI images and reported a significant volume increase in the first years of life, the volume reaching 77% by the age of 5 years [26].

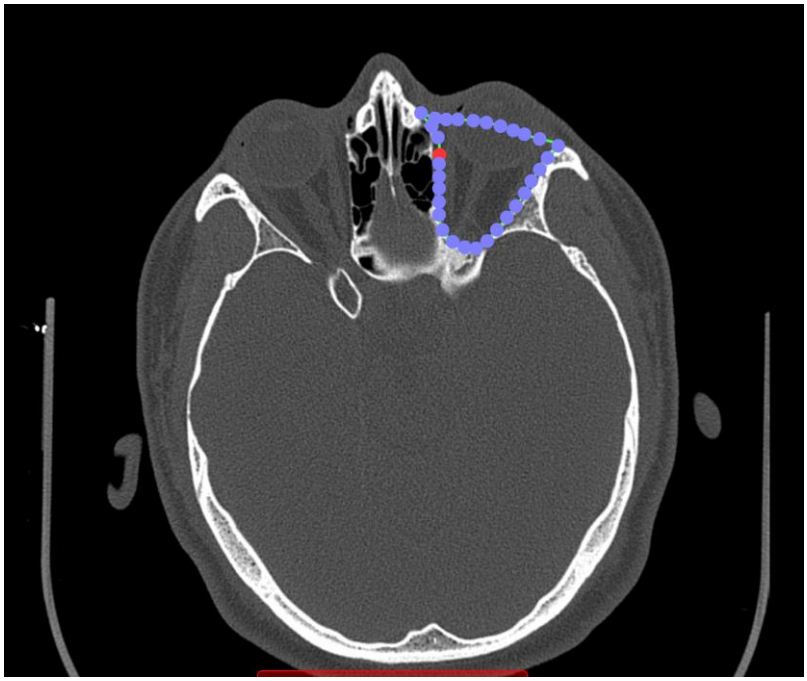

Figure 1. Manual selection of the ROI (Region Of Interest) with the closed polygon ROI tool on the 2D axial view. The anterior limit is the line uniting the anterior lacrimal crest (medially) and the lateral orbital rim. The posterior limit is the opening of the optic foramen into the orbit

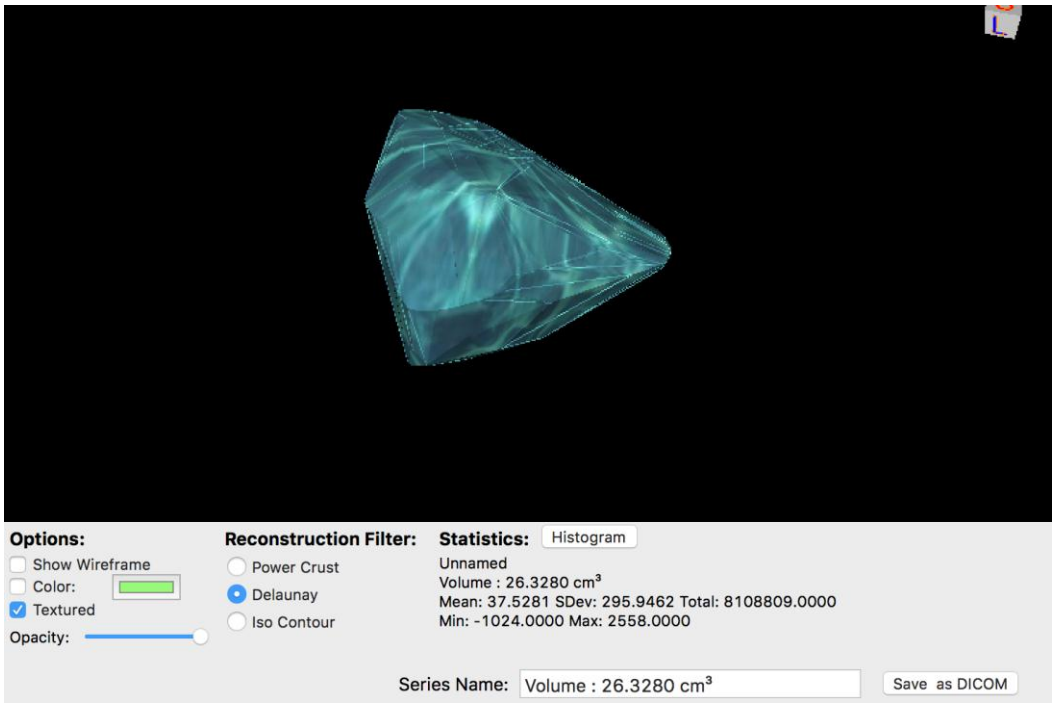

Figure 2. Exemple of orbital volume measurement using the compute ROI volume tool

CONCLUSIONS

Given the complex anatomy of the orbit different methods of determining the orbital volume have been described. The Gold Standard of measuring the orbital volume is the fluid displacement volume measurement.

The CT based reconstruction method is considered to be the most feasible methodology for orbital volume estimation. Is spite of the recent developments in the imaging techniques that led to a high level of accuracy of inter-rater and intra-rater volume measurements there is still no protocol for the orbital volume measurement. The complexity of the orbit anatomy, particularly the anterior limit led to different protocols of measuring the volume and hence different results that cannot be compared between studies. The ethnicity is also a very important factor but there are not enough studies following the same protocol in order to be able to draw a conclusion.

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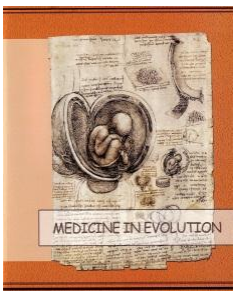
Prognostic Factors in the Survival of Multiple Myeloma Patients



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Abstract

Introduction: Multiple myeloma is a neoplastic disease pathogenetically characterized by an excess of plasma cells in the bone marrow, monoclonal proteins, osteolytic bone lesions, renal impairment and immunodeficiency.Therapeutic advances, as well as the diversity of treatment approaches depending on disease pathogenesis led to the inclusion of patients into risk classes based on the evolution of certain hematological, biochemical and immunologicalmarkers. Although many prognostic factors were described for multiple myeloma, none of these can explain the heterogeneity of this condition.

Aim: This study aims to analyse the hematological, biochemical and immunological prognostic factors in our group of patients and to establish correlations with their survival duration.

Methodology: The study was conducted on a group of 77 patients admitted in the Hematology Department of the City Clinical Emergency Hospital Timisoara between January 1st2011 and December 31st2015. Data were extracted from the medical records, with focus on anthropometric, hematological, biochemical and immunological parameters, type of treatment and response to treatment, as well as survival duration in months from the time of diagnosis up to the end of this study.

Results: In our study, 51.9% of the patients are aged between 40 and 60 years, 40.3% between 61 and 75 years and only 7.8% are aged over 75 years. Most patients are women (54.5%).A positive correlation was established between age, gender and survival time. Hematological, biochemical and immunological parameters were analysed as regards their influence on influence on the response to treatment and survival duration, with some of them having statistically significant influence.

Conclusions: Ascertainingthe negative prognostic factors that influence the evolution and the response to treatment in multiple myeloma is critically important in order to establish a personalised therapy for each patient. Combining several independent prognostic factors provides more useful clinical and therapeutic information.

Key words: prognostic factors, survival, multiple myeloma

INTRODUCTION

Multiple myeloma is a neoplastic disease pathogenetically characterized by an excess of plasma cells in the bone marrow, monoclonal proteins, osteolytic bone lesions, renal impairment and immunodeficiency. Several studies consider monoclonal gammopathies without clinical significance might develop into multiple myeloma[1,2].MM is a heterogeneous disease in which survival ranges fromone to more than 10 years. The average five-year survival rate is about 35%.Therapeutic advances, as well as the diversity of treatment approaches depending on disease pathogenesis led to the inclusion of patients into risk classes based on the evolution of certain hematological, biochemical and immunologicalmarkers. Although many prognostic factors were described for multiple myeloma, none of these can explain the heterogeneity of this condition. Presence of tumor masses and proliferation rate are two key indicators for the disease prognosis in MM patients. A series of studies were conducted to establish a prognosis;one of these prognosis schemes uses C-reactive protein (CRP) and beta-2 microglobulin to determine the survivalrate:[3]

- if serum levels of both proteins are less than 6 mg/l, the median survival is 54 months.
- if one of them is below 6 mg/l, the median survival is 27 months.
- if the values of both proteins are higher than 6 mg/l, the median survival is 6 months.

Other prognostic factors in the same scheme are: bulky disease, hypercalcemia, Bence Jonesproteinemia, renal failure (e.g., disease stage B or creatinine level >2 mg/dl at diagnosis) [4].

Aim

This study aims to analyse the hematological, biochemical and immunological prognostic factors in our group of patients and to establish correlations with their survival duration.

METHODOLOGY

The study has been performed on a group of 77 de patients admitted in the Hematology Department of the City Clinical Emergency Hospital Timisoara between January 1st, 2011 and December 31st, 2015. This is a retrospective study for the 2011 and 2012 years, as we have analysed the medical records of all patients admitted for the first time in the clinic and diagnosed with multiple myeloma *per primam* during that period; starting with 2012 the study became prospective and we included all the patients who addressed our clinic for a first diagnosis.

STATISTICAL ANALYSIS

Data were extracted from the medical records, with focus on anthropometric, hematological, biochemical and immunological parameters, type of treatment and response to treatment, as well as survival duration in months from the time of diagnosis up to the end of this study. Statistical processing was performed using the SPSS17.0 programme. For the descriptive statistics results for expressed as percentages and absolute values. The Kaplan-Meyer survival curve was employed to show the relationship between survival and hematological, biochemical and immunological parameters.

RESULTS

Age and gender

In our study, 51.9% of the patients are aged between 40 and 60 years, 40.3% between 61 and 75 years and only 7.8% are aged over 75 years. Most patients are women (54.5%).A positive correlation was established between age, gender and survival time. Mean survival was seen to be lower (approximately 30 months) in patients aged over 75 years, while in those aged between 60 and 75 years is about 49 months;the best survival rate is recorded in patients aged between 40 and 60 years (54 months). Survival rate is lower in men (38 months) than in women (44 months).

Values of hematological parameters are shown in Table II.

Table I. *Age and gender*

		Frequency	Percentage
Age	40-60 years	40	51.9
	61-75 years	31	40.3
	>76 years	6	7.8
Sex	M	35	45.5
	F	42	54.5

Table II. *Values of hematological parameters*

Parameter	Values	No. of patients	Percentage
Hb (g/dl)	<8	8	10.4%
	8-10	22	28.6%
	10-13	32	41.6%
	13-17	15	19.5%
Platelets (mm^3)	50,000-100,000	7	9.1%
	100,000-150,000	11	14.3%
	150,000-410,000	56	72.7%
	>150,000	3	3.9%
FAS (u/l)	35-105	44	57.1%
	>105	33	42.9%
Peripheral smear	FISIC	55	71.4%
	PLASMA CELLS	22	28.6%
ESR (mm/h)	3-10 mm	13	16.9%
	10-60 mm	11	14.3%
	>60 mm	53	68.8%
LDH (u/l)	100-190	58	75.3%
	>190	18	23.4%
	<100	1	1.3%
Fibrinogen (mg/dl)	200-400	27	35.1%
	>400	50	64.9%
Serum potassium (mmol/l)	<3.5	14	18.2%
	3.5-5.1	51	66.2%
	>5.1	12	15.6%
Serum calcium (mg/dl)	<8.8	23	29.9%
	8.8-10.2	14	18.2%
	>10.2	40	51.9%
Creatinine (mg/dl)	<0.8	29	37.7%
	0.8-2	25	32.5%
	>2	23	29.9%
Urea (mg/dl)	15-39	42	54.5%
	>39	35	45.5%

Not all the hematological parameters we have measured are statistically significantly correlated with the survival rate.

Patients with severe anemia (hemoglobin less than 8 mg/dl) had a lower survival rate than those with moderate anemia or normal hemoglobin values (28 months compared withthe average of 43 months).

Hypercalcemiawas found in 51.9% of patients, who had a survival rateof 35 months compared with 49 months in patients with normal serum calcium levels.

Another parameter that has proved to influence survival is serum creatinine.A statistically significant difference was found in terms of survival rate of patients with normal creatinine(45 months) and those with elevated levels (39 months).

Among the immunological parameters, beta 2 microglobulin and albumin are the prognostic factors considered in the staging of multiple myeloma. Survival rate of patients with albumin level >3.5 g/dl is 45 months compared with those with lower values of albumin (28 months), and the difference between the two groups of patientsis statistically significant.Values of beta2 microglobulin greater than 5.5 mg/l are accompanied by a survival rate of 40 months, as opposed to the group of patients having the beta 2 microglobulin level <3.5 mg/l, which has a survival rate 46 months.Total protein values lower than 64g/L and greater than 83g/L also correlate with a lower survival rate (40 months) as compared with the patients showing normal values of this parameter (49 months).

Table III. Values

Parameter	Values	Frequency	Percentage
Albumin (g/dl)	<3.5	39	50.6%
	3.5-5	30	39.0%
	>5	8	10.4%
Total proteins (g/l)	<64	10	13.0%
	64-83	38	49.4%
	>83	29	37.7%
ELFO	Lambda	25	32.5%
	Kappa	52	67.5%
Beta 2 microglobulin (mg/l)	<3.5	29	37.7%
	3.5-5.5	23	29.9%
	>5.5	25	32.5%
C-reactive protein (mg/l)	+	15	19.5%
	-	62	80.5%
IgG (g/l)	Absent	23	29.9%
	Present	54	70.1%
Ig A (g/l)	Absent	56	72.7%
	Present	21	27.3%
IgM (g/l)	Absent	75	97.4%
	Present	2	2.6%

We have assessed serum immunoglobulins levels as a prognostic factor of survival rate. Patients with elevatedIgG and IgA levels have lower survival rate than patients with lower levels of these parameters. Survival rate is also higher in patients with Kappa chains than in those with lambda chains, but the difference was not statistically significant (p> 0.3). No statistically significant correlations were found with other measuredparameters.

DISCUSSIONS

Survival rate for multiple myeloma patients ranges between 2.5 and 3 years on average, the disease showing a great variability from one patient to another. In order to

achieve a personalized treatment, a number of studies have tried to establish a number of negative prognostic factors that influence response to treatment and survival. IRC, hypercalcemia and severe anemia are some of the most well knownnegative prognostic factors [5,6,7].A study of 107 patients conducted at the Mayo Clinic showed that such factors as age, level ofC-reactive protein, albumin, Beta 2 microglobulin, thymidine kinaseand PCLI may negatively influence the survival duration of these patients.Among the parameters measuredin our study, wefound age over 75 years, male gender, hemoglobin less than 8 mg/dl, hypercalcemia and elevated creatinine (>2 mg/dl) to be negative prognostic factors.Similarly, out of the studied immunological parameters, albumin <3.5 g/dL, Beta 2 microglobulin>5.5 mg/l, elevated total protein, increased IgG and IgAlevelswere identified as negative prognostic factors.

CONCLUSIONS

Ascertainingthe negative prognostic factors that influence the evolution and the response to treatment in multiple myeloma is critically important in order to establish a personalised therapy for each patient. Combining several independent prognostic factors provides more useful clinical and therapeutic information.

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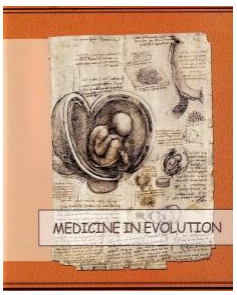
Clinical and evolutive characteristics of Elderly patients with heart failure



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Abstract

Heart failure has a higher prevalence in the elderly and is the leading cause of hospitalisation for the elderly. In the studies conducted in our clinic, we analysed two groups of patients, including 249 patients with heart failure, with the aim of identifying the clinical features of these patients, observing the quality of life, at disease onset and subsequently, assessing the effort capacity of patients with heart failure, atrial natriuretic peptide impact on the evolution of heart failure and on readmissions due to worsening, the evolution and impact of inflammatory markers, highlighting new markers with a prognostic role. Values of inflammatory biomarkers were significantly higher in the elderly patients. Elderly patients had a shorter walking distance in the 6MWT test and a significantly higher risk for depression. During the multivariate logistic regression analysis, we found that increased values of the inflammatory marker TNF-α were found to be significantly associated with total readmissions and readmissions due to HF aggravation in the nonelderly, as well as with noncardiovascular readmissions in the elderly.

Key words: heart failure, elderly patient, readmission, heart disease

INTRODUCTION

Heart failure has a higher prevalence in the elderly and is the leading cause of hospitalisation for the elderly. Quality of life and long-term prognosis in heart failure remain reserved, 5-year survival having even a worse prognosis than most neoplasia.

The important role that heart failure has in clinical practice is also revealed by the many studies conducted on large groups of patients. With all the progress in cardiology, the epidemiology of heart failure is less known and the severity of the disease persists with a prevalence and an incidence which tend to grow more and more, knowing that heart failure is a disease characteristic of people with an average age between 74 and 75 years.

In research conducted in our clinic, we analysed two groups of patients with the aim of identifying the clinical features of these patients, observing the quality of life of these patients at disease onset and subsequently, assessing the effort capacity of patients with heart failure, atrial natriuretic peptide impact on the evolution of heart failure and on readmissions due to worsening, the evolution and impact of inflammatory markers, highlighting new markers with a prognostic role.

MATERIAL AND METHODS

We have analysed a group of patients, whose population was represented by adults (aged >= 18) admitted to the ASCAR Cardiology Clinic of the Emergency Municipal Hospital in our city of Timisoara, from January 1, 2013 to December 31, 2013, showing a first episode of heart failure at admission with the left ventricle preserved ejection fraction. All eligible patients were included in this prospective study.

The diagnosis of heart failure with the left ventricle preserved ejection fraction was based on symptoms, physical signs, posteroanterior chest radiograph, echocardiography and the values of natriuretic peptides on admission, according to Guidelines for Diagnosis of the European Society of Cardiology for the Diagnosis of Heart Failure (1).

The **inclusion criteria** were the following: left ventricle ejection fraction (LVEF) >= 45% (measured by two-dimensional echocardiography using the Simpson method); E / E' >= 15 (measured by tissue Doppler imaging); atrial natriuretic peptide (BNP) levels > 150 pg / mL. (2,3). The **exclusion criteria** were the following: acute coronary syndrome in the last 30 days, acute myocarditis, acute pericarditis, acute pulmonary thromboembolism, pacemaker implant and need for cardiovascular surgery.

Patients were assessed by echocardiography; serum biomarkers determined at baseline were atrial natriuretic peptide (BNP) and N-terminal fraction of atrial natriuretic peptide (NT-proBNP), and served as markers of left ventricular dysfunction. The tumour necrosis factor (TNF-α), interleukin 6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) have been considered as markers of systemic inflammation.

In this study we evaluated the quality of life of patients with heart failure using the Minnesota questionnaire and patients also filled in the Fahrenberg Scale depression risk assessment questionnaire. To assess effort capacity, we used the 6-minute walk test.

After one year of their enrolment, patients were re-evaluated by clinical examination and laboratory tests. At the same time, patients were asked to provide all the medical documents on the development of health, from the time of their enrolment in this study until the end of the follow-up period (4).

In the second study we have analysed a group of patients, whose population was represented by adults, all patients aged >65 years who were discharged from the Cardiology Department of the City Hospital Timisoara with a diagnosis of acute new-onset HF, from January 2013 until November 2013. A diagnosis of HF was made based on patient's symptoms, physical signs, chest radiography, and an echocardiographically determined

LVEF <45% (Simpson method), according to the European Society of Cardiology Guidelines for the diagnosis of HF (6,7). Exclusion criteria were: a diagnosis of acute myocardial infarction, acute myocarditis, acute pericarditis, and acute pulmonary thromboembolism, and the need for cardiovascular surgery.

Patients with prolonged baseline hospitalizations were considered as those who exceeded the 75th percentile of hospitalization length, as measured in days. All-cause readmissions were registered during the follow-up period of 1 year. The causes of readmissions were assessed by examining the patients' hospital records. Readmissions due to worsening HF, atrial fibrillation, hypertensive crisis, acute coronary syndrome, pulmonary embolism, stroke, or acute peripheral ischemia were considered as cardiovascular readmissions. Other causes of readmissions were classified as noncardiovascular readmissions.

RESULTS

The results of the analysis of the first group of patients were as follows: the study population comprised a total of 178 patients with an average age of 64.6 ± 8.6 years. Of the total patients included in this study, 80 patients (45%) were women, and 98 patients (55%) were male. A total of 98 patients (55%) were aged >= 65, and the remainder of 80 patients (45%) were aged < 65.

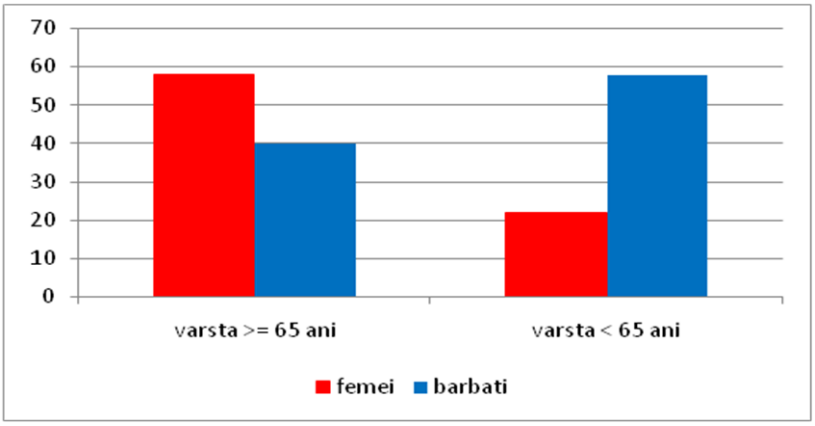

Figure 1. Distribution of the group of patients by gender and age

In the group of patients aged >= 65, women prevailed representing a total of 58 patients (59%), while, in the group aged < 65, men prevailed, women being represented only by a total of 22 patients (28%) (P = 0.0001).

If we refer to the treatment plan prescribed and followed by our patients, we can note that, in the group of patients aged >= 65, a treatment with beta-blockers, furosemide and spironolactone was recommended at a rate significantly higher than in the group of patients under 60. These patients received diuretics more frequently (P < 0.0001) (4). In the group of younger patients (under 60), the statistically significant treatment was the one with statins (P = 0.0001).

At the assessment after one year of follow-up, the value of BNP and NT pro-BNP cardiac peptides did not differ significantly between the two age groups with heart failure. Values of inflammatory biomarkers were significantly higher in the elderly patients (P <0.001 for TNF alpha and hs-CRP; P = 0.0001 for IL-6). The quality of life assessed using MLHFQ was similar, although elderly patients had a shorter walking distance in the 6MWT test (P less than 0.03) and a significantly higher risk for depression (P <0.003). (4)

Table 1. Differences between HFpEF patients according to age, at 1-year follow-up

Characteristics	Age ≥65 years (n=98)	Age <65 years (n=80)	*P*-value
BNP (pg/mL)	345 (214–598)	245 (267–435)	0.425
NT-proBNP (pg/mL)	753 (379–929)	485 (322–973)	0.406
TNF-α (pg/mL)	9.1 (7.6–13.0)	6.2 (4.8–11.0)	<0.0001*
IL-6 (pg/mL)	4.0 (1.9–5.4)	2.2 (1.5–3.0)	0.0001*
hs-CRP (mg/L)	6.6 (3.7–22.2)	2.5 (1.0–2.9)	<0.0001*

Notes: Categorical variables are presented as number (%). Continuous data are presented as mean ±1 standard deviation when normally distributed and as median (interquartile range) when skewed. *P-value <0.05.
Abbreviations: HFpEF, heart failure with preserved ejection fraction; BNP, brain natriuretic peptide; NT-proBNP, N-terminal-pro-brain natriuretic peptide; TNF, tumour necrosis factor; IL, interleukin; hs-CRP, high-sensitivity C-reactive protein; MLHFQ, Minnesota living with heart failure questionnaire; 6MWT, 6-minute walk test.

Using multivariate logistic regression analysis, we noticed that the independent variables associated with readmissions during the one year follow-up period in the group of elderly patients with heart failure with preserved ejection fraction were: BNP level > 450 pg/ml (sensitivity 73%; specificity 66%), TNF-alpha level of ≥ 10.1 pg/ml (sensitivity 64%, specificity 52%), depression score > 7.4 (sensitivity 62%, specificity 59%), walking distance ≤ 248m in 6MWT (sensitivity 68%, specificity 64%).

In the group of patients aged under 65 with heart failure with preserved ejection fraction, readmissions during the one year follow-up period were predicted independently by the following variables: NYHA functional class on enrolment, presence of coronary artery disease, presence of diabetes mellitus, presence of chronic kidney disease, depression score ≥ 7.4 (sensitivity 76%, specificity 50%), IL-6 level ≥ 2.5 pg/ml (sensitivity 67%, specificity 30%) and TNF-alpha level > 7.1 pg/ml (sensitivity 58%, specificity 61%).

Readmissions due to cardiovascular causes in the elderly group were independently predicted by NT-proBNP levels > 458 pg/ml (sensitivity 74%, specificity 71%) and a depression score ≥ 7.4 (sensitivity 47%, specificity 58%), while in the non-elderly group, no independent predictors were identified.

The independent variables which estimated readmissions in group of elderly patients due to worsening heart failure were: a BNP level > 450 pg/ml (sensitivity 73%, specificity 66%); and an NT-proBNP level > 477 pg/ml (sensitivity 68%, specificity 60%). In the group of non-elderly patients, worsening heart failure was estimated by BNP levels > 390 pg/ml (sensitivity 85%, specificity 56%) and a TNF-alpha level > 7.1 pg/ml (sensitivity 85%, specificity 59 %).

In the second study all 71 consecutive elderly patients with a first hospitalization for acute new-onset HF with LVEF <45% were included in the analysis. The patient mean age was 72.5±5.5 (range 65–84) years, and 50% of the patients were women, and it was observed that 42% of participants were living in villages. The demographic data are presented in the figures below.

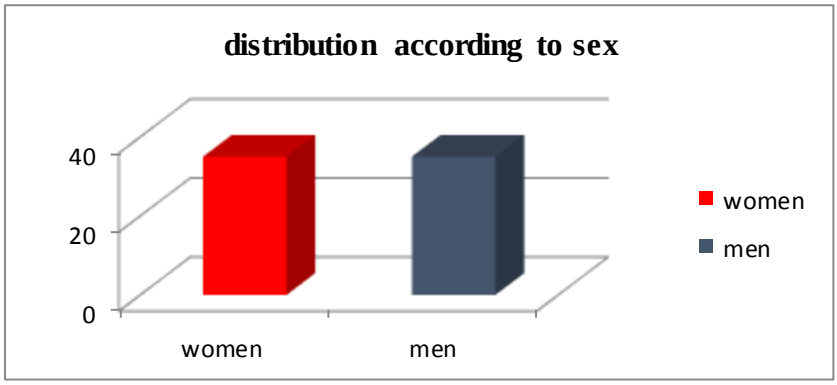

Figure 2. Patient distribution according to sex

The mean duration of baseline hospitalization was 9±4 (range 3–22) days, with a median of 8 days (IQR: 5–12 days) days. In all, 34 patients (48%) had prolonged hospitalization, which was defined as a baseline hospitalization stay longer than 12 days (□75 percentile of hospitalization length).

A total 19 patients (27%) experienced readmissions during the 1-year follow up, of which 12 (17%) had cardiovascular and seven (10%) had noncardiovascular causes. Univariate analysis revealed that the variables associated with rehospitalizations were the presence of any infection (P<0.020), the infectious exacerbation of COPD (P=0.015), one or more comorbidity (P<0.0001), and prolonged baseline hospitalization (P<0.0001).

During the 1-year follow-up period, seven deaths occurred (9.8%), of which four (5.6%) were assessed as having cardiovascular causes, while three (4.2%) were noncardiovascular. The only independent predictive variable for mortality was an NYHA functional class 4 at baseline hospitalization (P=0.001).

DISCUSSIONS

Our study was exclusively hospital based, with prospective recruitment of all patients hospitalized for a first episode of HFpEF. Similar to other HFpEF trials, (8,9) the elderly patients included in our study were characterized by the following: a higher prevalence of females; the presence of comorbidities (obesity, hypertension, CKD,); and a NYHA functional class of IV.

Concerning the biomarkers, the elderly HFpEF patients in our study had higher values of BNPs, both at baseline and at the 1-year follow-up. The natriuretic peptides, which reflect an afterload excess, were independently associated with rehospitalisation due to cardiovascular causes, especially due to HF aggravation. Overall, patients with HFpEF have lower levels of BNP and NT-proBNP than do HF patients with reduced LVEF, but for a given BNP level, the associated risk of all-cause mortality and HF hospitalization was shown to be at least as high as in patients with low LVEF.

The elderly HFpEF patients included in our study presented with significantly higher levels of hs-CRP and TNF-α when compared to the nonelderly group. This fact could be explained by the higher prevalence of comorbidities in the elderly group. During the multivariate logistic regression analysis, we found that increased values of the inflammatory marker TNF-α were found to be significantly associated with total readmissions and readmissions due to HF aggravation in the nonelderly, as well as with noncardiovascular readmissions in the elderly. Our results are concordant with those of Putko et al (10).

The readmission rate of the 71 elderly HFREF was 27% during the 1-year follow-up period, with slightly more frequently occurring cardiovascular (17%) than noncardiovascular (10%) causes observed in this cohort. Factors associated with the readmission of elderly HF

patients included prolonged baseline hospitalizations, as well as the presence of comorbidities, infections, and COPD exacerbation.

The 1-year all-cause mortality rate in our study was 9.8%, with no significant difference between cardiovascular deaths (5.6%) and noncardiovascular deaths (4.2%). The only independent predictor for 1-year mortality in the elderly patients with HFREF included in our study was an NYHA functional class of IV at initial hospitalization.

We have chosen to use the age of 65 years as a cutoff for the elderly participants in our study because it coincides with the retirement age in Romania and is accepted by WHO as the age that defines elderly individuals (11). The mean age observed for the elderly individuals in our study is also representative of Romania, where life expectancy is 74.5 years (71 years for men, 78 years for women), which is lower than in the central and western European countries (12).

CONCLUSIONS

A patient with heart failure faces a lot of challenges in managing the case, such as: difficulties in diagnosis, comorbidities, systolic dysfunction versus diastolic dysfunction, the interaction of multiple etiologies and precipitating factors, altered pharmacokinetics, decreased renal clearance, concomitantly administered medication, treatment compliance and medical indications, disease understanding, priorities regarding treatment: symptoms versus survival.

Unfortunately, there are many similarities between heart failure and cancer! The clinical evolution of heart failure is not the same as cancer... but there are similarities. Heart failure is a syndrome in which patients can oscillate between poor health (near death) and reasonably good health, a better quality of life. It is also very important to differentiate between the category of patients with severe heart failure, which causes functional impotence, NYHA class, III-IV, but which respond to aggressive treatment, and those who have reached a degree of intractable heart failure. It is important that physicians and medical staff not to treat these patients as "end stage cancer patients".

A number of questions remain. Can we involve a very sick patient or rather can he or she make an informed and correct decision as to the treatment of his illness, for example, inotropic medication, diuretics, which can improve symptoms but increase the risk of sudden cardiac death? At what point does "extended life" turn into "prolonged death"? What medication can be used safely to alleviate symptoms versus medication which may be interrupted?

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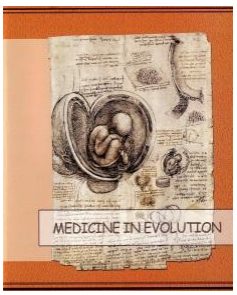
Correlations between the urodynamic findings of detrusor instability and several urinary symptom questionnaires in female patients with mixed urinary incontinence



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Abstract

Aim: The main objective of our study was to elaborate a new questionnaire for the diagnosis of mixed urinary incontinence, composed of the most relevant questions of several already established questionnaires for stress/urge urinary incontinence and overactive bladder, which were selected based on a statistical model of urodynamic detrusor instability, followed by urinary leakage.

Material and methods: We have selected a group of female patients with mixed urinary incontinence, referred to our outpatient Department, between 01 January 2014 and 31 December 2014. All the patients have completed seven validated questionnaires, and underwent a filling cystometry. Statistical correlations were calculated between the previously defined urodynamic parameter of detrusor instability, and each question of the chosen questionnaires.

Results: A total number of 30 patients have been included in our study. After the completion of the urodynamic testing, nine patients (30%) presented uninhibited detrusor contractions, followed by urine loss. An additional number of five patients had associated symptoms suggestive of overactive bladder syndrome. We have analyzed each question from the seven questionnaires, and we have found that 14 questions had a very good correlation with detrusor instability, making them good candidates for inclusion in a new questionnaire.

Conclusions: Our research has confirmed the potential value of a new questionnaire in establishing the diagnosis of mixed incontinence in female patients. The future validation of such a questionnaire will lead to the reduced use of urodynamic tests, diminishing the diagnostic costs and increasing patients' quality of life.

Key Words: mixed urinary incontinence, detrusor instability, urodynamic testing

INTRODUCTION

Mixed urinary incontinence (MUI) is defined by the International Continence Society as "the involuntary loss of urine associated with urgent urination, but also to physical effort, sneezing or coughing" [1]. MUI is a condition with high prevalence – up to one third of the females diagnosed with urinary incontinence present mixed symptoms [2]. These patients have a significantly lower quality of life, compared with those with stress urinary incontinence or urge urinary incontinence alone [3]. The correct diagnosis of MUI is very important, since these patients usually have no significant symptom improvement after the surgical correction of the stress urinary incontinence component [4].

Objective

Taking into account the fact that a diagnosis of mixed urinary incontinence is actually very difficult to establish in the absence of urodynamic testing, the elaboration of a new questionnaire for symptom evaluation is very useful, reducing significantly the duration of the diagnostic process and the related costs.

The main objective of this study is to elaborate a new questionnaire for the diagnosis of mixed urinary incontinence, composed of the relevant questions of several already established questionnaires for stress/urge urinary incontinence and overactive bladder, basing on statistical model of urodynamic detrusor instability, followed by urinary leakage.

MATERIAL AND METHODS

Patient selection

In order to start our research, we have selected a group of female patients with mixed urinary incontinence, which were referred from the Outpatient Urology Department of the Timisoara Clinical Emergency County Hospital, between 01 January 2014 and 31 December 2014.

The selected patients have fulfilled the following **inclusion criteria**:

- Female patients;
- Age less than 70 years;
- Stress incontinence clinically diagnosed at the moment of the current evaluation (by provoked cough test);
- Symptoms suggestive for urgency incontinence or hyperactive bladder.

Subsequently, we have defined the following **exclusion criteria**:

- Genital prolapse (second degree, or more);
- Post-void residual volume > 100 mL;
- Bladder outlet obstruction;
- History of acute urinary retention;
- Active urinary tract infection;
- Insterstitial cystitis;
- Major anomalies of the urinary tract;
- Significant polyuria
- Neurological disease with low urinary tract symptoms;
- Peripheral neuropathy;
- Severe cardiovascular disease
- Diabetes mellitus;
- Diabetic neuropathy;
- History of surgery of the lower abdomen/pelvic area;

Recent therapy with alpha-blockers, antimuscarinics, antidepressants.

Study design

After the application of the above mentioned inclusion and exclusion criteria, the patients were informed about our research and have signed an informed consent form, in accordance with the international norms of good clinical practice (ICH-GCP). Thereafter, the patients have completed seven validated questionnaires, which were considered the most significant for the evaluation of stress urinary incontinence, urge urinary incontinence, and overactive bladder. We have selected and used the following questionnaires, translated into Romanian:

a. The Hunskaar Severity Index [5];
b. The MESA Questionnaire;
c. The Female Incontinence Questionnaire;
d. The PISQ-12 Questionnaire [6];
e. The ContiLife Questionnaire [7];
f. The Urinary Symptom Questionnaire;
g. The OAB-Q SF Questionnaire [8].

At the end of our evaluation, all the patients underwent a filling cystometry. In order to evaluate the whole range of questions we have established an urodynamic parameter of detrusor instability, which was defined by the following: at least one uninhibited detrusor contraction (with an amplitude of at least 15 mm H2O), followed immediately by an episode of urinary incontinence, during the urodynamic testing (filling cystometry with pressure-flow study), at a bladder filling of maximum 300 ml.

Statistical analysis

After the completion of the questionnaires, followed by the urodynamic tests, all the obtained data was entered in a computerized database and statistically analyzed. We have used the advanced statistical analysis pack included in the Microsoft Excel 2013 Professional software application. The preferred method of analysis was linear regression: the correlation was done between the urodynamic parameter of detrusor instability previously defined (having a 0 value for the absence and a 1 value for the presence of detrusor instability), and each question of the chosen questionnaires, with a variable range of values.

We have calculated the **coefficient of determination (R^2)**, which is considered a good evaluation method for the degree of correlation between two independent variables, and **the adjusted R^2 coefficient**, which indicates the predictive value of the studied dataset.

RESULTS

In the mentioned 1-year time interval we have consulted 98 female patients with different degrees of stress urinary incontinence. We have applied the inclusion and exclusion criteria on this group and 44 patients were considered for further evaluation. Of these 44 patients, a number of 30 patients have agreed to participate to the study, signing the informed consent form, completing the questionnaires and finally undergoing the urodynamic testing.

The demographic data of the 30 patients are presented in Table 1.

Table 1. Demographic data

Number of patients	30
Average age	53.4 years (38-69)
Education level	
- High School	4
- College	17
- University	9
Marital status	
- Married	18
- Not married/Widow	12

After the completion of the urodynamic testing, we have established that nine patients (30%) presented also features specific for detrusor instability, having during the cystometry at least one episode of uninhibited detrusor contraction, followed by urine loss. Maximum cystometric capacity in these patients had an average value of 140 ml, while in the other patients it was 285 ml ($P < 0.001$).

From the group of 21 patients without urodynamic features of detrusor instability, an additional number of five patients had associated symptoms suggestive of overactive bladder syndrome.

According to the methodology previously presented, we have analyzed each question from the seven questionnaires. The results are presented in Tables 2 – 8.

Table 2. Statistical evaluation of the questions from the Hunskaar Severity Index

Question No.	R^2	Adj. R^2	Correlation
1. How often do you experience urinary leakage?	0.57	0.54	Good
2. How much urine do you lose every time?	0.55	0.51	Good
3. Did you bring your bladder symptoms to the attention of your clinician?	0.50	0.47	Poor
4. Have you received treatment for your bladder symptoms?	0.52	0.49	Poor

Table 3. Statistical evaluation of the questions from the MESA Questionnaire

Question No.	R^2	Adj. R^2	Correlation
1. Does coughing gently cause you to lose urine?	0.57	0.54	Good
2. Does coughing hard cause you to lose urine?	0.51	0.48	Poor
3. Does sneezing cause you to lose urine?	0.52	0.48	Poor
4. Does lifting cause you to lose urine?	0.51	0.47	Poor
5. Does bending cause you to lose urine?	0.53	0.50	Poor
6. Does laughing cause you to lose urine?	0.58	0.54	Good
7. Does walking briskly/jogging cause you to lose urine?	0.53	0.50	Poor
8. Does straining when constipated cause you to lose urine?	0.59	0.55	Good
9. Does getting up from sitting cause you to lose urine?	0.58	0.54	Good
10. How often do you lose urine with little/no warning?	**0.63**	**0.59**	**Very good**
11. How often do you lose urine before you reach toilet?	**0.65**	**0.62**	**Very good**
12. Do you lose urine when you suddenly feel your bladder full?	**0.61**	**0.57**	**Very good**
13. Does washing your hands cause you to lose urine?	**0.61**	**0.58**	**Very good**
14. Does cold weather cause you to lose urine?	0.57	0.54	Good
15. Does drinking cold beverages cause you to lose urine?	0.53	0.50	Poor

Table 4. Statistical evaluation of the questions from the Female Incontinence Questionnaire

Question No.	R^2	Adj. R^2	Correlation
1. Do you have leakage with coughing or sneezing?	0.53	0.50	Poor
2. Do you have leakage with lifting?	0.53	0.50	Poor
3. Do you have leakage with active exercise?	0.51	0.48	Poor
4. Do you have leakage with minimal exercise?	0.53	0.50	Poor
5. Do you have leakage with sleeping?	0.56	0.53	Good
6. Do you have leakage with nervousness or increased anxiety?	**0.61**	**0.58**	**Very good**
7. Do you have leakage unrelated with any cause?	0.59	0.55	Good
8. Is your clothing damp, wet, or soaking wet?	0.52	0.49	Poor
9. For protection do you use pads, tissue, or diapers?	0.57	0.54	Good
10. How many protective pads do you use per day?	0.53	0.50	Poor
11. Are the damp, wet, or saturated at each change?	0.53	0.50	Poor
12. Do you leave puddles of urine on the floor?	0.51	0.47	Poor
13. Do you lose urine by continuous dribbling?	0.52	0,49	Poor
14. Do you lose urine in small spurts?	0.50	0.47	Poor
15. If yes, is related to physical activity?	0.52	0.48	Poor
16. When you have desire to urinate, do you lose urine before	**0.64**	**0.61**	**Very good**

Question No.	R^2	Adj. R^2	Correlation
getting to the toilet?			
17. Do you get a severe urge in the cold weather?	0.58	0.55	Good
18. Do you get a severe urge with running water?	0.59	0.56	Good
19. Do you get a severe urge at the front door of your house/restroom?	0.56	0.52	Good
20. Do you have bladder pain when you have a strong urge to urinate?	0.55	0.51	Good
21. How often do you pass urine during the day?	**0.63**	**0.60**	**Very good**
22. How often do you pass urine after going to bed?	0.56	0.52	Good
23. Is the volume of urine you pass usually large, average, or small?	0.58	0.54	Good
24. Do you empty your bladder frequently, before you have the desire to pass urine, just to remain dry?	0.58	0.55	Good

Table 5. Statistical evaluation of the questions from the PISQ-12 Questionnaire

Question No.	R^2	Adj. R^2	Correlation
1. How frequently do you have sexual desire?	0.44	0.41	Poor
2. Do you climax when having sexual intercourse with your partner?	0.39	0.35	Poor
3. Do you feel sexually excited when having sexual activity?	0.43	0.39	Poor
4. How satisfied are you with the variety of sexual activities?	0.44	0.40	Poor
5. Do you feel pain during sexual intercourse?	0.53	0.50	Good
6. Do you leak urine with sexual activity?	**0.61**	**0.58**	**Very good**
7. Does fear of incontinence restrict your sexual activity?	0.57	0.54	Good
8. Do you avoid sexual intercourse because of bulging in the vagina?	0.54	0.51	Good
9. Do you have negative emotions when you have sex with your partner?	0.51	0.47	Poor
10. Does your partner have an erection problem affecting your sexual activity?	0.42	0.39	Poor
11. Does your partner have a problem with premature ejaculation affecting your sexual activity?	0.40	0.37	Poor
12. How intense are the orgasms you have had in the past six months?	0.47	0.44	Poor

Table 6. Statistical evaluation of the questions from the ContiLife Questionnaire

Question No.	R^2	Adj. R^2	Correlation
1. Do your urinary problems bother you when you are away from home?	0.53	0.49	Poor
2. Do your urinary problems bother you when you are driving?	0.50	0.47	Poor
3. Do your urinary problems bother you when going up/down stairs?	0.53	0.50	Poor
4. Do your urinary problems bother you when shopping?	0.51	0.48	Poor
5. Do your urinary problems bother you when waiting/queuing?	0.50	0,47	Poor
6. Do you take frequent breaks for urinary problems?	**0.61**	**0.57**	**Very good**
7. How often have you woken up having wet yourself?	0.58	0.55	Good
8. Do your urinary problems bother you when lifting heavy objects?	0.53	0.49	Poor
9. Do your urinary problems bother you when doing sport?	0.53	0.50	Poor
10. Do your urinary problems bother you when sneezing/coughing?	0.53	0.50	Poor
11. Do your urinary problems bother you when laughing?	0.55	0.51	Good
12. How often have you felt less attractive due to your urinary problems?	0.48	0.45	Poor
13. How often were you afraid of giving off an unpleasant odor?	0.52	0.49	Poor
14. How often were you afraid that others are aware of your	0.53	0.50	Poor

Question No.	R^2	Adj. R^2	Correlation
problems?			
15. How often were you afraid of leaving stains?	0.51	0.48	Poor
16. How often did you have to change your clothes?	0.53	0.50	Poor
17. How often have you felt good in spite of your urinary problems?	0.44	0.40	Poor
18. Have you been bothered by having to wear pads?	0.58	0.55	Good
19. How often have you felt discouraged due to your urinary problems?	0.51	0.47	Poor
20. How often have you lost patience due to your urinary problems?	0.51	0.48	Poor
21. How often have you been warried by a possible urinary accident?	0.53	0.50	Poor
22. How often have you had the feeling of not being able to control?	0.48	0.45	Poor
23. How often have you felt obsessed by your urinary problem?	0.51	0.47	Poor
24. How often did you think about taking pads with you before going out?	0.57	0.54	Good
25. How much have you felt anxious of having sexual intercourse?	0.52	0.49	Poor
26. How much have you changed your sexual practices?	0.48	0.44	Poor
27. How much have you been afraid of urinary leaks while having sex?	0.53	0.50	Poor
28. How would you assess your quality of life?	0.53	0.49	Poor

Table 7. Statistical evaluation of the questions from the Urinary Symptom Questionnaire

Question No.	R^2	Adj. R^2	Correlation
1. Frequent urination during the daytime hours is bothering you?	0.53	0.50	Poor
2. An uncomfortable urge to urinate is bothering you?	0.58	0.55	Good
3. A sudden urge to urinate with no warning is bothering you?	0.59	0.55	Good
4. Accidental loss of small amounts of urine is bothering you?	0.56	0.52	Good
5. Frequent urination in the evening is bothering you?	0.49	0.46	Poor
6. Waking up from sleep to urinate is bothering you?	0.53	0.49	Poor
7. An uncontrollable urge to urinate is bothering you?	0.59	0.55	Good
8. Urine loss with a strong desire to urinate is bothering you?	**0.63**	**0.60**	**Very good**
9. Urine loss associated with physical activities is bothering you?	0.51	0.48	Poor
10. Urine loss assoc. with sneezing/coughing is bothering you?	0.53	0.50	Poor
11. Feeling you are unable to empty you bladder is bothering you?	0.47	0.44	Poor
12. If you were to spend the rest of your life with your urinary condition how would you feel about that?	0.58	0.55	Good

Table 8. Statistical evaluation of the questions from the OAB-Q SF Questionnaire

Questions	R^2	Adj. R^2	Correlation
OAB-Q SF - Part 1. During the past 4 weeks, how bothered were you by:			
1. An uncomfortable urge to urinate?	0.57	0.54	Good
2. A sudden urge to urinate with little/no warning?	0.54	0.51	Good
3. Accidental loss of small amounts of urine?	0.50	0.47	Poor
4. Nighttime urination?	0.53	0.50	Poor
5. Waking up at night because you had to urinate:	0.52	0.48	Poor
6. Urine loss associated with a strong desire to urinate?	**0.66**	**0.63**	**Very good**
OAB-Q SF - Part 2. During the past 4 weeks, how often have your bladder symptoms:			
1. Caused you to plan escape routes to toilets in public places?	0.58	0.55	Good
2. Made you feel like there is something wrong with you?	0.58	0.55	Good
3. Interfered with your ability to get a good night's rest?	0.57	0.54	Good
4. Made you frustrated about the amount of time spent in the toilet?	0.53	0.50	Poor
5. Made you avoid activities away from toilets?	**0.61**	**0.57**	**Very good**

Questions	R^2	Adj. R^2	Correlation
6. Awakened you during sleep?	0.57	0.54	Good
7. Caused you to reduce your physical activities?	**0.61**	**0.57**	**Very good**
8. Caused you to have problems with your partner/spouse?	0.52	0.49	Poor
9. Made you uncomfortable while travelling due to the need to stop to go to the toilet?	0.56	0.52	Good
10. Affected your relationships with family and friends?	0.53	0.49	Poor
11. Interfered with getting the amount of sleep you needed?	0.57	0.53	Good
12. Caused you embarrassment?	0.55	0.51	Good
13. Caused you to locate the closest toilet in a new place?	**0.60**	**0.57**	**Very good**

DISCUSSIONS

During our study we have established that 9 of the 30 patients with stress urinary incontinence had also urge incontinence, corresponding to the complete definition of mixed incontinence. The obtained percentage (of 30%) was in accordance with larger epidemiological studies, where the incidence of mixed incontinence was between 29% and 35% of all female patients with stress urinary incontinence [9, 10].

Moreover, during the analysis of the urodynamic recordings we have found an interesting difference: while in patients with stress urinary incontinence (alone) the average maximum cystometric capacity was 285 ml, in patients with mixed incontinence the average maximum cystometric capacity was 140 ml. This finding demonstrates once again the value of urodynamic testing, which preserves its consistency, even when applied on smaller patient populations [11, 12].

Regarding the main objective of our research, the reason for choosing the specific seven questionnaires was the fact that they have the largest number of validation studies at an international level, possessing the highest and most recognized discriminative capacity for urinary incontinence and overactive bladder syndrome.

The main limitation of our study is represented by the relatively small sample size, which has reduced the degree of statistical significance. This shortcoming was compensated by our idea of using the adjusted R^2 coefficient, which had a significant predictive value in thirteen of the questions from the chosen questionnaires, making them useful for further studies.

CONCLUSIONS

The analysis of the correlation between the urodynamic parameters specific to detrusor instability and the various related questions from several validated questionnaires has confirmed the potential value of a new questionnaire in establishing the diagnosis of mixed incontinence in patients with already diagnosed stress urinary incontinence.

The elaboration and future validation of such a comprehensive questionnaire, based on the most relevant items from other well-known questionnaires, will lead to the reduced use of urodynamic tests, diminishing the diagnostic costs and increasing patients' quality of life.

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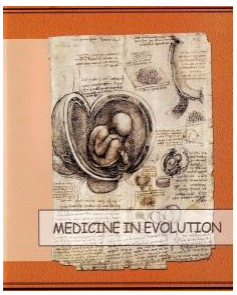
Role of kinetotherapy in treating musculoskeletal pain assessed by a questionnaire applied to dental medicine students



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Abstract

Aims and objectives: The study aimed to assess the influence of kinetotherapy on musculoskeletal pain in Dental Medicine students.

Material and method: 113 students responded to an assessment questionnaire (10 questions). Students were classified into 2 groups: group 1 (91 students) and group 2 (22 students who underwent at least one medical rehabilitation treatment during the previus year).

Results: Statistically significant lower values regarding the 9 questions (including the one on musculoskeletal pain during the previous month) were recorded in students who underwent a home-adjusted kinetotherapy programme (group 1) and in those who followed kinetotherapy as a part of a rehabilitation treatment (group 2). Students who underwent kinetotherapy as part of the medical rehabilitation exhibited a stronger correlation between the number of electrotherapy procedures and the number of painful anatomic regions.

Conclusions: Home-adjusted kinetotherapy contributes to a decrease in musculoskeletal pain symptoms. Kinetotherapy must be included into the complex medical rehabilitation even if pain related symptoms would only recommend antialgic treatments, as kinetotherapy allows an adequate treatment adjustment to present symptomatology thus leading to better results.

Keywords: students, questionnaire, musculoskeletal pain, kinetotherapy.

INTRODUCTION

The pain syndrome includes musculoskeletal pain, among other symptoms. Musculoskeletal pain exceeding 6 months is defined as chronic pain syndrome (1).

Musculoskeletal pain is still encountered in dentists, with prevalences between 64 and 93% cited by literature. Professional activities performed by dentists favour predisposition to vicious postures during seated or orthostatic positions together with repetitive movements which lead in their turn to articular and musculo-ligamentar disbalances. These disbalances lead to uneven strain upon musculo-ligamentar structures of the spine, as well as of the musculo-ligamentar structures, tendons and bursae of the upper limb. These uneven strains may contribute to musculoskeletal pain (2,3). Incorrect posture may contribute to spinal musculoskeletal pain, while repetitive movements may lead to pain of the upper limb (4). Psycho-social factors have a secondary role in the development of musculoskeletal pain (2).

The impact of musculoskeletal pain is complex. It has a physical effect with a significant decrease in life quality. At present, granting life quality represents an important objective in the therapeutic approach of a disease. A secondary effect is the decrease of work capacity with a consecutive decrease in productivity and even work incapacity in severe cases (1,2). Musculoskeletal pain is the most frequent reason for early retirement of dentists (5).

According to literature data, musculoskeletal pain may already occur in dental medicine students, percents between 46 and 71% being cited (6). These students are predisposed to articular and musculo-ligamentar disbalances due to the fact that their learning process includes practical activities performed by dentists. Considering the above mentioned aspects, studies on musculoskeletal pain are increasingly being conducted on dental medicine students (2).

The therapeutic approach of musculoskeletal pain includes hygiene and diet measures, medication and medical rehabilitation (1). Hygiene and diet measures include maintaining an adequate posture while sitting or standing, alternating seated with orthostatic postures and adequate adjustments and fine tuning of working equipments (5,7,8). Medication includes nonsteroidal antiinflammatory drugs and antialgic therapeutics. Medical rehabilitation includes electrotherapy, manual thyerapy, hydrothermal therapy and kinetotherapy. Electrotherapy includes low frequency currents (transcutaneous electrical nerve stimmulation - TENS, iontophoresis), medium frequency currents (interferential current) and high frequency currents (ultrasound, short waves). Manual therapy is represented by relaxation and profound transversal massage, while hydrothermal therapy consists of superficial thermal application. Kinetotherapy includes stretching, progressive muscle tonification and aerobic exercises (1,9). Home-adjusted kinetotherapy must include upper limb and neck stretching exercises, as well as exercises aiming to maintain muscle force (5,8).

MATERIAL AND METHODS

113 students responded to the assessment questionnaire presented in table 1.

Table 1. Assessment questionnaire

Question	1 point	2 points	3 points	4 points
1. For how long have you been working in a dental practice?	6-12 months	1-5 years	5-10 years	over 10 years
2. How much time do you work daily in the dental practice ?	Less than 4 hours	4-6 hours	6-8 hours	over 8 hours
3. During the last month, have you experienced dorsal musculoskeletal pain (spinal, muscle pain) or upper limb pain (shoulder, elbow, fist, hand)?	Absence of pain	Mild pain	Medium pain	Intense pain

Question	1 point	2 points	3 points	4 points
4. During the last month, how many hours a day did your back or upper limb musculoskeletal pain last ?	1-2 hours	2-6 hours	6-12 hours	All day long
5. During the last month, after how many hours of work did your back or upper limb musculoskeletal pain start?	After over 8 hours	After 4-8 hours	After 1-4 hours	Immediately after starting the professional activity
6. During the last month, have you experienced difficulties when manipulating medical instruments (caused by musculoskeletal pain) while performing daily professional procedures?	No difficulties	Mild difficulty	Medium difficulty	Intense difficulty
7. During the last month, did you need medication (antialgic, antiinflammatory) to alleviate your musculoskeletal pain?	No	Occasionally (1-2 days)	3-5 days	More than 7 days
8. During the last month, on how many days did you need to take unscheduled pauses as a consequence of musculoskeletal pain?	None	Occasionally (1-2 days)	3-5 days	On more than 7 days
9. During the last 12 months, did you seek specialized medical rehabilitation advice due to musculoskeletal symptoms?	No	1 visit	2-3 visits	≥ 4 visits
10. During the last 12 months, how many work incapacity days caused by musculoskeletal problems did you experinece?	None	1-7 days	7-14 days	More than 14 days

Studetnts who were not examined by a medical rehabilitation specialist were included in group 1 (91 students). An additional question on a home-adjusted medical rehabilitation programme was formulated. Fiftysix students underwent a home-adjusted kinetotherapy programme and 35 students did not.

Group 2 (22 students) included students who were examined within the previous 12 months by a medical rehabilitation specialist, these students being treated according to 2 therapeutic regimens. Ten students received therapy including medication, electrotherapy, massage, and hydrothermal therapy. Twelve students received therapy including medication, electrotherapy, massage, hydrothermal therapy and kinetotherapy. In group 2 there were 2 additional questions regarding the number of painful anatomic regions (spinal cord, shoulder, elbow, fist or hand) and regarding the number of electrotherapy procedures recommended as part of the therapeutic regimen.

The differences between the groups were represented by the presence or absence of a home-adjusted kinetotherapy programme (group 1) and by the presence or absence of kinetotherapy in the medical rehabilitation programme (group 2).

For the statistical analysis we used descriptive statistics (mean, standard deviation), confidence interval (95%), the nonparametric Wilcoxon rank-sum test and linear correlation using the Pearson linear correlation coefficient. The level of statistical significance was set at $p<0.05$ (10).

RESULTS

Table 2. Descriptive statistics for the 2 groups

Question	Group	Mean	SD	CI [95%]
1	1	1.758242	0.5236763	(1.649181 – 1.867703)
	2	1.681818	0.5679004	(1.430025 – 1.933611)
2	1	1.725275	0.7610801	(1.566772 – 1.88377)
	2	1.772727	0.6119304	(1.501413 – 2.044042)
3	1	2.087912	0.6773863	(1.94684 – 2.228985)

Question	Group	Mean	SD	CI [95%]
	2	2.136364	0.8888438	(1.742272 – 2.530455)
4	1	1.252747	0.5694716	(1.134149 – 1.371345)
	2	1.772727	1.151885	(1.26201 – 2.283445)
5	1	2.032967	0.8226049	(1.861651 – 2.204283)
	2	2.090909	0.6837635	(1.787745 – 2.394073)
6	1	1.186813	0.3919209	(1.105192 – 1.268435)
	2	1.590909	0.7963662	(1.23782 – 1.943998)
7	1	1.175824	0.3827795	(1.096106 – 1.255542)
	2	2.318182	1.249242	(1.764299 – 2.872065)
8	1	1.186813	0.4693278	(1.089071 – 1.284555)
	2	1.909091	0.9211324	(1.500684 – 2.317498)
9	2	2.454545	0.6709817	(2.157049 – 2.752042)
10	1	1.065934	0.2495417	(1.013964 – 1.117904)
	2	1.454545	0.5096472	(1.228581 – 1.68051)

(SD – standard deviation, CI – confidence interval)

Table 3. Influence of kinetotherapy over musculoskeletal pain

		Question 3	Question 4	Question 5
		Mean (SD)	Mean (SD)	Mean (SD)
Home-adjusted kinetotherapy programme (Group 1)	absent (35 students)	2.285714 (0.6217352)	1.485714 (0.7810788)	2.171429 (0.7853704)
	present (56 students)	1.964286 (0.6866066)	1.107143 (0.3120939)	1.946429 (0.8403385)
Wilcoxon rank-sum test		p=0.0289	p=0.0022	p=0.1804
		Question 3	Question 4	Question 5
		Mean (SD)	Mean (SD)	Mean (SD)
Kinetotherapy as part of the rehabilitation treatment (Group 2)	absent (10 students)	2.6 (0.6992059)	2.4 (1.173788)	2.1 (0.3162278)
	present (12 students)	1.75 (0.8660254)	1.25 (0.8660254)	2.083333 (0.9003366)
Wilcoxon rank-sum test		p=0.0254	p=0.0081	p=0.7490

Table 4. Influence of kinetotherapy on the following: difficulty to manipulate medical instruments, need for medication, need to take unscheduled breaks and work incapacity, respectively

		Question 6	Question 7	Question 8	Question 10
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Home-adjusted kinetotherapy programme (Group 1)	absent (35 students)	1.314286 (0.4710082)	1.285714 (0.4583492)	1.371429 (0.6456057)	1.142857 (0.3550358)
	present (56 students)	1.107143 (0.3120939)	1.107143 (0.3120939)	1.071429 (0.2598701)	1.017857 (0.1336306)
Wilcoxon rank-sum test		p=0.0142	p=0.0304	p=0.0023	p=0.0201
		Question 6	Question 7	Question 8	Question 10
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Home-adjusted kinetotherapy programme (Group2)	absent (10 students)	2 (0.942809)	2.9 (1.197219)	2.4 (1.074968)	1.7 (0.4830459)
	present (12 students)	1.25 (0.452267)	1.833333 (1.114641)	1.5 (0.522233)	1.25 (0.452267)
Wilcoxon rank-sum test		p=0.0435	p=0.0359	p=0.0327	p=0.0392

Students in group 2 had more pronounced symptoms with higher values recorded for the musculoskeletal pain during the last month (question 3) and for the duration of musculoskeletal pain during the last month (question 4). More intense symptoms led to higher levels of the following: difficulty to manipulate medical instruments during the last month (question 6), need for medication during the last month (question 7), need for unscheduled breaks during the last month (question 8) and work incapacity during the last 12 months (question 10) (Table 2).

Comparisons made depending on the presence or absence of a home-adjusted kinetotherapy programme and on the inclusion of kinetotherapy in the medical rehabilitation programme showed important results.

In the case of students who underwent a home-adjusted kinetotherapy programme (group 1) or in the case of those who also received kinetotherapy as part of their medical rehabilitation treatment (group 2) statistically significant lower values were recorded for: musculoskeletal pain during the last month (question 3), duration of musculoskeletal pain during the last month (question 4), difficulties in manipulating medical instruments during the last month (question 6), need for medication during the last month (question 7), need for unscheduled breaks during the last month (question 8) and work incapacity during the last 12 months (question 10) (Tables 3 and 4).

The home-adjusted kinetotherapy programme and inclusion of kinetotherapy in the medical rehabilitation treatment did not determin statistically significant lower values regarding the period after which musculoskeletal pain occurred during the last month (question 5) (Table 3).

Table 5. Correlations between of number of electrotherapy procedures – number of painful anatomic regions and musculoskeletal pain – number of painful anatomic regions

		Number of painful anatomic regions	Pearson correlation coefficient	Number of painful anatomic regions
		Mean (SD)		
Kinetotherapy included in the medical rehabilitation treatment (Group 2)	absent (10 students)	2.3 (0.6749486)	Musculoskeletal pain	0.7534 (p=0.0119)
			Number of electrotherapy procedures	0.7014 (p=0.0238)
	present (12 students)	2 (0.7385489)	Musculoskeletal pain	0.7107 (p=0.0096)
			Number of electrotherapy procedures	0.8846 (p=0.0001)
		t test – p=0.3359		

Important results were revealed by the study of the number of painful anatomic regions and the study on the number of electrotherapy procedures applied in group 2. We did not record a statistically significant difference in the number of electrotherapy procedures in the case of students who did not undergo kinetotherapy as part of their medical rehabilitation treatment as compared to those who did receive kinetotherapy (p=0.3359). This result allowed the presentation of comparative results. The correlation between musculoskeletal pain (question 3) and the number of painful anatomic regions was approximately equal and statistically significant in the case of those who did not receive kinetotherapy (r=0.7534), as well as for those who did have kinetotherapy included in their therapeutic regimen (r=0.7107). The correlation between the number of electrotherapeutic procedures and the number of painful anatomic regions was significant and higher in the case of those who underwent kinetotherapy (r=0.8846) as compared to those who did not (r=0.7014). (Table 5).

DISCUSSIONS

The importance of home-adjusted kinetotherapy was revealed by statistically significant lower values of musculoskeletal pain experienced during the last month in students who underwent such a programme. Statistically significant lower values of musculoskeletal pain duning the last month were also recorded in students who received medical rehabilitation treatment including kinetotherapy. This result reveals the importance of kinetotherapy in medical rehabilitation treatments even if the more pronounced algic symptoms in group 2 would have only required antialgic treatment (medication, electrotherapy, massage, hydrothermal therapy).

The home-adjusted kinetotherapy programme plays an important role as students who followed such a programme had statistically significant lower values regarding the duration of musculoskeletal pain during the last month, as well as of the difficulty in manipulating medical instruments, requirements of medication during the last month, need for unscheduled breaks during the last month and work incapacity during the last 12 months, respectively. Statistically significant lower values were also obtained in students who underwent medical rehabilitation treatments which included kinetotherapy, thus demonstrating its beneficial role. Statistically significant differences were lower in group 2 as compared to group 1 because p values were higher in group 2 as compared to group 1 and algic symtoms were more pronounced in group 2 as compared to group 1. Specialized examinations were required due to more severe pain symtoms.

The degree of algic symptoms is correlated to the number of painful anatomic regions. A higher correlation between the number of electrotherapy procedures and the number of painful anatomic regions was interpreted as an adequate number of electrotherapy sessions reported to the number of painful anatomic regions, this higher correlation being found in students who also received kinetotherapy as part of their medical rehabilitation treatment. A lower correlation corresponded to a higher number of electrotherapy procedures reported to the number of painful anatomic regions.

Addressing musculoskeletal pain only in dentists would lead to a delayed implementation of prophylactic measures through the home-adjusted kinetotherapy programme. Any delay increases the risk of chronic musculoskeletal pain. Due to this fact, approaching dental medicine students proves to be useful. This statement is supported by the results of the present study.

CONCLUSIONS

The activity of Dental Medicine students combines didactic and practical activities in a dental practice. Practical activity is oriented according to the professional activity after graduation. Musculoskeletal pain linked to practical activities remains an element requiring increased attention.

The home-adjusted kinetotherapy programme contributes to a decrease of algic symptoms both quantitatively and qualitatively, as well as to an increased performance of professional activities in the dental practice.

The periodical presentation of the home-adjusted kinetotherapy programme leads to its increased implementation. This contributes to an increase in life quality by its effect on professional activities.

Specialized medical advice may be needed in cases with pronounced algic symptoms. Kinetotherapy must be included into the complex medical rehabilitation treatment even if algic symptoms would only recommend antialgic treatment. Kinetotherapy allows the achievement of a better correlation between the number of electrotherapy procedures and the number of painful anatomic regions, this signifying a correct adjustment of treatment to the symptoms with better final results.

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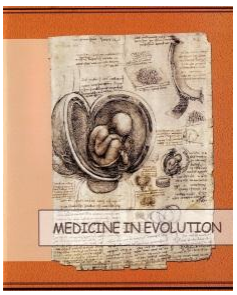
Cutaneous malignant melanoma: subtle histopathological diagnosis in a 16 years old male



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Abstract

Cutaneous malignant melanoma is rare finding in children. In this case report we present the case of a malignant melanoma surgically removed in the Department of Pediatric Surgery of the Pediatrics Hospital of Piteşti and diagnosed in the Department of Pathology of the same hospital using conventional histopathological techniques. The diagnosis of CMM is very tricky in pediatric pathology especially influenced by the oncologic protocols that apply in this kind of disease.

Keywords: melanoma, childhood, paediatric, spitzoid melanoma, proliferative nodule, adolescent

INTRODUCTION

Cutaneous malignant melanoma (CMM) is a proliferation of melanocytes that is malignant in nature; these cells are found mainly inside the structure of the epidermis but also in different structures of the eye and other parts of the human organism, thus, being considered one of the most aggressive cancers investigated today. The melanocytes are responsible for skin, iris and hair color. The term pediatric encompasses the group of patients aged less than 18 years at diagnosis. Thus, the term 'pediatric melanoma' becomes a most heterogeneous group of lesions from which we present the case of a CMM. The incidence have doubled over the past 30 years, with estimated 73,870 cases in 2015. It seems that sunburns during childhood would significantly increase the risk. Between 55 and 72% of all children are sunburned. Regarding altered gene inheritance, the melanoma survivors children risk are at twofold or higher, regardless of their later sunburn protection and other UV screen methods. Data collected from the Carlifornia Cancer Registry regarding melanoma surviving mothers, reported that 43 % of their children sufferd from sunburns [1]. The United States National cancer Institute for Surveillance, Epidemiology and End Results database (SEER) incidence for annual melanoma was 5.4 per 1 million children and adolescents in the U.S. Therefore, below 10 years of age, the annual incidence was 1.1 per 1 milion (95% CI, 0,3-1,8), while in older children – 10 years and more – it became 10 cases per 1 milion (95% CI, 7,6 – 12.5). Although the numbers remain small, the overall melanoma incidence among patients younger than 20 years old increased with 50%, during long period follow up studies [2]. Indoor tanning for adolescent children may become an important risk factor for CMM, especially those methods using UVA and UVB. In many countries, parental consent is necessary for indoor tanning procedures, promotion of eye protection and to limit the intensity of UVA electron radiation. These guidelines have been purposed and adopted by the World Government – World Health Organization. In the US, a particular law has been adopted regarding the indoor tanning for children [3]. Also, clothing may reduce or increase the incidence for CMM. Thus, in Hungary, a study revealed that children wearing T-shirts may increase the risk, while a large hat in sunny days reduces it. Due to the CMM risk, it has been observed that the vast majority of pediatric patients may be categorized either in behavioral risk – not using sun-screen, T-shirt, hat and sunglasses – or constitutional risk children – fair skin, eyes, hair color, presence of freckles and naevi [4].

CASE REPORT

Anamnesis

A 16 years old male presented with a nevus on the frontal region to the pediatric surgical department from our hospital for closer medical inspection and resection. The family states that the lesion appeared "de nuovo", in one year duration, on the scalp, with recurrent bleeding from it.

Clinical examination data

The surgical specimen was sent to our laboratory as a rhomboidal shaped tissue, with its diameters 2,1/1 cm having a elevated, ovoid lesion, with 0,4/0,6/0,7 cm, consistently brown with pin-point areas coloured blue to violet, with a net contour and elastic consistency (figure 1).

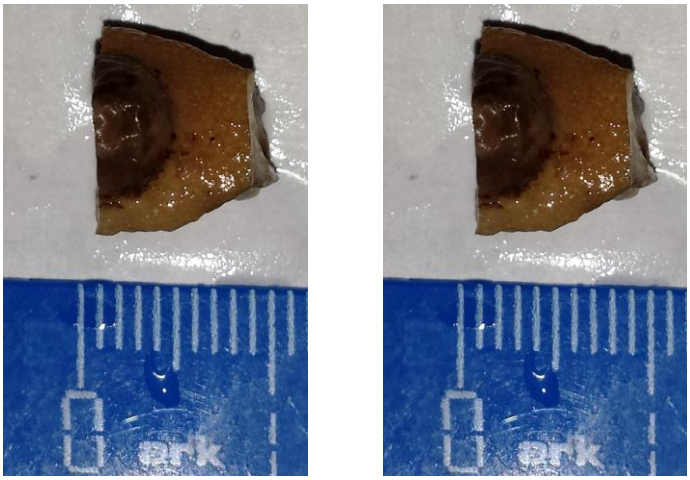

Figure 1. Sectional aspect of the excised and fixed specimen from the 16 years old boy. A brown, expansile lesion with bluish areas is visible, having a net contour and firm-elastic consistence (10% buffered formalin)

Laboratory data

The routine blood samples and laboratory analysis proved no deviation from normal. Furthermore, all clinical and paraclinical tests were normal, with no detectable nor palpable lymph ganglia.

Aditional paraclinical investigations

The samples of tissue were fixed with 10% buffered formalin and processed trough histological conventional methods: successive baths in 70 and 80, with other three baths of 96 degrees alcohol. Further dehydration in izopropylic alcohol was performed, in order to preserve imunohistochemical epitopes and antigens [5]. After tissue processing, paraffin embedding and haematoxilin and eosin staining, at first sight, it looked like a lentiginous melanic lesion, however, at closer examination (40x), the basal layer proved the presence of melanocytes with obvious cytological atypia: nuclear grooves, conspicuous nucleoli, condensed chromatin, and cytoplasmic elongations with rare atypical mitoses (less than 4 mitoses per high power field – 40x) together with a tendency of pagetoid spread (figure 3). The intercurrent epidermal basal layer remained intact. Furthermore, the dermis looked very fibrotic, with scant, adnexial vicinity non-specific inflammatory infiltrate and scattered cells with vesicular nuclei and conspicuous nucleoli, interspersed within the fibrotic strands of dermis. Actinic fibrosis is visible, in all sections. In some areas, there could be visible metastatic intravascular malignant melanocytes inside the upper dermis (figure 4). The hypoderm was fibrotic with no obvious invasion. The largest extent of the invasion was 6.8 mm in depth, with a 3rd degree Clark level, as the lesion appears in an elevated nevus. The final diagnosis was that of a *dysplastic nevus with areas of desmoplastic and superficial spreading cutaneous malignant melanoma* (figure 2).

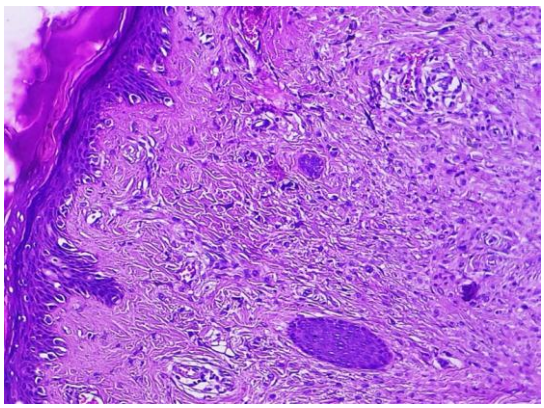

Figure 2. Malignant melanocytic cells inside the dermis and basal layer of the epidermis; HE 40x

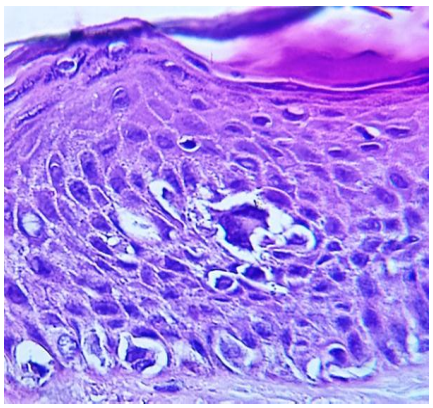

Figure 3. Pleomorphic melanocytic cells with variable nuclear shape and mitotic activity; HE 100x

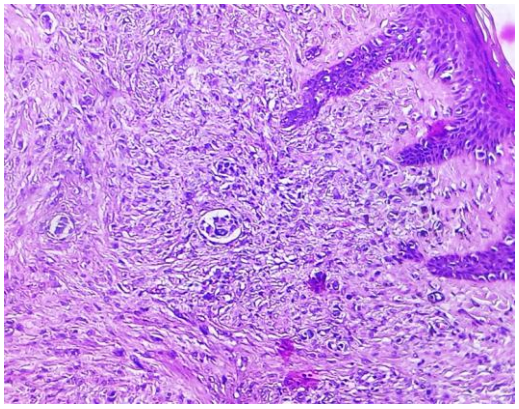

Figure 4. Diffuse appearance of tumor cells in skin melanoma, with vascular invasion; HE 100x

Treatment and evolution

The child was reffered to the regional oncological department of Arges county, for further investigations and applied chemotherapy protocols.

DISCUSSIONS

The desmoplastic CMM is a rare entity in children. The differential diagnosis between proliferative nodule and melanoma arising within the dermal component of a CMM could be very challenging. In adolescents and in certain adults, pathology suspicion is raised when atypical junction melanocytic proliferation is observed. Proliferative nodules within CMM in children clinically present as a distinct brown, pink or black papules or macules [6]. The typical histology of nodular CMM is represented by spindled or epitheliod cells with scant or no mitotic activity. This could be interpreted as "atypical proliferative nodule": sharp demarcation, expansile growth, epidermal effacement, mucinosis, and pagetoid spread [6]. Necrosis might become a worrisome lesion, in all melanocitic tumors arising in sun-exposed skin of children, especially regarding naevi. A diagnosis of pediatric CMM stands on solid grounds when there is a detectable combination between a high mitotic count (i.e, more than 5 pe mm^2) necrosis, ulceration, and expansile/destructive tumor for patients outside the neonatal group [7]. Spitzoid CMM might be differentiated from other forms of CMM due to uniform epidermal hyperplasia, symmetrical silhouette and dispersal and maturation with descent into the epidermis. However, spitzoid CMM are difficult to diagnose on conventional stains, but some lesions prove HAS1 and BAP1 molecular abnormalities [8]. Furthermore, after the age of 10, superficial spreading melanoma becomes an increasingly frequent diagnosis, representing one of the more common malignancies in young adolescents [9]. Immunohistochemical analys might be useful with dual MIB-1, Melan-A, p16, and HMB45 for

spitzoid lesions, while chromosomial lesion assessed with classical 4-probe FISH procedure might be somewhat of limited value. Deletions like 6q23 and 3p21 are associated with indolent outcome, while 9p21 have an adverse outcome with a poor prognosis [10]. Lesions of 'adult type' become increasingly frequent in the pubertal and post-pubertal years, with different prognostications between histological tumors in very young patients when compared with adolescent or young adult patients. A firm diagnosis of CMM should not be easily applied to an apparent atypical melanocytic lesion in any child younger than 10 years old. Such a lesion would be very difficult to revise later. Better understanding of histopathological, genetic and molecular abnormalities implicated in onset, progression and metastasis of CMM provides a great opportunity for further research of targeted therapy. New potentially therapeutic agents are currently being researched.

CONCLUSIONS

Conflict of interests

The authors declare no conflict of interests

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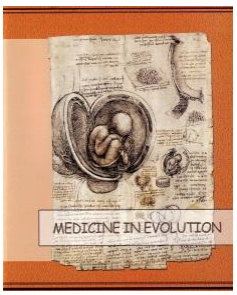
The silent burden of a population: chronic hepatitis C. General population screening



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Abstract

Aim and objectives: evaluating the epidemiology of hepatitis C in Romania by comparing few targeted and relevant studies conducted to date.

Material and methods: analytical study, descriptive, summarizing several relevant cross studies, conducted during 2004 – 2015, in order to obtain a meaningful ecological study. The data used in the article were identified by searching in medical databases (Medline, Medscape, Embase).

Results: the study on HCV genotyping revealed 97% prevalence of genotype 1 and subtype 1b 88.91%. In our study, we determined DALY, for Romania 604.16 DALYs per 100,000 population.

Conclusions: changing the protocol for inclusion in the treatment the patients prior by RFLP genotyping and inclusion without other prior treatments to treatment without interferon list. Primary prevention by population education programs, with the support of family physicians, infectious disease physicians, gastroenterologists, specific associations and foundations, under the coordination of all state authorities in these tasks.

Keywords: hepatitis C, mortality and DALY, prevalence, genotype

INTRODUCTION

Hepatitis C (HCV) is equally a ubiquitous disease, but also global. Global infection with hepatitis C virus (HCV) is about 170 million people, representing about 3% of world population [11].

From the diseases included in liver pathology, this disease starts to become, aggressive and silent, the main cause of death.

Between the complications of the disease, the most powerful is hepatic cirrhosis and hepatic cancer. According to estimates, it is expected that within two complications to grow for at least another two decades, and hepatitis C mortality increase from 56 377 cases in the period 1990 – 1999 to 283378 during 2020-2029 for the US [9].

From the sero-prevalence study conducted from 2006 to 2008, for persons with age from 18 to 69 years, resulted the prevalence of hepatitis C resulted in Romania was 3.23% [4].

The sero-epidemiological study of the prevalence of infection with hepatitis B virus (HBV) and hepatitis C (HCV), conducted by the National Institute of Public Health (INSP) in 2013, using a sample simple random, resulted in a proportion of people with Ac anti-HCV positive 5.6% [10].

As economic burden, from nationally data, collected in 2011, were settled by the DRG system a number of 4,658,463 admissions. 1.23% of hospitalized patients had a diagnosis of HCV primary or secondary [1].

As virological burden, most common genotype in Romania is 1 and subtype b, responsible for nosocomial transmission, disease aggressiveness, length of treatment, resistance to standard treatment, relapse and the emergence of hepatic cancer, data confirmed by comparative genotyping study conducted during 2004 to 2006, on a group of 103 patients chronically infected with HCV, where the prevalence of genotype 1 was 97% and the overall prevalence of subtype 1b was 88.91% [8].

As a sociological burden, WHO proposed using indicator DALY (Disability Adjusted Life Years). One DALY (Disability Adjusted Life Year) can be considered as a lost year from "healthy" life years. The amount given to the entire population, or the burden, is calculated by the difference between current health status and an ideal situation health, where the entire population lives to old age, without the burden of illness or disability [13].

Aim and objectives

Evaluation the epidemiology of hepatitis C in Romania by comparing few targeted and relevant studies conducted to date. Establish a procedure to be followed for identifying, measuring, monitorizing and treating potential patients infected with hepatitis C (secondary and tertiary prevention) and to initiate preventive measures paramount.

MATERIAL AND METHODS

Analytical study, designed by synthesizing more descriptive, relevant, cross-sectional studies conducted in the period 2004 - 2015, in order to obtain a meaningful ecological study.

The data used in the article were identified by searching in medical databases (Medline, Medscape, Embase), using different search engines and data filtering. The period for which the data were originally sought was November 2010 - July 2015, but because the data found were unsubstantial, we extended the period to January 2004 - July 2015.

The search terms used were: ,,hepatitis", ,, HCV", ,,hepatic cirrhosis", ,,hepatic cancer" ,,complications", ,,morbidity", ,,mortality", ,,DALY", ,,epidemiology", ,,prevalence", ,,genotype".

Data were staged, layered or organized in clusters and have undergone processes of analysis and meta-analysis.

The results were computerized using software Microsoft Excel 2007, to stratify and organize data and calculations epidemiological prevalence and incidence and Epi Info 7.1.5. By comparison statistical methods, they were calculated weighted arithmetic averages, confidence intervals and standard deviations. For an index of probability of 95, they were calculated the confidence limits and the critical values, z.

RESULTS

From searches in the databases mentioned above, we extracted few data, we considered relevant to the prevalence of the disease, genotype prevalence, mortality rate and social impact (negative).

Among the genetic study conducted during 2004 to 2006, the serum was analyzed, from 103 patients with chronic HCV, after previously was confirmed presence of anti-HCV and HCV RNA presence. The analysis was carried out by the comparative method (RFLP and 5 'UTR, the NS5B sequencing) and there was obtained a prevalence for 1 genotype of 97% (**Table I**), and for subtype 1b, overall prevalence, was 88.91% (almost pathognomonic for Romania) [8].

The sero-prevalence study, conducted during 2006 to 2008, analyzed serum from a number of 13,460 subjects, selected on the basis of region, age, gender, consistent with national representation. In calculating the final prevalence (**Table I**), could be quantified only a number of 13146 subjects, with participation rate of 74.69% [4].

In the technical report of ECDC, in September 2010, on prevalence, burden of disease and screening policies for HCV and HBV, in European Union countries, it was shown the analysis of a batch of 8,039 randomly selected subjects (**Table I**), based on the expected prevalence of> 2% and a confidence interval of +/- 0.40, calculated to an accuracy of 95% [3].

The Eurostat study on mortality in the European Union countries in 2012, according to the causes of illness according to ICD 10, age and gender, resulted in a total number of 253 716 deaths for Romania, in 2012 (**Table I**), total deaths for both genders and all age groups by HVC 392, representing 0.15%, total deaths for both genders and all age groups liver cancer was 2,758, accounting 1.09%. Among chronic liver diseases, deaths for genders and all age categories was 9,508, representing 3.75%.

To determine deaths from complications of HCV, we used the average value of HCV complications mortality that resulted from the global study on HCV mortality and complications on 2013, obtaining an average mortality of HCV cirrhosis-induced about 29.3%, from all deaths of hepatic cirrhosis. For hepatic cancer-induced, we obtained an average mortality of HCV about 41.87% of all cases of death from hepatic cancer [5, 7].

In the sero-epidemiological study, conducted by the National Institute of Public Health (NIPH), in 2013, the prevalence of HBV and HCV infection, it was tested a number of 3,266 serum samples (**Table I**), remained in laboratories, from hospitalized patients for diseases other than those of hepato-biliary-pancreatic sphere.

To determine the sample, the methodology used was simple random, in compliance with the population distribution by county, age groups and gender, laboratory tests were made in three locations: Cluj, Iasi and Timisoara and was aimed to obtain a prevalence study, nationally representative, for HBV, HCV and HBV-HCV co-infection [10].

Table I. Comparative analysis of total prevalence of HCV among studies conducted during 2004 -2015

Current number	Name of study	Type of study	Sampling method	Cases number	Expected prevalence	Confidence limit to an accuracy of 95%	Ratio/ prevalence obtained
1	The genetic study	analytical, comparative	clusters	103	unknown	< 3	97.0 for genotype

Current number	Name of study	Type of study	Sampling method	Cases number	Expected prevalence	Confidence limit to an accuracy of 95%	Ratio/ prevalence obtained
	conducted in 2004-2006 [8]						1, 88.91 for subtype 1b
2	Sero-prevalence study from 2006 to 2008 [4]	descriptive, transversal, prevalence	random, stratified, clusters, multicenter	13146	unknown	3.18 – 3.28	3.23
3	Technical ECDC report in September 2010 [3]	secondary, prevalence	random	8039	>2	3.10 – 3.90	3.50
4	The study on HCV mortality and complications in 2012 [5]	secondary, meta-analysis	stratified	253716	unknown	1.66 – 1.76	1.71
5	Sero-epidemiological study of prevalence of HBV and HCV infection in 2013 [10]	descriptive, transversal, prevalence	random, simple	3266	5 – 10%	3.10 – 8.10	5.60
6	The study on the social impact of HCV (DALYs) in 2010 [6]	secondary meta-analysis	stratified	7772167	unknown	1.13 – 1.36	1.33
7	The study of global mortality of HCV and complications in 2013 [7]	secondary meta-analysis	stratified	54863.8 (thousands)	unknown	1.22 – 1.37	1.28

For the study on the social impact of HCV, we analyzed DALY (disability adjusted life years) for our country in 2010 [6]. The formula for calculating DALYs, besides the deaths, are quantified both years lived in disability (L) and life expectancy in years (LE) [13]. The formula for calculating DALYs, besides the deaths, has quantified both years lived in disability (L) and life expectancy in years (LE) [13]. To determine DALY determined from complications of HCV, we used the methodology described above.

The study of global mortality of HCV and complications in 2013 is virtually the last relevant study on HCV mortality and complications made. In this study, it was determined, comparative, mortality by causes of diseases, in the period 1990 - 2013 [7].

The true incidence of new cases of HCV infection is actually much higher (most cases are asymptomatic). Thus, from 100 people infected, manifested form is found only in 20% of cases [11].

In analyzing gender they were taken into account only 4 studies (**Table II**), the prevalence by gender in our country could not be quantified for other, as there were insufficient data.

Among sero-prevalence study, from 2006 to 2008, with an overall prevalence of 3.23% for HCV, it was determined the number of subjects by gender, resulting in a total of 5,516 male subjects, representing 41.96% from the total of 13,146 subjects tested. It was determined

the prevalence of the male type, resulting in a prevalence of 2.85%, confidence interval 2.42 to 3.32, to a precision of 95%.

Table II. Comparative analysis of HCV prevalence by gender

Current number	Name of study	Total cases number	Total ratio/ prevalence obtained	Ratio/ prevalence obtained for male gender	Ratio/ prevalence obtained for female gender
1	Sero-prevalence study from 2006 to 2008 [4]	13146	3.23	2.85	3.51
2	The study on HCV mortality and complications in 2012 [5]	253716	1.71	1.96	1.44
3	Sero-epidemiological study of prevalence of HBV and HCV infection in 2013 [10]	3266	5.60	4.90	6.40
4	The study on the social impact of HCV (DALYs) in 2010 [6]	7772167	1.33	2.83	1.20

For the female gender, it was determined the number of subjects, resulting in a number of 7,630, representing 58% of the total. It was determined the prevalence of the female gender, resulting in a prevalence of 3.51%, confidence interval 2.42 to 3.32, to a precision of 95% [4].

In the study on HCV mortality and complications in 2012, we determined the number of deaths by gender, resulting in a number of 2,591 male deaths, the ratio of final mortality was 1.96%, in a number of 1,742 female patients, the ratio of final mortality was 1.44%. To adjust the proportion of initial mortality, we used a similar methodology to that described above for complications [5].

Among the sero-epidemiological study of prevalence of HBV and HCV infection in 2013, we determined the number of patients with HCV by gender, resulting a prevalence of 4.90%, for male gender and a prevalence of 6.40% for the female gender [10].

In the study on the social impact of HCV (DALYs) in 2010, we determined the number of DALY for HCV and complications by gender, resulting in a ratio of 1.96%, for male gender and in a ratio of 1.44 %, for female gender [6]

On the analysis by age groups, we have established main relevant age groups to statistical calculations on the epidemiology of the disease and resulted in seven intervals (0-4 years, 5-14 years, 15-24 years, 25-34 years, 35-44 years, 45-64 years and > 65 years). Only 3 studies could be considered, the other could not be quantified prevalence by age groups in our country, as there were insufficient data.

Table III. Comparative analysis of HCV prevalence by age groups

Current number	Name of study	Total cases number	Total ratio /prevalence obtained	0-4 years	5-14 years	15-24 years	25-34 years	35-44 years	45-64 years	≥ 65 years
1	The study on HCV mortality and complications in 2012 [5]	253716	1.71	0.07	0.29	5.96	3.31	3.27	3.46	1.04
2	Sero-epidemiological study of prevalence of HBV and HCV infection in 2013 [10]	3266	5.6	2.0	3.5	1.9	3.0	5.7	5.4	13.4
3	The study on the social impact of HCV (DALYs) in 2010 [6]	7772167	1.33	0.03	0.13	0.09	0.24	1.17	2.84	0.99

In the study on HCV mortality and complications in 2012 [5], we determined the number of deaths for each age group and we calculated the mortality ratio by age groups, achieving the following results (**Table III**): for the age group 0-4 years 1 case (0.07%), for the age group 5-14 years 1 case (0.29%), for the age group 0-4 years 87 cases (5.96%), 25-34 years 74 cases (3.31%), 35-44 years 215 cases (3.27%), 45-64 years 1,759 cases (3.46%), >65 years 1,977 cases (1.04%). To adjust the proportion of initial mortality, we used a similar methodology to that described above for complications [5].

We tried to identify data about the geographical distribution of HCV according to the population distribution by counties or historical regions. We did not find any study that meet the criteria set.

Another issue that remained unsolved for now was the distribution of HCV infection at national and regional level by risk groups.

DISCUSSIONS

Prevalence data from the few studies conducted in Romania are contradictory, even reporting European Centre for Disease Control and Prevention (ECDC) and the World Health Organization (WHO), making the standardization impossible.

From the study on HCV genotyping, data resulted in a prevalence of 97% genotype 1, and 88.91% subtype 1b, are consistent with data reported by the neighboring countries: Serbia and Montenegro 57.9% for genotype 1, for subtype 1b, overall prevalence, 54.9% and Moldova prevalence of genotype 1 subtype b was 88%. The obtained data are consistent with previous data for Eastern Europe, genotype 1 subtype b being the most common in this region. Given the aggressiveness of this subtype (fibrosis ≥ 4, very high viral load, significant histological activity), resistance to therapy (combination therapy with ribavirin and interferon or a long period of treatment), relapses, the high risk of hepatic cirrhosis and hepato-cellular carcinoma, affecting predominantly active population (> 40 years), nosocomial transmission, would be useful an inexpensive and rapid genotyping method for screening and validation (eg.: RFLP) and interferon free therapy for all patients confirmed by genetic testing [8,11,12].

From the sero-prevalence study during 2006 to 2008, the prevalence achieved of 3.23% not confirms previous results (5.96% in a study of 1,843 subjects, in 1997). Possible explanations for this could be: different sampling methods, population migration from Romania, after joining the European Union, to other countries in Western Europe and thus in our country appears a false decrease in prevalence [2, 4].

The study on HCV mortality and complications, in 2012, gave us a mortality of 1.71%, with a significant increase in the age group 15-24 years (5.96%), an increase of 248.54% compared to the average mortality. The figure is very worrying for that age group. Possible explanations for this: increased injecting drug use, at ages increasingly smaller and using the same needle for injection, sex at early ages, without a minimal education on STDs and contraception, vertical transmission from mother to child (mothers under-diagnosed) [5].

From the study of global mortality and complications of HCV, in 2013, have emerged several assumptions. In fact, the analysis itself is more interesting, as do a global comprehensive analysis, comparative causes of mortality in 240 countries, genders and ages. The first assumption that resulted was the global increase of deaths in 2013 to 7.3951 million, compared to 1990, with average growth of 321,526 cases per year. Possible explanations for this phenomenon could be poverty, with increasing social disparities on a global scale, poor nutrition or unhealthy diet, chaotic lifestyle, more aggressive and mutations of pathogens, increased resistance to standard treatments and pollution in large cities.

Another hypothesis has been increasing the number of deaths from HCV, from 2,300 cases in 1990 to 3,500 cases in 2013, an increase ratio of 52.17%. For hepatic cirrhosis due to HCV infection, it was an increase of 67.9%, from 213,100 cases in 1990 to 357,800 cases in 2013. HCV-induced hepatic cancer increased by 291.88%, from 87,400 cases in 1990, to 342,500 in

2013. The statistics are impressive and could be explained by under-diagnosis of many cases (in the 90s), knowing that the disease evolves mostly asymptomatic, for that we called it ,,the silent burden" in the title of the article and, the natural history of the disease, the average of developing complications is 20-30 years [7]. According to the study on potential years of life lost (yll), conducted in 2013, showed that hepatic cirrhosis was on 3rd place in our country, after ischemic heart disease and stroke, showing a climb into the top 10 causes of death from 4th place in 2010 (where he was located after lumbar inter-vertebral) [6,7].

To determine the social impact of the disease, WHO has proposed the use of two structural indicators: Healthy Life Years (HLY) - years of healthy life expectancy, as a positive indicator and Disability Adjusted Life Years (DALY) - disability adjusted life years or disease burden as a negative indicator. Since the last report of Eurostat, Romania ranks last in the EU 28 on life expectancy (LE), with 78.7 years for women, compared to the EU average of 83.3 and 71.6 years in men, compared to the EU average of 77.8 (second only to countries such as Macedonia and Bulgaria - women and Latvia, Lithuania and Bulgaria - men) and HLY for Romania is 57.9 for women compared to the EU average of 61.5 and 58.6 for men compared to the EU average of 61.4 (last place). This indicator (HLY) is irrelevant for our country, it is an indicator of prosperity and welfare, and we are very far from that status, being one of the poorest countries in Europe according to Eurostat. Basically, the only relevant indicator of our country's disease burden remains DALY or disease burden [5, 6, 13].

In Europe, annually, it is estimated that approximately 1.2 million DALYs are lost due to hepatitis C, with an average of 134.5 DALYs per 100,000 population. Also in this region, the highest level of DALYs lost is registered in Eastern Europe where were 155 DALYs lost per 100,000 population [11].

From the study on the social impact of the disease in 2010, we determined DALY for Romania, that was 604.16 DALYs per 100,000 population, well above the regional average [6].

According to recent studies, analyzes and forecasts that were made, the World Health Organization recently stated that hepatitis can be eradicated if they put more emphasis on prevention, diagnosis and treatment [13].

CONCLUSIONS

1. From the analyzed studies, the most relevant were sero-epidemiological study of prevalence of HBV and HCV infection in 2013 and the study of global mortality of HCV and complications during 1990 to 2013.
2. The prevalence resulted from the sero-epidemiological study was 15.5% for women over 65, data that could be explained by decree no. 770 of 10.01.1966, which the abortions were forbidden in Romania (the age group analyzed was at that time of childbearing potential), illegal abortions were common practice thereafter, without always respected aseptic conditions and sterilization of the instruments.
3. From the study of mortality from HCV resulted, in 2013, an increase in the number of cases of death from cirrhosis due to HCV infection by 67.9% compared with 1990 and for HCV-induced hepatic cancer, an increase of 290.8% compared with 1990, which confirms that this silent burden, hepatitis C virus is a disease that kills slowly and surely.
4. The full research of general population by screening methods would be useful for detecting patients with HCV through a government program, similar to the program on health monitoring in primary care population, conducted from 2007 to 2008 or the replay of the old program with the introduction of new laboratory investigations, specific for the disease.
5. The screening data obtained will be validated and equally etiological hypotheses will be tested by group risk genotype and social impact by a new study with a similar

methodology like SEPHAR study, conducted in Romania successfully in two stages: in 2005 SEPHAR I and SEPHAR II during October 2011 - March 2012.

6. Sampling will be done by stratified combined selection to achieve reliability and representativeness as good or even clusters selection, a method considered by WHO as the most representative, the clusters structure provided comply with fully population characteristics (age, gender, geographic region, population size of the village).
7. Given the disabling of the disease, should be introduced HVC, in the framework contract, on the list of chronic diseases with a major impact on diseases burden, together with high cardiovascular risk of hypertension, dyslipidemia, type 2 diabetes, asthma, chronic obstructive respiratory disease (COPD), chronic kidney disease and introduction DALY indicator in all statistical monitoring situations of the evolution of these diseases.
8. It is necessary to amend the protocol for inclusion in treatment with genotyping of patients prior using the RFLP (the cheapest and sufficient for our endemic area) and direct inclusion (without prior treatments) of patients on the list of next generation treatments (interferon free), with the aim of healing the disease and increasing the quality of life in the chronically ill and tertiary prevention in the absence of a specific vaccine.
9. Primary prophylaxis will be done through public education programs, with the support of family physicians, infectious disease physicians, gastroenterologists, associations and foundations profile through a national program coordinated and funded by Ministry of Health, in cooperation with the National Health Insurance and the Ministry of Education and Scientific Research.

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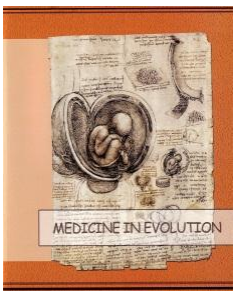
The influence of milk formula consumption on the immune system, weight status and attention in young children



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Abstract

Breast milk is a protective factor in the prevention of various gastrointestinal, pulmonary and brain pathologies, helping to reduce infant mortality and morbidity.

Aims: The aim of this research is to demonstrate the long-term benefits of exclusive breastfeeding during the first six months of life.

Methods: The study was conducted on a sample of 126 subjects, 3 years of age, living in Mureş County. Data was collected through an interview consisting of 30 open questions.

Results: Significant correlations were observed between the use of breastmilk substitutes and the development of attention deficit ($p<0.0001$), the presence of immune system problems ($p=0.0028$) and weight problems ($p=0.0019$).

Conclusions: The substitution of breast milk during the first six months of life with other products is associated with an increased risk of developing attention deficit, immunity and weight problems in young children.

Keywords: breastfeeding, infant, attention deficit, protective factors, morbidity

INTRODUCTION

Initiation of breastfeeding in the first hour of life is the first step to ensure the health of the newborn, therefore, the WHO (World Health Organization) recommends the initiation of breastfeeding in the shortest possible time after birth and further feeding the child exclusively, with breast milk for at least the first six months of life. [1,2]

Medical research shows the importance of breastfeeding as a factor in the prevention of various pathologies of the gastrointestinal tract, lungs and brain, being a protective factor against diabetes and also as an important factor in reducing infant mortality and morbidity. [3] Breastfeeding is an important factor in ensuring maternal health, it is positively affecting the physical/mental condition and recovery of the mother after childbirth, also being a protective factor against breast cancer. [4]

The statistics published by the WHO for the European Union shows that during the period 2006-2012 only 25% of infants where fed with human milk. In these cases, substitution formulas are used (animal or vegetal) and sometimes unprocessed mammal milk (cow, sheep, goat). Although milk formula has been modified and improved significantly over time, being adapted to the needs of infants, their content differs from breast milk, without having the same health benefits. [5,6,7]

Background and aims

The aim of the research is to demonstrate the long-term benefits of exclusive breastfeeding for the first six months on infant's weight, attention and immunity, from birth to 3 years, compared to the consumption of other products designed for infants.

MATERIAL AND METHODS

This is a retrospective observational study conducted on a sample of 126 - 3 years old subjects. The necessary data for the study were collected during the period June-December 2015. The study was conducted in the town Tîrgu Mureş, Romania. The subjects included in the study were enrolled in four kindergartens with extended schedules, activating in the city. Kindergartens were selected from different areas, respectively from the 4 main districts of the city. The inclusion criteria of the subjects were: birth at term, 3 years of age, residence in Mureş County, enrollment in one of the four kindergartens included in the study. Eligibility criteria for kindergartens were: extended schedule, similar number of children and the management's agreement. Exclusion criteria for the study were: children born before term, diagnosed with chronic diseases, fed with other products than breast milk or formula for the first six months of life. The necessary data were provided by the legal tutor of the minor, same as the signed consent of participation.

The necessary data for the study were collected through an interview consisting of 30 open questions related to gestational age, Apgar score, weight and length at birth, weight and height measured at the time of the interview and the feeding method during the first six months of life. The interview aimed to also characterize the levels of attention and immunity from birth to the moment the interview took place. The level of attention has been evaluated by one of the subjects' teacher, according to his participation in curricular activities, level of excitement, activity level and impulsivity, the subjects being divided into 2 groups: with attention deficit or normal/high attention.

Immunity was characterized by the number of bacterial/viral infections during one year and the cases of intolerance/allergy. The subjects were divided into 3 groups: a group with low immunity (diagnosed with allergy or intolerance and/or more than 3 bacterial infection/year), one with medium immunity (maximum 3 bacterial infections/year) and one with high immunity (maximum one infection during the previous year).

Anthropometric data considered normal for newborn consists of: birth weight between 2500 grams and 4000 grams, 48-54 cm in lenght, while data that does not fit into this category was considered abnormal. [8,9] Actual weight analysis was based on WHO percentile charts according to height, age and sex. [10,11]

Statistical data was obtained using GrapPad Prism 6.0 software, descriptive statistical analysis regarding: mean, median, standard deviations, minimum and maximum values. Risks, correlations and errors were obtained by performing Fisher's exact test and Pearson correlations; the confidence interval used for the tests was 95%. Data was considered significant, from a statistical point of view, when the p-value was less than 0.05.

RESULTS

Among the subjects included in the study 43.65% (n=55) were male and 65.34% (n=71) were female; 39.68% (n=50) coming from rural areas and 60.31% (n=76) from urban areas.

Table I presents descriptive statistical data of the sample. The weight in the newborn stage is measured and expressed in grams and the current weight of the children, in kilograms.

Table I. Descriptive statistical data of the sample

		Percentage%	Mean	SD	Median	Minimum	Maximum
Apgar score	1 min.		9.937	0.275	10	8	10
	5 min.		9.992	0.089	10	9	10
Newborn`s weight	Normal	62.69	3691	400.7	3500	3100	4300
	Small	0					
	Big	37.3					
Child`s actual weight	Normal	57.936	15.94	1.756	16	12	18.3
	Small	0.793					
	Big	41.269					

The infants' diet during the first 6 months of life was characterized as follows: 56.34% (n=71) of the subjects were breastfed exclusively and the other 43.64% (n=55) were formula fed. Groups represented in Table II are divided according to the type of food used and characteristics of immunity, attention and the weight, measured at the time of the interview. The data presented in the table below is expressed as percentage, relative to the total number of subjects included in the study (n=126).

Table II. Sample`s characteristics depending on nutrition, immunity, attention and weight

%		Breastmilk	Milk formula
Immunity	Normal/higher	42.063	20.634
	With problems	14.285	23.015
Attention	Normal/higher	55.555	28.571
	With problems	0.793	15.079
Child`s weight	Normal	30.952	26.984
	Smaller	0	0.793
	Bigger	25.396	15.873

There is no association between the use of milk formula and the weight of the newborn or the Apgar score. (Table III)

Table III. Correlation between milk formula consumption and the data of the newborn

	r value	CI 95%	p value	Significant?
Newborn`s weight	-0.035	-0.214 to 0.145	0.694	No
Apgar score at 1 min.	-0.005	-0.185 to 0.174	0.950	No
Apgar score at 5 min.	-0.078	-0.255 to 0.102	0.380	No

Relevant statistical results have been obtained by calculating the risk of problems associated with immunity, attention and weight, resulting from the consumption of breastmilk substitutes, where all the results are significant. Risk, error, sensitivity, specificity and predictive values were calculated by applying Fisher's exact test.(Tabel IV)

Table IV. Statistical data about the risk caused by the use of milk formula

						Predictive value	
	OR (CI95%)	p value	Significant ?	Sensitivity (CI 95%)	Specificity (CI 95%)	Positive (CI 95%)	Negative (CI 95%)
Risk for immunity problems	3.284 (1.547 to 6.971)	0.0028	Yes	0.617 (0.463 to 0.754)	0.670 (0.556 to 0.772)	0.527 (0.388 to 0.663)	0.746 (0.629 to 0.842)
Risk for attention deficit	30.12 (3.882 to 233.8)	<0.0001	Yes	0.95 (0.751 to 0.9987)	0.6132 (0.513 to 0.706)	0.3167 (0.202 to 0.449)	0.9848 (0.918 to 0.999)
Risk for abnormal weight	3.313 (1.682 to 6.941)	0.0019	Yes	0.6038 (0.460 to 0.735)	0.6849 (0.565 to 0.788)	0.5818 (0.441 to 0.713)	0.7042 (0.584 to 0.806)

DISCUSSIONS

The statistical results show a strong correlation between the consumption of breast milk substitutes and attention deficit ($p<0.0001$), the lack of natural food is a risk factor for the development of attention deficit by the age of 3 years (OR=30.12). Breastfeeding is mentioned in many studies as a protective factor for problems related to attention, cognition and brain issues. [12] Fonseca et al, in a study published in 2013, put at the forefront another benefit of long-term consumption of breast milk - a higher level of intelligence [13], the same idea being outlined in Victora`s et al research. [14] Copper C. explanation for the increase in the level of intelligence in breastfed children is that there is a higher breastfeeding rate among mothers with higher IQs, a fact which genetically determines an increased IQ in their children compared to others; therefore, breast milk is not a boosting factor for intelligence. This conclusion raises an important question: is milk a real protective factor for the development of some diseases or is it all about genetics? [15] Even if we assume that breast milk is a neutral factor in relation to IQ, analyzing our results (Table IV) and the literature, we consider the link between the consumption of milk formulas and attention, weight and immunity to be important.

Another important relation is the one between the consumption of breastmilk and protection against abnormal weight gain; the data we obtained, demonstrates that the lack of breast milk in children's diets during the first 6 months of life represents a risk factor in the development of overweight/obesity (OR=3.313). Similar data was obtained by other researchers, who correlated obesity [16] and other anthropometric data; for example, a study

conducted in on the prevention of malnutrition, on a sample of children with ages similar to the ones' included in this study (2-3 years), has reached similar, significant results. [17]

A study with results opposite to the ones obtained by this study was conducted by Puddler et al., who demonstrated the impact of nutrition on the weight of children aged between 7 and 14 years. In their prediction, results were not significant for obesity, although they cannot explain their results, only outlining the importance of further research on this topic. [18]

Significant statistical correlations were obtained between the intake of milk formula and the risk of attention deficit in children (OR=30.12), Türkoglu et al. concludes the same in a study published in 2015, saying that the benefits of breast milk consumption are felt in the protection against ADHD (Attention Deficit and Hyperactivity Disorder). [19]

A research conducted in India supports the benefits of exclusive breastfeeding for the first 6 months of life and continued breastfeeding for up to 2 years, as it is also recommended by the WHO. The importance of a balanced diet of the breastfeeding mother in order to maintain a high milk quality is also specified in the Indian study- aspect which we consider useful in defining the benefits for the child, though this correlation was not analyzed by the present research. [1,20]

An ecological study published by Buccolin et al. presents the administration of breast milk as a protective factor against neonatal mortality and also for the prevention of immunological problems, stating that maximal effects are obtained by starting breastfeeding within the first hour after birth, the effects being observed both in the short and long term; total or partial replacement of natural nutrition with other products is a risk factor for the occurrence of the immune system disorders, the data we obtained being significant for this correlation (p=0.0028). [21]

In a more detailed analysis of the correlation between breastfeeding and immune disorders, we found a cohort study conducted between 1997 and 2009 that analyzed the number of hospitalization during the first 6 months of life, the percentage of hospitalized breastfed children being significantly lower than the one of formula fed children of the same age. The most common problems reported in the study were related to immunity (infections), but cases of diabetes and asthma were also taken into consideration. [22]

Although the benefits of breastfeeding have been mentioned and proved in numerous scientific papers, there are cases where this practice is not possible or desired, which is why alternative means of infant nutrition are used, the substitution formulas based on goat milk being a better choice than the ones based on cow`s milk. However well adjusted these formulas are, they still present a possible allergy occurrence risk, as opposed to breastmilk which is not an allergy producing factor, but, according to the present research and other research, a protective one. [23]

CONCLUSIONS

Breast milk consumption is a protective factor against the development of immunological and attention deficit disorders; it is also a protective factor for normal weight gain in infants.

Replacing breast milk with formula, prones children under 3 years of age to immune system disorders, abnormal weight gain and the development of attention deficit disorder.

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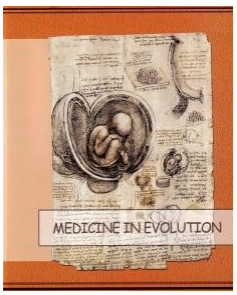
Acromegaly: focus on facial, oral, and dental anomalies



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Abstract

Introduction: Acromegaly represents a rare endocrine condition caused by a growth hormone producing pituitary tumour. Classical features include arthropathy, arterial hypertension, cardiomyopathy, diabetes mellitus, and colonic polyps. Facial, oral and dental disturbances are reviewed.

General data: Face changes are marked by frontal skull overgrowth. Special software allows early recognition before phenotype is clinically recognizable meaning 6-10 years of prior hormone excesses. Increased risk of sleep apnea (confirmed at polisomnography) and laryngeal obstruction is expressed as nocturnal stridor, disrupted sleep, chronic cough, caused by hypertrophy of supraglottic soft tissue, laryngo-pharyngeal reflux, reduced mobility of vocal fold, macroglosia. Airways obstruction is correlated with insulin-resistance, cardiac impairment. Dental anomalies, particularly associated with acromegaly duration, involve mandible protrusion (in association with larger mandibular plane angle and reduced facial angle), spaced teeth, and malocclusion thus frequently prostodontic rehabilitation is necessary.

Conclusion: Complex work-up of maxillofacial and oral specialists requires collaboration with a multidisciplinary team including endocrinologists, neurosurgeons, cardiologists, etc.

Key words: acromegaly, growth hormone, prognathism, sleep apnea

INTRODUCTION

Acromegaly represents a rare chronic endocrine condition (with an estimated prevalence of 1:140,000 - 250,000 people or, with other words, about 3 to 50 persons of every million) caused by growth hormone (GH) excess mainly associated with a GH producing benign pituitary tumour. (1, 2) GH pathologically increase causes an elevation of Insulin Growth Factor (IGF1) at the level of liver and the associated anomalies may be seen into the human body as an effect on either one or both molecules, overall acromegaly representing a complex package of co-morbidities and some with a high rate of mortality. (3) The classical clinical features are: swelling of the soft tissue (as feet, hands), joint pain and deformities (arthropathy) in association with high risk metabolic and cardiovascular disturbances as arterial hypertension, cardiomyopathy, concentric biventricular hypertrophy, hyperlipemia, arrhythmias, valvular heart disease, insulin resistance, diabetes mellitus, cerebrovascular events, and non-endocrine tumours development (like colonic polyps with an elevated potential of malignancy transformation), etc. (4, 5) The upper limb of the body is affected by progressive disfigurement especially related to face but also oral and dental aspects are described. (6) Generally, GH is essential for normal growth of the body, of the skeleton and its deficiency during childhood causes dwarfism while its excess causes gigantism if the growth cartilages are opened. (7) Both hypo and hyper-pituitarism display effects on skull, facial and oral structures including dental health. (8) The acromegaly therapy is targeted to the pituitary tumour and it also aims to control the cardiovascular and metabolic anomalies; the first line is pituitary surgery as used in other hormones secreting hypophyseal adenomas; medication as somatostatin analogues (traditionally octreotide and lanreotide and modern pasireotide), dopamine agonists (as bromocriptin, cabergoline), GH receptor blockers (pegvisomant) and radiotherapy. (9,10,11) Once the GH and IGF1 secretion is controlled, many complications are remitted or improved; however, the majority of the bone and dental deformations are permanent and a multi-level management and follow-up is life-long required. (12, 13 14)

Aim/Objective

We aim to introduce aspects related to acromegaly involving facial, oral, and dental particularities

METHOD

This is a review based on a systematic research of the literature using Pub Med database. The figures with patients are original and they are obtained from the clinical experience of the authors. The informed consent of the subjects was obtained between 2015 and 2016.

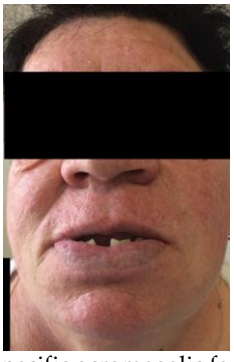

Figure 1A. Specific acromegalic facial features: enlargement of the frontal skull, and nose, jaw protrusion; spaced teeth, edentation; hyperhydrosis

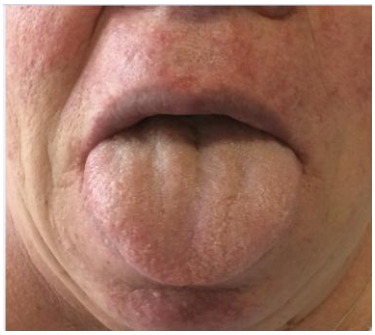

Figure 1B. Macroglosia

Figure 1. This is a 51-year old female diagnosed with acromegaly at age of 48. Pituitary surgery was done one year later and she is currently under octreotide and cabergoline medication (still active disease)

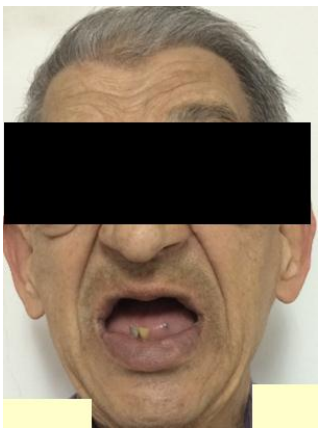

Figure 2. This is a 76-year old male diagnosed with acromegaly at age of 66. He was treated with pituitary surgery and radiotherapy and currently the disease is controlled under octreotide and pegvisomant: loss of teeth, enlarged inferior lip, enlargement of nose

General data

Facial and skull anomalies

Face changes are marked by the overgrowth of the frontal skull and protrusion of the jaw. (15) A study published in 2015 on 21 adult subjects with acromegaly compare with 22 healthy controls by using Mann-Whitney U-test for statistical analysis showed that anterior, poster as well as middle cranial lengths are higher in patients cu GH excess (statistically significant) and so was the enlargement of Turkish sella while face had the most affected bones the frontal bone and mandible in association with smaller airways at the level of mandible, nose and pharynx. (16) Also, a few cases have been published with onset of the disease consisting in oro-facial pain and paraesthesia. (17) Due to facial characteristics, computer programs have been developing to recognize the disease. (18) For example, a support vector machine using a model to compare a set of patients' photographs has encouraging results. (19) The clinical diagnosis of the acromegaly means that the condition is priory presented for at least 6 to 10 years thus special classification software based on frontal and side photos of the face might help the practitioners for an early detection. (20) The technique of facial image analysis is extended to other endocrine (as Cushing's syndrome) or genetic conditions (as Down's syndrome). (21, 22)

Oral and superior airways disturbances

Acromegalic patients have an increased risk of sleep apnea and laryngeal obstruction (expressed as nocturnal stridor, loud snoring, disrupted sleep, and sometimes as chronic cough) caused by hypertrophy and inflammation of supraglottic soft tissue, laryngopharyngeal reflux, and reduced mobility of vocal fold. (23) Uvula and macroglosia are particularly related to the pathogenesis of obstructive syndrome. (24) Sleep apnea, if clinically is suspected, should be confirmed by polisomnography. (25) Cardiovascular complications of the acromegaly and, also, impaired quality of life are exacerbated by sleep-disordered breathing. (26) A study published in 2015 confirmed that only subjects with severe SAHS (sleep apnea-hypopnea syndrome) associate cardiac damage reflected by hypertrophy, ventricular dysfunction and, eventually, cardiac acute complications. (27) Other observations confirm the impact of sleep apnea on insulin resistance and glucose metabolism disturbances. (28) Therapy with CPAP (continues positive airway pressure) applied through a mask during night sleep offers a better outcome of laryngeal symptoms since some medications have been developed for sleep apnea of other causes and the results are not encouraging while a few surgical procedures represent an alternative therapy for severe cases. (29, 30) However, the best prognosis is obtained if the underlying condition is controlled based on endocrine and neurosurgical specific intervention despite residual sleep disorders after acromegaly control. (31, 32) Moreover, due to increased risk of otolaryngic complains, the sleep apnea evaluation

is necessary in every case (also for peri-operative and anesthetic assessment) as well as audiologic test and thyroid ultrasound. (33) Acromegalics represents a challenging population for anesthesia team if pituitary neurosurgery is planed because of the airways anatomical anomalies (together with previously mentioned associated medical conditions) and difficulties during intubation might be expected. (34)

Dental conditions

A part from somatic general anomalies, acromegaly involves dental and jaw disorders with a higher prevalence than registered in general population. (35) Some studies described these anomalies in association with severity of the condition and the time since GH was persistently high. (36) Mandible deformities are considered the most important facial complication. (37) From an oral point of view, the most important features are represented by mandible protrusion in association with enhanced space between lower teeth and macroglossia, frequently prostodontic rehabilitation been necessary. (38) A study on Turkish population confirmed this aspect after analyzing the bit force and the craniofacial morphology (by using a strain-gage transducer for maximum bit force, lateral X-Ray standard scans in centric occlusion, and cephalograms). (39) The results pointed out higher length and height of frontal sinuses, a negative discrepancy between mandible and maxillary protrusion and especially women with acromegaly display a larger mandibular plane angle and reduced facial angle. (39) However, the maximum bit force was similar with healthy controls and this is an essential point of view for offering dental treatment or prosthesis in these subjects. (39) Adult acromegalics present diastema mediale (almost half of them); the overbite, the mandibular protrusion and length is positively correlated with malady duration; prognathism is found on more than a half of affected people usually associating asymmetrical movement of the mandible. (40) For instance, malocclusion, apertognathia may be the first signs of discovering the pituitary tumor in some cases. (41, 42) Recently, specialists (including data published in 2016) encourage the use of scores for identify acromegaly as ACROSCORE which includes spaced teeth as criteria among others (like diabetes mellitus, hyperhydrosis, goiter, colorectal polyps, carpal tunnel syndrome). (43) Acromegaly from Sotos syndrome (a genetic multi-organ condition) includes a specific dental picture with premature eruption of teeth, pointed chin and, also, highly arched palate. (44)

DISCUSSIONS

Although modern medicine and access to screening tests allow an early diagnosis of acromegaly, cases with delayed recognition and thus multiple facial anomalies might need surgical correction in association with specific endocrine treatment (or best after the diseases is remitted/cured) involving a plastic surgeon and/or an oral surgeon to perform osteotomy for frontal protrusion, rhinoplasty, tongue resection for macroglossia, bimaxillary procedures. (45, 46, 47) All these procedures may help the patient regained the self respect and confidence but the complications and associated costs should be taken into account, that is why it is better to have an accurate, early diagnosis and adequate treatment. (48) The consistent medical and surgical approach of oral deformities is reflected in the treatment of malocclusion, and prosthetic rehabilitation together. (49) Overall, the specific dental and facial changes management is part of a larger complex picture in acromegaly. (50)

CONCLUSIONS

Acromegaly involves not only cardio-metabolic, oncologic and direct pituitary tumour complications but also complex disturbances at the facial, superior airways and dental levels which are strongly correlated with the severity and duration of the disease. A complex work-up of maxillofacial and oral specialists requires collaboration with a multidisciplinary team

including endocrinologists, neurosurgeons, cardiologists, gastroenterologists, general practitioners, etc.

Conflict of interest

None.

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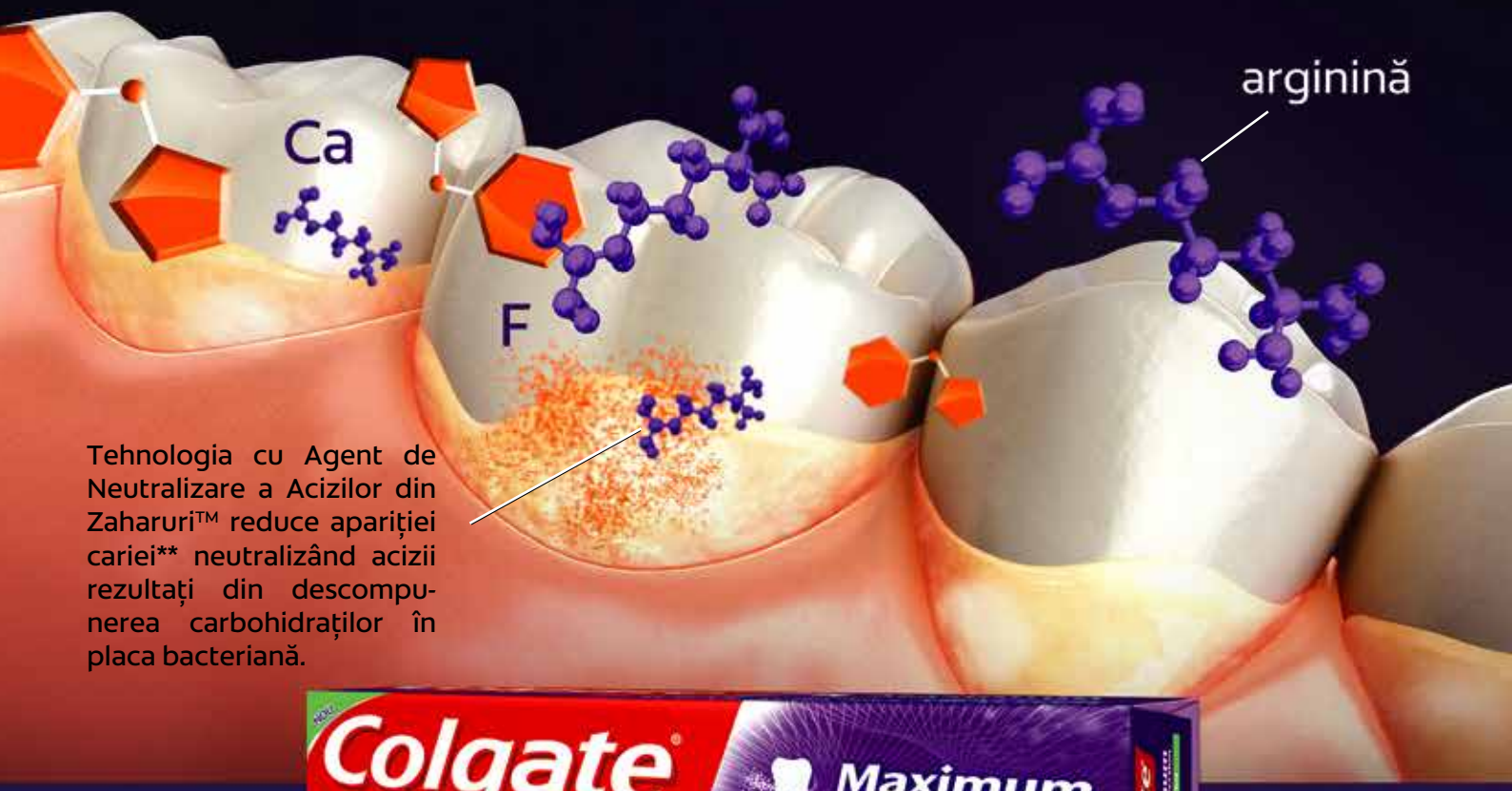

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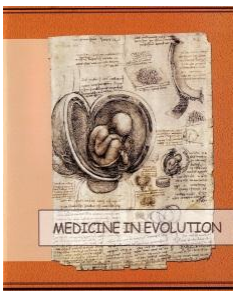
Non-orthodontic treatment approach in a case of maxillary anterior misalignment



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Abstract

Due to the advances in dental technology, materials and techniques, prosthodontics rehabilitation can be a successful alternative option for smile design rehabilitation, when orthodontic treatment cannot be accomplished.

This case report will outline a treatment plan for a patient with frontal misalignment. Her major complain was the excessive facial inclination of the upper left central incisor and the sheer disharmony in position and form between the all four maxillary incisors. The patient firmly declined any orthodontic treatment options and requested an exclusively prosthetic rehabilitation. After wax-up, mock-up and provisional restorations, the final prosthetic rehabilitation with veneers and all ceramic crowns satisfied both the patient and the dentist-dental technician team. This particular case report represents an example that minor orthodontic anomalies can be successfully concealed by adequate prosthodontic treatment, whenever patients decline orthodontic procedures.

Keywords: *esthetics, prosthodontics, misalignment, all ceramic, veneers*

INTRODUCTION

The rehabilitation of the smile design requires professional comprehension of the natural dentition aspects and a careful treatment plan. Good communication between the patient and the dental team is essential and represents the basic guidance for treatment planning and understanding the patient's vision of his or hers smile appearance. [1,2]

When treating a dento-facial disharmony that requires a multi-disciplinary approach, the two key factors are time and budget. At times, patients are lacking one or both factors and their cases become a challenge for the dental team. The decision, if a prosthodontic approach by itself could be possible, would be taken only after a good treatment plan with a dento-facial analysis, dental analysis, diagnostic wax- up, mock-up and functional occlusal tests have been made. [3]

The selection of adequate materials and techniques that make optimal esthetic results possible should be carried out in order to make the restoration closely resemble the natural dentition. [4, 5]

CASE REPORT

Anamnesis

A 26-year-old female patient with no relevant medical history was referred to the Clinic of Prosthodontics (Faculty of Dental Medicine, Timişoara) with the concern to improve the appearance of the anterior teeth. She was particularly unhappy with the shape and alignement of her central and lateral incisors. She did not want an "artificial" – looking smile and also had no desire to pursue orthodontic options. We obtain the inform consent and she agreed to provide us with her written consent for publishing photos with her clinical case for scientific purposes.

Clinical examination

The clinical evaluation included comprehensive exo- and endobucal examination, digital photographic analysis, panoramic radiograph and study cast examination. Her major complain was the excessive buccal inclination of the upper left central incisor and the sheer disharmony between the all four maxillary incisors as far as the position and form were concerned (Fig.1).

Occlusion was also evaluated to rule out any traumatic interferences and canine guidance was observed without noting any posterior excursive interferences. The patient exhibited no symptoms of any temporo-mandibular joint disorder and appear asymptomatic during TMJ evaluation.

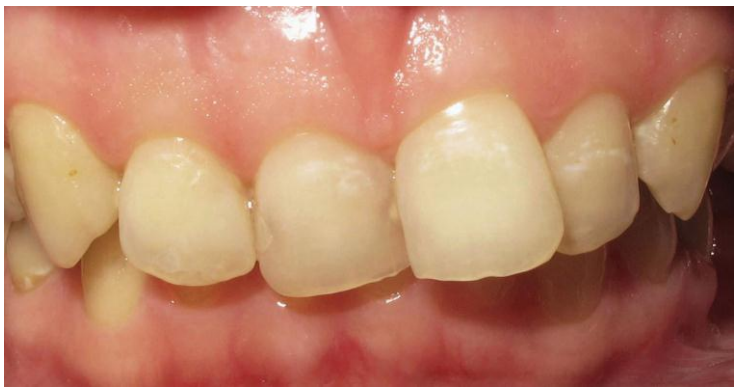

Figure 1. Frontal retracted view of the shape, size and position of frontal teeth

Treatment and evolution

After discussing these aesthetic anomalies with the patient, she firmly declined any orthodontic treatment options and requested an exclusively prosthetic rehabilitation.

The evaluation of the actual teeth position triggered the possibility of improving the patient's aesthetic appearance and functionality with 3 ceramic veneers and one all ceramic crown on her four maxillary incisors. The treatment plan was guided by the patient's written consent and approval to take digital photographs before and during the treatment.

Prior to the prosthetic rehabilitation itself, both dental arches were bleached using Zoom Advanced Power whitening system and, consequently, all carious lesions were treated.

The first step of the prosthetic phase implied the diagnostic wax-up of the four maxillary incisors (Fig.2) and the subsequent intraoral temporaries (mock-up) in order to analyze the shape and position of the future restorations, and, moreover, to satisfy the biological, mechanical and aesthetic requirements. The gingival contour of the upper right central incisor was enhanced by gingivectomy procedure and the aesthetic preoperative temporaries proved to meet patient's requests until the final restorations were inserted (Fig.3).

The patient's feedback was thoroughly positive and the prosthetic treatment plan was agreed upon three minimally preparation veneers for teeth 1.2, 1.1 and 2.2 and one all ceramic crown for tooth 2.1. The shade was registered by both conventional (Vita 3D Master shade guide) and digital method (Vita Easy Shade).

After teeth preparation (Fig.4), a polyvinyl siloxane impression material (Elite HD, Zhermack), in two consistencies (putty and light) and one step technique were used in order to obtain the master models.

Aiming to achieve the best combination between strength and esthetics, the dental technician fabricated the 3 lithium disilicate ceramic veneers and one all ceramic crown (IPS e.max. Press, Ivoclar, Vivadent for the framework itself and IPS e.max Ceram, Ivoclar, Vivadent for the layering process).

The final restorations thoroughly established the dento-facial and interdental harmony, by enhancing both the position and form of the four upper incisors (Fig.5, Fig.6). The clinical examination revealed an excellent biological, functional and esthetical status of each restoration. Moreover, the dento-labial relation was greatly improved (Fig.7)

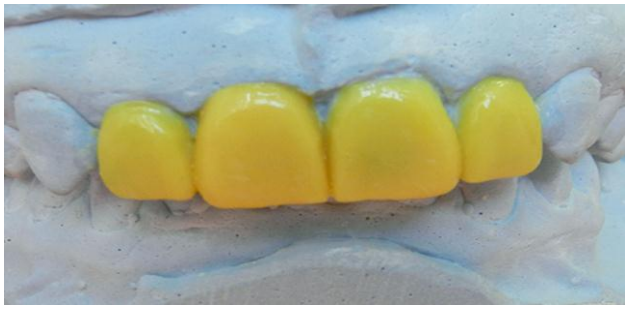

Figure 2. Diagnostic wax-up

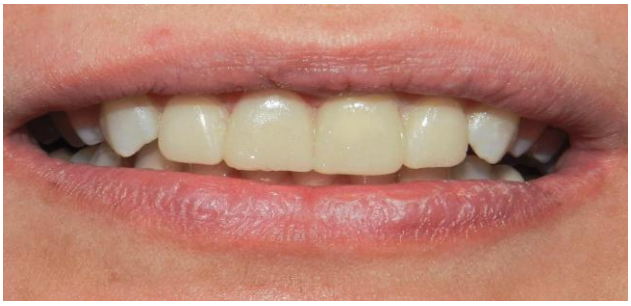

Figure 3. Provisional restoration set in place

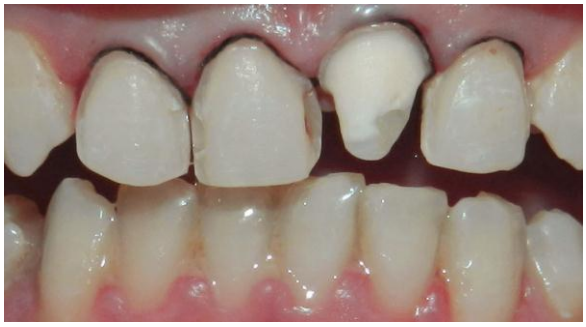

Figure 4. Teeth preparation for three veneers (#7, #8 and #10) and the all ceramic crown (#9)

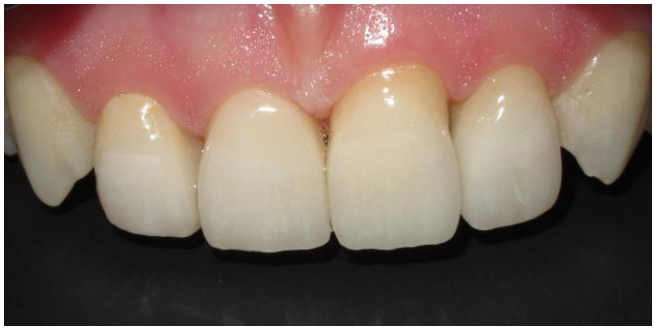

Figure 5. The final result after cementation (frontal view)

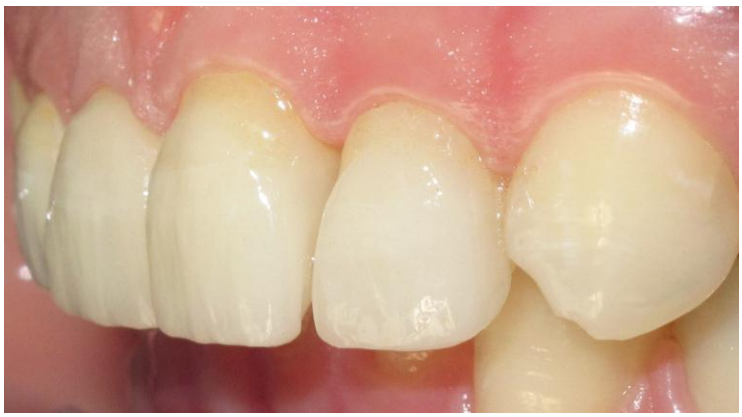

Figure 6. Lateral retracted view one month after prosthetic rehabilitation

DISCUSSIONS

Good communication between the patient and the dental team is essential and represents the basic guidance for treatment planning and understanding the patient's vision of aesthetics. The selection of adequate materials and techniques that make optimal esthetic results possible should be carried out in order to get restoration as close to the natural dentition as possible [6]. Advances in restorative dentistry and development of ceramic systems with biomechanical properties, combined with mimetic requirements, allow the fabrication of restorations with aesthetic and long- lasting results. Noninvasive porcelain veneers represent an extremely conservative treatment option with excellent esthetic results when performed in accordance with a well-defined treatment plan and following strict diagnostic, laboratory, and clinical steps. [7]

This particular case presentation represents an evidence-based example that orthodontic anomalies can be successfully concealed by adequate prosthetic means, whenever patients decline orthodontic procedures.

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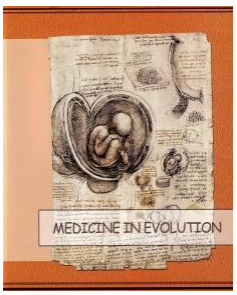
Management of iatrogenic disorders in the aesthetic area



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Abstract

Introduction: Iatrogenic disorders located in the aesthetic area often represent borderline cases in respect to the dentist's skill. "First, do no harm" turns into "first, correct the wrong caused by another", a task strewn with hardship that requires tenacity and rigor.

Case presentation: We report the case of a 37-year-old patient with periodontal symptomatology who requested replacement of four fixed prosthetic restorations situated in the aesthetic area. Clinical examination emphasized the iatrogenic specificity: inflammation was restricted to the vicinity of the old overflowing restorations. Following their removal and the implementation of non-surgical periodontal therapy, four temporary crowns were made and applied; they were later adapted in order to stabilize the marginal contours. Cementing of the final crowns was performed 6 weeks later. Patient evolution was good and complete healing occurred 3 months after prosthetic intervention.

Conclusions: Correcting iatrogenic disorders in the frontal area demands coherence in the development of a treatment plan and a strict completion of each therapeutic stage. Hierarchical distinctions between aesthetics, functionality and biocompatibility must be avoided at all costs otherwise harm caused by the initial iatrogenic fault may very well end up reiterating itself, despite the best efforts to mend it.

Keywords: dental iatrogenic disorders, periodontal damage, aesthetic area

INTRODUCTION

The word "iatrogenesis", as introduced to medical dialectics, comes from the greek terms "iatros", which stands for doctor, healer, and "genesis", which stands for origin. Following the historicity of this concept, a first reference to its harmful nature is made by Hippocrates himself in one of his principles: "First, do no harm" (primum non nocere). The validity of this principle transcends any temporal frame but, although medicine has undergone significant changes over the past two millennia, the medical approach is still prone to risks; iatrogenic injuries represent, to this day, a reality. In dentistry, iatrogenic disorder can affect both teeth and periodontal tissues. Instruments, chemicals and materials used in the treatment of various caries or gum lesions, coupled to a faulty practice, can produce disastrous effects for the patient. Iatrogenic damage can stem from a wrong choice of treatment, from omitting some steps that are essential in therapeutic success, from the interference of management flaws or from deficiencies in the cooperation between the dentist and the dental technician. The role of iatrogenic factors in the etiology of periodontal disease and the influence that dental restorations exert on periodontal health have been established since the beginning of the last century. Studies have concentrated their attention on various aspects of the periodontal–restorative interaction, such as position of the restoration with respect to the gingival margin, presence of overhangs, presence of marginal leakage, roughness of the surfaces and the type of restorative material.[1] All of these issues become even more pronounced when iatrogenic disorder affects the frontal area thus enhancing the therapeutic effort implied by the aesthetic value of treatment.

CASE PRESENTATION

A 37-year-old male pacient suffering from gum bleeding and inflammation of the marginal gingiva located next to four overflowing fixed prosthetic restorations in the frontal area requested treatment. Clinical examination revealed the limited nature of inflammation, inflammatory signs (a red-purple marginal gingiva with smooth texture and increased consistency, bleeding index, probing depths) being restricted to the immediate vicinity of the old, overflowing restorations. (Figure 1). A dental radiography was required in order to expose the bone defect that justified the increase in probing depths (Figure 2). Establishing the diagnosis of localized periodontitis by confirming iatrogenic damage has allowed for setting up a course of treatment: removal of old fixed prosthetic restorations (Figure 3), non-surgical periodontal therapy, reconstruction of the dental abutments using fiberglass, stabilization of the gingival contours by employing provisional crowns and cementing the final crowns. After peforming a dental impression, the old, inadequate prosthetic restorations were removed. Suppressing supra and subgingival pathogenic microflora and hampering bleeding and inflammation were therapeutic objectives attained by scaling and root planning.[2] We then proceeded with cleaning the dental abutments of residual cement and decrepit dentin, preparing the root canals for the insertion of fiberglass posts, embedding the fiberglass posts and restoring the dental pillars. After polishing the dental abutments, four provisional crows were devised and put in place. The following sessions focused on monitoring gingival evolution and marginal adjustment of the provisional crowns using low viscosity composite material. Four weeks later, the complete dissolution of the initial clinical layout allowed for the final dental impression. Next, the lithium disilicate Emax capes were subjected to an adequacy test (Figure 4) and, after being loaded with Emax ceramic, the final restorations were cemented. Inflammatory symptoms mitigated considerably shortly after removal of the overflowing restorations. The remission of clinical signs was closely monitored during each therapeutic step, guaranteeing the success of periodontal treatment and providing a favorable prognosis for the subsequent development of prosthetic treatment. Three months after

cementing the final prosthetic restorations, a follow-up confirmed the effectiveness of treatment by bringing forth evidence of complete healing (Figure 5).

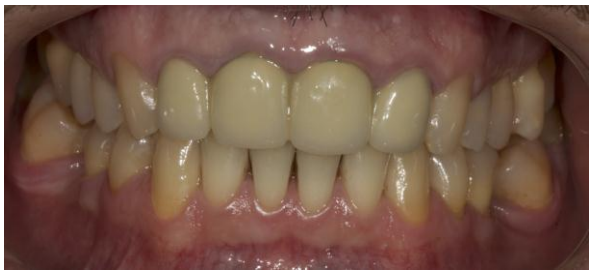

Figure 1.

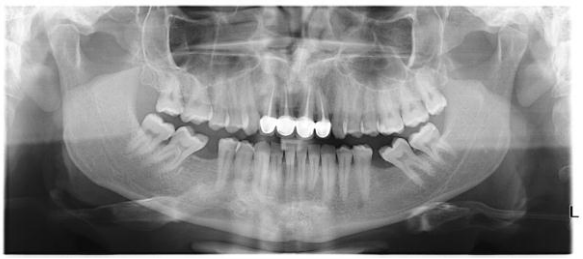

Figure 2.

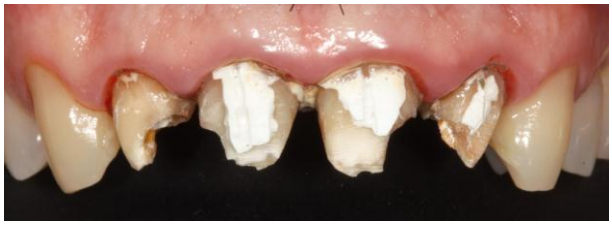

Figure 3.

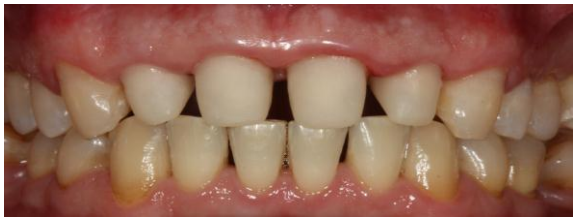

Figure 4.

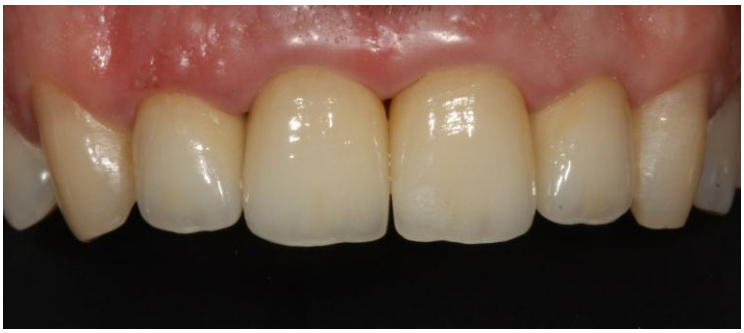

Figure 5.

DISCUSSIONS

Periodontal tissues play an important role in proper aesthetics, function and comfort of the dentition. A healthy periodontium is required for all prosthetic and restorative therapies as a prerequisite for successful outcome.[3] By reversing its course but retaining the universal nature of this statement it is safe to proceed to another: a successful prosthetic restoration is required, in turn, for maintaining periodontal health. Prosthetic iatrogenic disorders are often accompanied by periodontal damage. Restorations may impinge on the biologic width by being placed deep in the sulcus or within the junctional epithelium. This may promote inflammation and loss of clinical attachment with apical migration of the junctional epithelium and reestablishment of the attachment apparatus at a more apical level.[4] A crucial factor in correcting these iatrogenic disorders is the proper adaptation and functionality of the provisional crowns which help shape and stabilize the marginal gingiva prior to the cementing of the final prosthetic restoration.

CONCLUSIONS

From a praxiological viewpoint, iatrogenic disorder imposes itself as a multilateral situation whose resolution requires a judicious leaning towards the therapeutic field. Dealing with frontal iatrogenic disorder poses an even greater difficulty considering the importance gain associated with the aesthetic component of treatment. Proper management consists of an

interdisciplinary approach at the end of which both the fixed prosthetic restoration and its adjacent periodontal structures consolidate each other's value.

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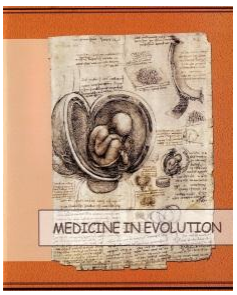
Heroin consumption- the impact on general and oral health status of the consumers - Case Reports



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Abstract

Heroin consumption has devastating effects on oral health- at the clinical examination of the consumers it can be noted an increased number of cavities, of missing teeth and of teeth that have underwenth interventions of odontotherapy.

These facts can lead to cronic malnutrition, poor oral hygiene due to the alteration of the motor function and to a series of neurological phenomena with direct impact on the general status and to the individual capacity to integrate in the society and to carry out the activities of daily living.

The heroin mode of administration can be one of the causative factors of the infection with HIV virus, with hepatitis B or C virus, or with other viruses that can be inoculated by injection.

The management of such a case assumes in many situations a challenge for the medical team and always requires collaboration with other medical specialties to minimize the risks of therapeutic acts both for the patient and for the medical personnel implicated in the treatment.

The degree of comprehension and involvement of the patient regarding the need of oral health it is an issue that cannot be concrete rated since the beginning, often the patients abandons the treatment plan after solving the acute problems.

Keywords: heroin, case management, cervical decay, poor oral hygiene

INTRODUCTION

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 The term opiate is used to define the compounds derived directly from opium, as morphine, codeine any many other semi-synthetic substances from the same class as morphine.

Heroin (diacetylmorphine) belongs to the class of opioids, it was synthesized by Bayer in 1898 and it was originally developed as a morphine substitute with reduced potential to create addiction.

As effects on the general status we encounter psychological effects as: anxiety, depression, cognitive impairment and physiological effects: anemia, weight loss, constipation, loss or delaying of menstrual cycle, various infections.

As on the oral status we observe effects like multiple dental caries with massive coronary destructions, localized in early stage in the cervical area of the tooth, xerostomia, poor oral hygiene because of the low interest for health of the patient who consumes drugs.

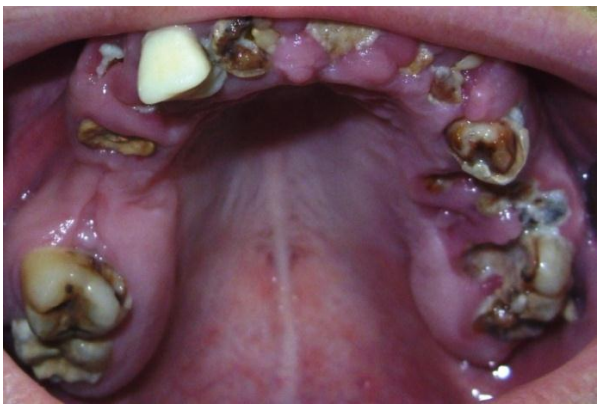
CASE REPORTS

Case No. 1

Patient A. T., male, 24-year-old, heroin and ethno botanicals consumer introduces himself to our clinic for a consult between medical specialties, following that after establishing a treatment plan, to come to the related therapy sessions.

In the anamnesis, he declares that he suffers from hepatitis B, C and infection with HIV virus.

On clinical examination we observed multiple dental caries with massive coronary destructions, loss of teeth and as a result, the loss of masticatory units, the presence of demineralization injuries localized at the cervical level of the teeth and in particular areas, in which normally the decay doesn't exist as the top of the teeth's cusps. The oral mucosa was congestive, and gingival inflammation signs were present with consecutive bleeding (Fig. 1 a, b, c).



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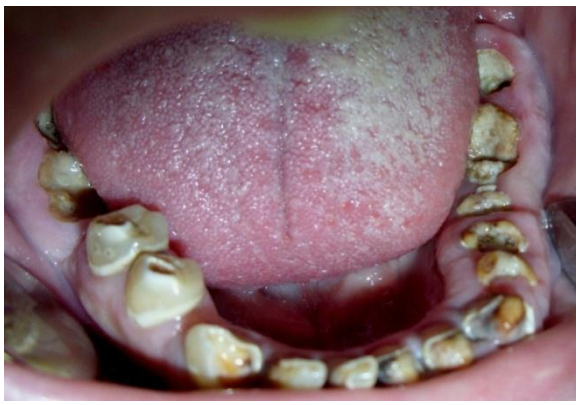

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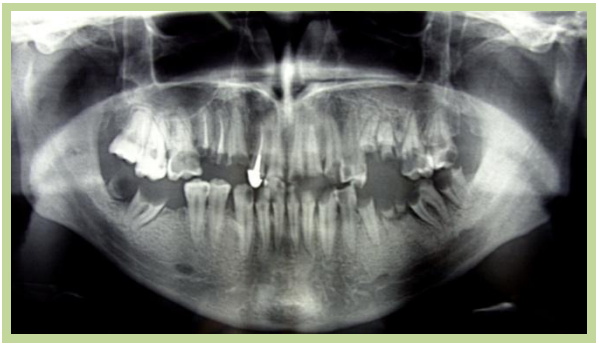

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Figure 1. a. massive coronary destructions, loss of teeth; b. presence of demineralization injuries localized at the cervical level of the teeth; c. initial X-ray that shows the presence of multiple irrecoverable dental roots

After the treatment of the emergencies - the extraction of the irrecoverable dental roots from quadrants number 2, 3 and 4, the patient doesn't return for further oral rehabilitation.

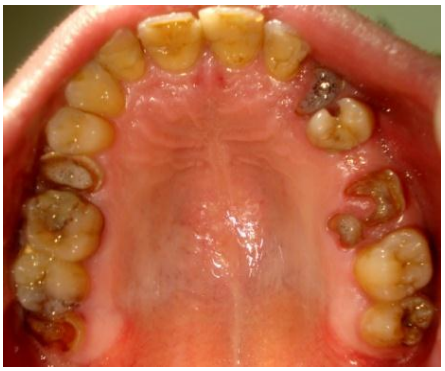
Case No. 2

Patient P. S., male, 37-year-old, former consumer of heroin, has as pathological issues infection with Hepatitis B and C viruses.

On clinical examination we observe by inspection the presence of multiple cavities, multiple coronary destructions, the loss of masticatory units, the presence of dental injuries localized at the cervical level of the teeth, moderate gingival inflammation (before the periodontal treatment it was a severe inflammation).

Also, it is obvious the lack of dental treatment needed in this case, because the patient declares that he has not been to a dental consult since ten years ago (Fig. 2. a, b, c, d, e).

After the extraction of the irrecoverable dental roots for the maxillary and of the both molar one of the mandible, the patient does not return to continue the treatment.



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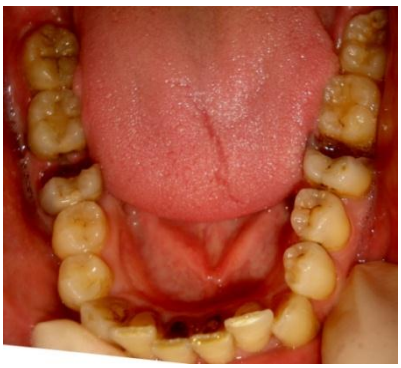

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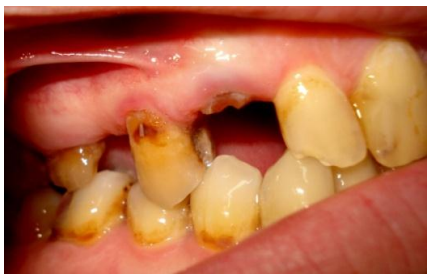

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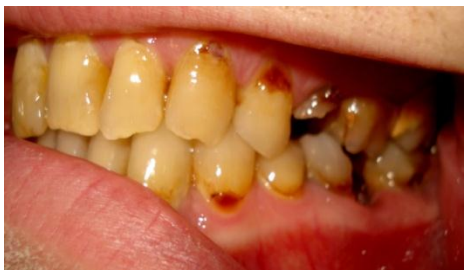

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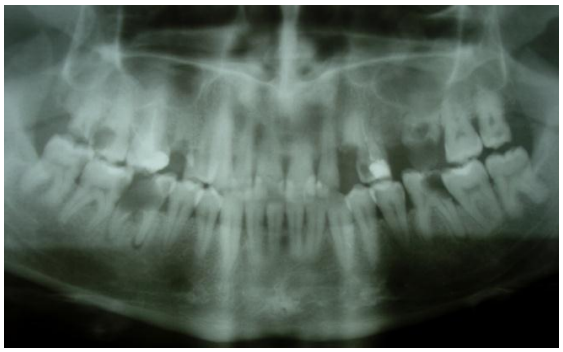


e

Figure 2. a. presence of dental caries, of massive coronary destructions; b. poor oral hygiene; c, d. presence of demineralization injuries localized at the cervical level of the teeth; e. initial X-ray that shows the presence of multiple irrecoverable dental roots and of periapical reactions

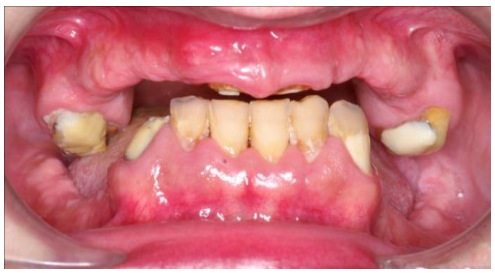
Case No. 3

Patient C. D., male, 33 year-old, former consumer of heroin, he declares in the anamnesis that he suffers from hepatitis B.

On clinical examination, we observed the loss of masticatory units - at maxillary, after losing 1.1, it remained a situation of subtotal edentation, and at mandible the edentation is a bi-terminal one.

It can be noted that dental caries and demineralization injuries localized at the cervical level of the teeth are present, as well as a poor oral hygiene (Fig. 2. a, b, c, d).

The patient is compliant and came to the most of the treatment sessions.



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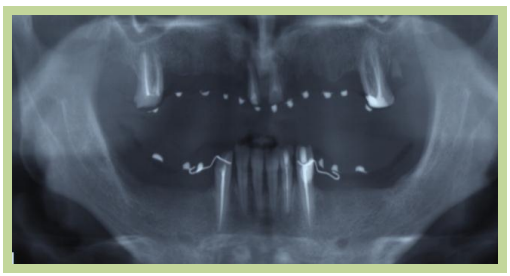

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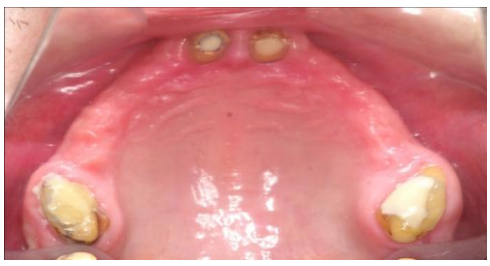

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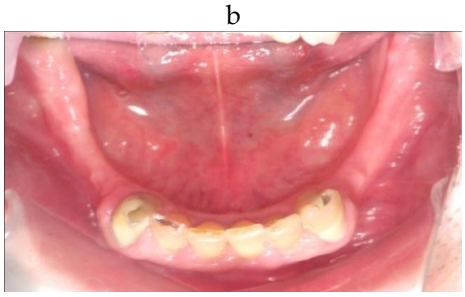

d

Figure 3. a. presence of demineralization injuries localized at the cervical level of the teeth;
b. initial X-ray showing the loss of maxillary bone and the poor implantation of the remaining teeth; c. massive coronary destructions; d. the presence of decay in nonspecific places as the tip of the canine cusps and the incisal edge of the inferior incisors

DISCUSSIONS

The heroin consumption can be associated with the consumption of other drugs, case in which the effects are cumulative and boosted, and the desintoxication and rehabilitation therapy becomes more complex and can take longer time.

Types of drugs that can be associated: cannabinoid (marijuana - cannabis, hashish), sedatives (barbiturates), incentives (amphetamines), hallucinogenic (LSD - lysergic-diethylamide acid), cocaine.

All the actions of opiates can be stopped with synthetic antagonists of opiates (ex.: naloxone, naltrexone) that have action on opiate receptors [1].

All the opioid analgesics are metabolized in the liver, as so, they have to be administrated with caution to the patients with liver diseases [2].

The consumption of these substances has devastating effects on oral health - in the case of heroin consumers it can be noted an increased number of cavities, of missing teeth and of teeth that have underwenth interventions of odontotherapy.

These facts can lead to chronic malnutrition, poor oral hygiene due to the alteration of the motor function and to a series of neurological phenomena [3] - analgesic effects, sleepiness, changes of mood, muscle weakness and respiratory depression. The analgesic effect is not accompanied by the loss of the state of conscious. If not outdated the anesthetic doses, an euphoric state appears and, sometimes, this will be followed by a deep sense of peace that can last several hours before the advent of a state of sleepiness, drowsiness and motor hypokinesia.

Other effects of the heroin are: miosis, hypotension (by inducing histamine release), nausea, vomiting, effects on the gastrointestinal system: decrease of the production of the gallbladder and of the pancreas that have as an effect the slowing of the intestinal transit at the level of the small intestine, the decrease of the intestinal peristalsis and the increasing of the tonic activity at the intestine level, that may cause spasms [2].

CONCLUSIONS

The methods of administration of heroin are by smoking or by injecting it. Because of the second method of consuming it, the associated risks as the infection with HIV virus, AIDS, Hepatitis B or C viruses are increased. Using the same injecting equipment by several consumers or of an equipment used several times, might be one of the ways of transmission of these viruses. As a result, we can encounter manifestations of these disorders, associated with the default effects of consuming heroin at the oral area.

Often the management of such a case is difficult, considering the psychological and social implication of this type of patients. The oral pathology is a complex and various one at the same time, the existing diseases requiring multiple treatment sessions on which the patients don't show or come too late. Also, we have to consider the issues related to finances, that most of the times are a problem and stop the patient to follow a complete treatment plan according to their clinical status. The inability of integration on the labor market and the complex social status - provenance form poor families, the existence of minor age children in care, the costs of the heath treatments in the case of the patients that don't have medical insurance, put on a second plan the interest for oral health for this category of patients.

The lack of correct and complete information regarding the oral hygiene and the lack of integration of the basic skills for performing it, increase the degree of odonto-periodontal damage. The affectation of mental function in various degrees, depending on the dose of drug used and on the association with other types of drugs, may vary from strong cortical excitation, to depression, their alternation or even delirium. In these situations, the awareness of the diseases and of the need for dental treatment is almost null.

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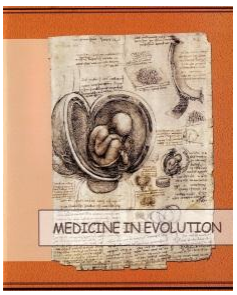
   Source: http://www.oralhealthgroup.com/news/dental-management-of-patients-with-a-history-of-substance-abuse-with-special-consideration-for/1002126007

The relationship between teenagers' oral health literacy, dental use behavior and dental health knowledge



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Abstract

Objective. This cross-sectional study aims to evaluate the relationship between the level of knowledge in dentistry, behavior regarding visiting the dentist and oral health literacy in a group of 150 teenage students with mean age 14.29 (SD±1.66), from Bucharest.

Material and method. They were collected data on literacy with REALD-30 word recognition test. Health literacy was correlated with self-reported oral health status, knowledge about risk factors for tooth decay and periodontal diseases and addressing to the dentist office behavior.

Results. Mean score for REALD-30 was 24.23 (SD ± 3.25). Only 28% of adolescents have an increased level of oral health literacy. The level of oral health knowledge is low.

Conclusions. Lack of medical knowledge is a strong predictor for the low level of health literacy. Oral health education in schools could be an important component of a strategy to increase oral health literacy among adolescents.

Key-words: oral health literacy, health knowledge, teenagers

INTRODUCTION

The concept of health literacy relates to the ability of individuals to perform base reading and numerical tasks needed to manage the health care environment and pursue on health care information system[1]. In other words, health literacy is the degree to which a person has the capability to get, manage and understand basic health data and health services necessary to make proper decisions related to health[2]. Health literacy is interplay between health behaviors and/or knowledge, level of education and health status[3]

Similarly, oral health literacy refers to individual ability to understand and manage dental health information, related to oral health knowledge and behaviors. In this context, it is useful to focus on the role of health knowledge, because this factor is relatively easy amenable to change.

Getting oral health information, understanding its concepts and adequate choosing oral health prevention and treatment needs a skill development named oral health literacy[4,5]. Low level of (oral) health literacy manifests in poor (oral) health status and outcomes[6,7]. Achieving and preserving general and oral health needs one individual to be able to get, understand and act on any type of health data. Research is required to assess the level of oral and general health literacy among adolescents and its effect on their ability to make adequate decisions about their health and using health care services. Obtaining medical information, understanding concepts and appropriate choice of methods of prevention and treatment in the field of dentistry, require the development of oral health literacy skill[8].

Poor dental and medical status has many reasons, namely: reduced access to regular preventive health care, lack of access to early treatments in, low health literacy level and inadequate knowledge of health principles[9].

Oral health knowledge includes understanding the effects and role of oral bacteria, carbohydrates from the diet, regular personal oral health care behavior (tooth brushing and use of dental floss), tobacco and alcohol on oral health. Thus, research is needed to assess the level of health literacy in adolescents and the impact on their ability to make appropriate decisions about their health and health care services[10,11]. Also, it is important to understand the importance of regular dental check-ups to maintain oral status and to find pathology in its early stages[12].

Preventive care in dentistry could be less effective in individuals with low knowledge and a low literacy level because they do not follow medical instructions or do not understand the importance and role of prophylaxis[13,14].

The interrelation between knowledge and literacy is bidirectional: on one hand, literacy skills (reading fluency) of an individual could increase vocabulary and, on the other hand, increased vocabulary improves comprehension of health information. Counseling, as a literacy intervention, might be effective in increasing medical knowledge and thus may be a strategy to be used in order to raise the level of low health literacy[15].

Aim And Objectives

This study aim is to assess the association of knowledge, dental care visits and oral health status with oral and general health literacy in a group of adolescents in Bucharest. The hypothesis was that low oral health literacy level is related to poor self-reported oral health status and decreased level of dental knowledge.

MATERIAL AND METHODS

This cross-sectional population-based survey was conducted in 2015 among adolescents in Bucharest from 4 national colleges and schools.

The ethics committee of the UMP "Carol Davila" approved this study supported by UMF „Carol Davila" in a Young Researchers project 33898/11.11.2014. Schoolchildren and managers were informed before being invited to this survey about the goal of this research, voluntary participation, and right to withdraw at any time.

Were collected data about oral health literacy in a sample of 150 teenagers. They were also interviewed about factors that might be associated with health literacy level: self-reported oral health status and knowledge regarding risk factors for tooth decay and periodontal disease.

The oral health literacy level was measured using a word recognition test called the Rapid Estimate of Adult Literacy in Dentistry (REALD-30)[13]. The test score ranges from 0 (lowest literacy) to 30 (highest literacy). Word-recognition tests have a strong correlation with reading ability and comprehension[16]. Studies also have shown that if someone has difficulty pronouncing medical or dental words, then this person could have difficulty with comprehension and might have a poorer health status than other person who prove to be better at recognizing medicine words[17,18].

The self-reported oral health status was assessed using the National Health and Nutrition Examination Survey item: ''How would you describe the condition of your mouth and teeth/general health?'' with five-point Likert-type response scale: excellent, very good, good, fair and poor. For analysis, the first three categories were combined for a measure of "good/very good self-reported oral health" and the last ones for the measure of "fair/poor" self-reported oral health status.

Dental services use was assessed related to the time since the last visit at dental office (coded as a 2 variables (<6-12 months and >1 year/never).

Schoolchildren' knowledge regarding the main risk factors for dental caries and for periodontal diseases was assessed with multiple answer questions.

The significance was set at $p<0.05$. Data were analyzed using SPSS software (17.0).

RESULTS

Totally 150 adolescents participated in this study. Mean age of participants was 14.29 (SD±1.66) and ranged from 11 to 16 years. Of the whole study sample, 52.7% were female schoolchildren.

Mean score for REALD-30 was 24.23 (SD±3.25), with a minimum of 12 points and a maximum of 30 points.

About one third (N=49) of adolescents in the study had high levels of oral health literacy (scores between 26 and 30 points), are therefore 67.3% (N=101) of the students need oral health education lessons (Figure 1).

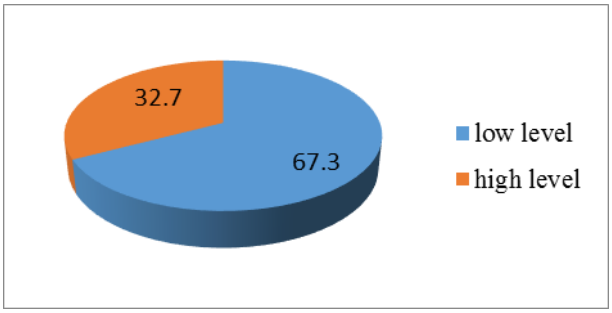

Figure 1. Oral health literacy level assessed with REALD-30 (%)

Most of the adolescents (57.3%) evaluated their own oral health status as fair or poor, fewer (42.7%; N=74) are those who considered it good and very good (Figure 2).

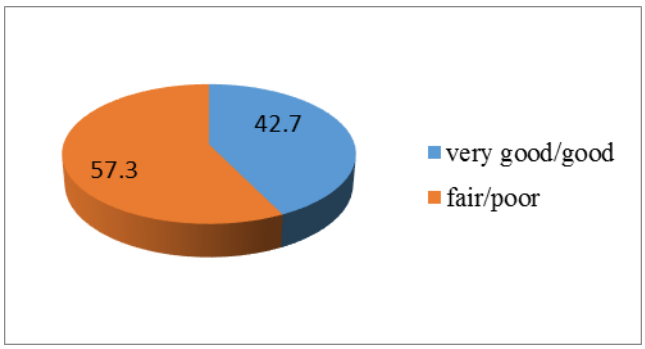

Figure 2. Self-reported oral health status for all subjects (%)

Regarding the frequency of visits to the office dental, half of subjects (50.7%; N=76) behaved correctly, (were present at 6 months or 1 year), the remaining 49.3% (N=74) went sporadically to the dentist, were no longer for dental check-ups for years (Figure 3).

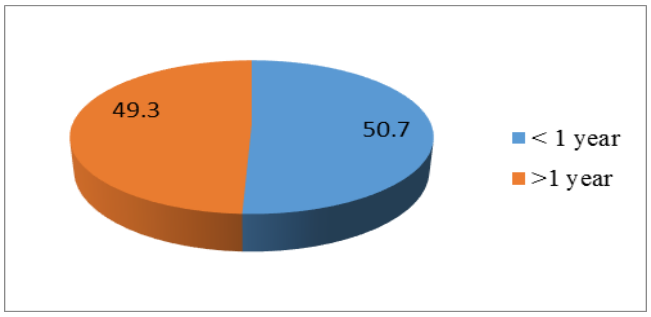

Figure 3. Frequency of visiting dentist among adolescents (%)

Less than one third of students (N=42) knew about risk factors for dental caries, the majority (72%; N=108) answered incorrectly or didn't know (Figure 4).

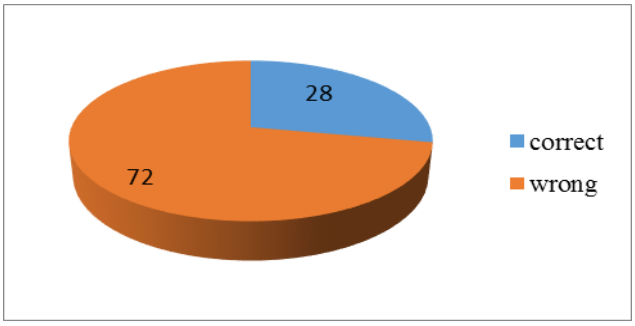

Figure 4. Knowledge regarding risk factors for dental caries (%)

In terms of the knowledge regarding periodontal disease risk factors, level is very low, 93.3% (N=140) answered incorrectly or did not know this aspect (Figure 5).

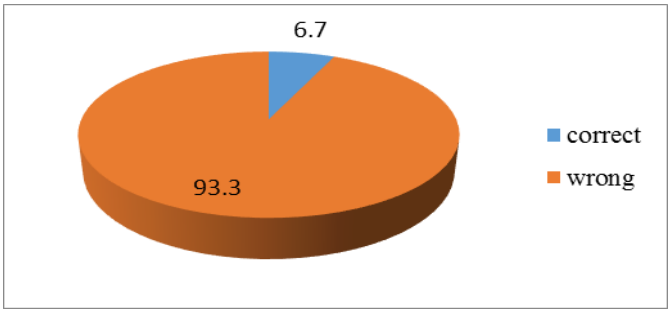

Figure 5. Schoolchildren' knowledge about risk factors for periodontal diseases (%)

In order to assess the relationship between literacy and the factors studied, have been analyzed Pearson bivariate correlations.

Results showed that subjects with an increased level of health literacy , self-report their oral health as being good and very good, but without reaching the threshold of statistical significance (r=0.055, DF=150, p=0.507).

Students who had high levels of oral health literacy had a correct behavior, presenting to the dentist frequently (annually or biannually) and the correlation is statistically significant (r= 176, DF=150, p=0.032).

Adolescents with increased levels of literacy in dental medicine have high levels of knowledge about the risk factors involved in tooth decay, but not statistically significant (r=0.111, DF=150, p=0.175).

Regarding risk factors for periodontal diseases, the correlation is inverse and statistically significant (r=-0.015, DF=150, p=0.85), which may be explained by the extreme low level of knowledge, which requires information on these health conditions, especially that gingivitis is common in this age group.

DISCUSSIONS

The above mentioned results show a low oral health literacy level for most of the subjects included in the study. Knowledge about risk factors for dental caries is low (less than a third answered correctly), and in terms of periodontal diseases, risk factors are less known, less than 10% are aware of this. Behavior regarding visiting the dental office is incorrect for about half of the teenagers.

We therefore consider the need for oral health education lessons that address notions of the main risk factors for oral disease and pupils aware of the importance of regular checkups to the dentist and the need to avoid or reduce exposure to risk factors.

CONCLUSIONS

The results of this study confirm the hypothesis, proving that lack of dental knowledge is a strong predictor for low oral health literacy level. A large number of subjects have low levels of oral health literacy that may interfere with their ability to process and understand basic dental care information. Therefore, receiving continuing education in schools could be an important component of literacy strategy to improve oral health outcomes for adolescent schoolchildren. About one third (32.7%) of adolescents in the study had high levels of oral health literacy, thus oral health education lessons are needed for 67.3% of students. Health information must be tailored to the age group and their level of understanding, after identifying subjects with low health literacy and lack in medical knowledge.

Acknowledgment

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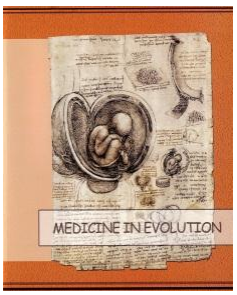
The importance of the histopathological diagnosis in cases of gingival and alveolar mucosa hyperplastic lesions



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Abstract

Gingival and alveolar mucosa hyperplasic lesions, due to their multiple forms of presentation, represent a challenge for the clinician in formulating a perfect diagnosis.

The aim of the study is to draw attention to the early stages of malignant gingival and alveolar hyperplasic pathology which could take a benign appearance.

This study is a retrospective archival review of 44 cases of hyperplastic lesions of the oral cavity.

A total of 44 patients with oral mucosa hyperplasic lesions were examined during one year period at the Department of Oral and Maxilo-Facial Surgery, University of Medicine and Farmacy "Victor Babes", Timisoara. Each lesion was histopathological analyzed and clinical correlations were made. The following data were collected: gender, location and the histopathological type.

Results: The age ranged from 12 to 63 years, with a mean age of 40.5 years. The most common lesions were epulis fibromatous in 29,5% of the total cases, followed by epulis granulomatosa in 22,7% of the cases, giant cell granuloma in 15,9%, followed by epulis fissuratum and granuloma pyogenicum in the equal percentage (13%). An incipient form of squamous cell carcinoma was found in two cases.

Conclusions: The clinician must take into account the malignant gingival and alveolar hyperplastic pathology even the clinical appearance is benign. Teamwork in healthcare promotion is important in the management of the early stages of the malignant oral tumors.

Keywords: hyperplastic lesion, epulis fibromatous, epulis granulomatosa, epulis fissuratum, granuloma pyogenicum, squamous cell carcinoma

INTRODUCTION

Gingival and alveolar mucosa hyperplasic lesions, generally called"epulis", are a large group of tumors that may arise as a result of different kinds of irritants such as microorganisms, trauma, plaque, dental restaurations or dental appliances.

A first description of this type of gingival tumors was made in 1940 by Axhausen. He described gingival granulomas as the most frequently with an unclear aethiopathogenesis. Further he postulated that epulis is a benign tumor and only giant cell epulis is similar to a neoplastic lesion and all other forms of epulis have an inflammatory cause [1].

A first classification of the hyperplasic oral lesions was made in 1983 by Anneroth and Sigurdson. He proposed a separation in three groups: granulomatous group, fibromatous group and giant cell lesions [2].

1998 Schroeder named granulomatous epulis as granuloma pyogenicum because these lesions consist of inflamed granulated tissue.

The nowadays classification of hyperplasic mucosal lesions into the four groups is still maintained but the term "epulis" is omitted, particularly among specialists.

Oral reactive lesions frequently present diagnosis challenges since they mimic diverse pathology [3]. While their duration is extensive, it is not atypical to see ulceration to the epithelial surface [4]. These ulcerated forms have an appearance that may be confused with a malignant lesion. Conversely, some malignant lesions seen in an early stage may be mistaken for a benign disorder [5].

As a general therapeutic protocol, a period of 12-14 days is considered an appropriate period of time to evaluate the response of a lesion to therapy. In cases with no positive response to the therapy, a definitive diagnosis is required.

MATERIALS AND METHODS

The study was a retrospective archival review of 44 oral hyperplasic lesions during one year period at the Department of Oral and Maxilo-Facial Surgery, University of Medicine and Farmacy "Victor Babes", Timisoara. Microscopic sections were examined by two pathologists. Clinical data of each patient: age, gender, location and histopathological type were collected.

RESULTS

The age ranged from 12 to 63 years, with a mean age of 40.5 years.

In the present study 14 cases (31.8%) occurred in males and 30 cases (68.2%) in females. Male to female ratio for reactive lesions of oral cavity was 1:2. Figure 1 shows the distribution of hyperplasic lesions of oral cavity in different genders.

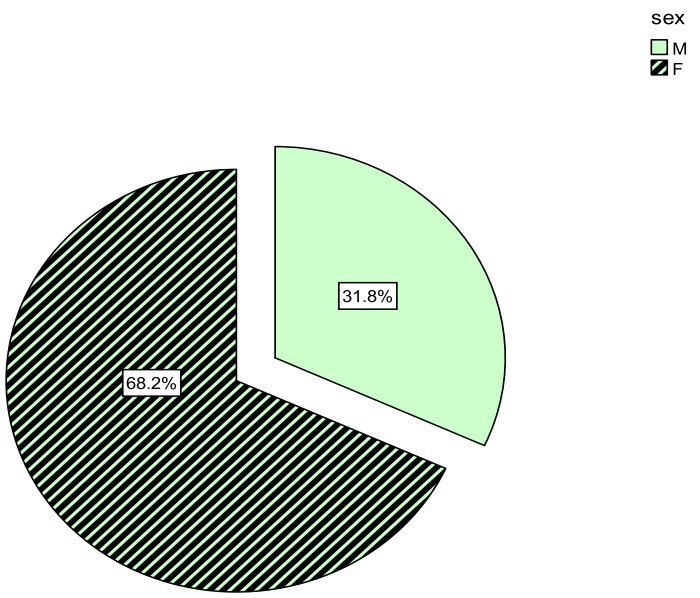

Figure 1. Distribution of hyperplasic lesions of oral cavity in different genders

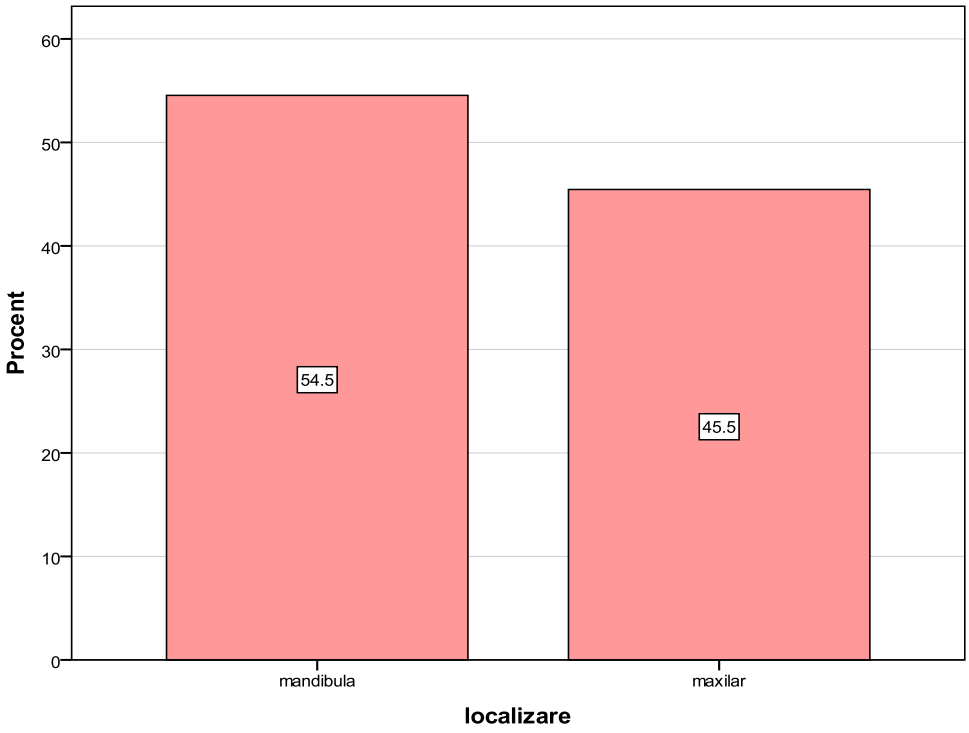

Figure 2. Distribution of hyperplasic lesions of oral cavity in different locations

The hyperplasic lesions were found more frequent at the level of gingival and alveolar mandibular mucosa than in the maxilla. Figure 2 shows the distribution of hyperplasic lesions of oral cavity at the mandible and maxilla level.

After the histopathological examinations, six different types of gingival and alveolar mucosa tumor-like hyperplasia were found. The most common lesion was epulis fibromatous in 29,5% of the total cases, followed by epulis granulomatosa in 22,7% of the cases, giant cell granuloma in 15,9%. Epulis fissuratum and granuloma pyogenicum were found in an equal percentage (13%). In two cases, 4,5%, the histopathological examination showed squamous cell carcinoma.

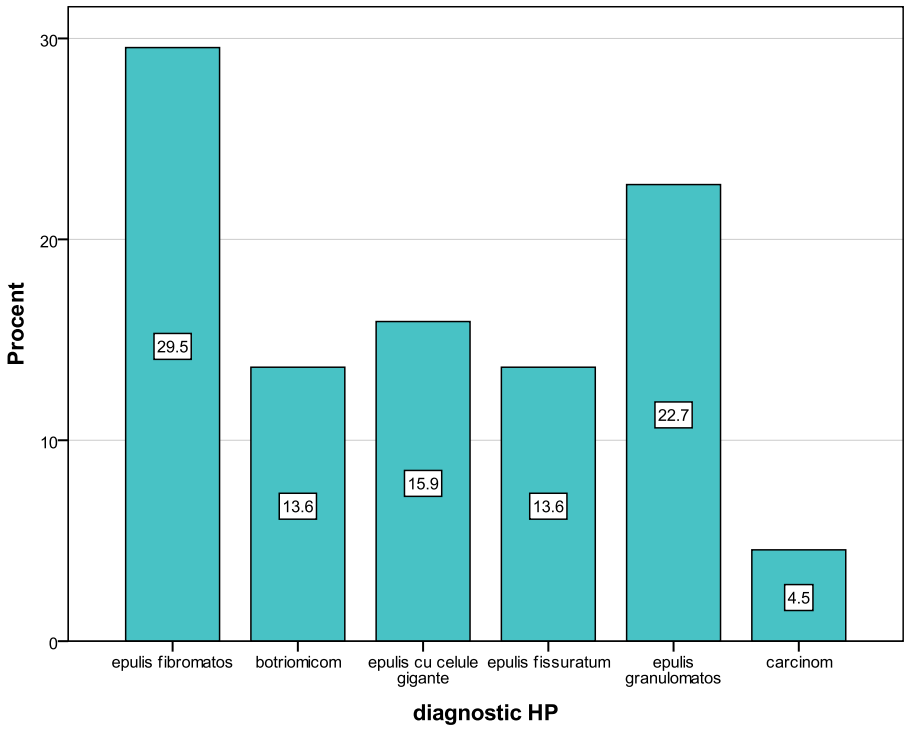

Figure 3. The distribution of oral hyperplastic lesions in oral cavity

The distribution of the hyperplastic lesions of oral cavity in different genders was analyzed. Epulis fibromatous and epulis granulomatosa were more frequent in female patients (20,5% and 18,2%) compared with the same histopathological types in male patients (9,1% and 4,1%). The two cases of squamous cell carcinoma were found only in female patients.

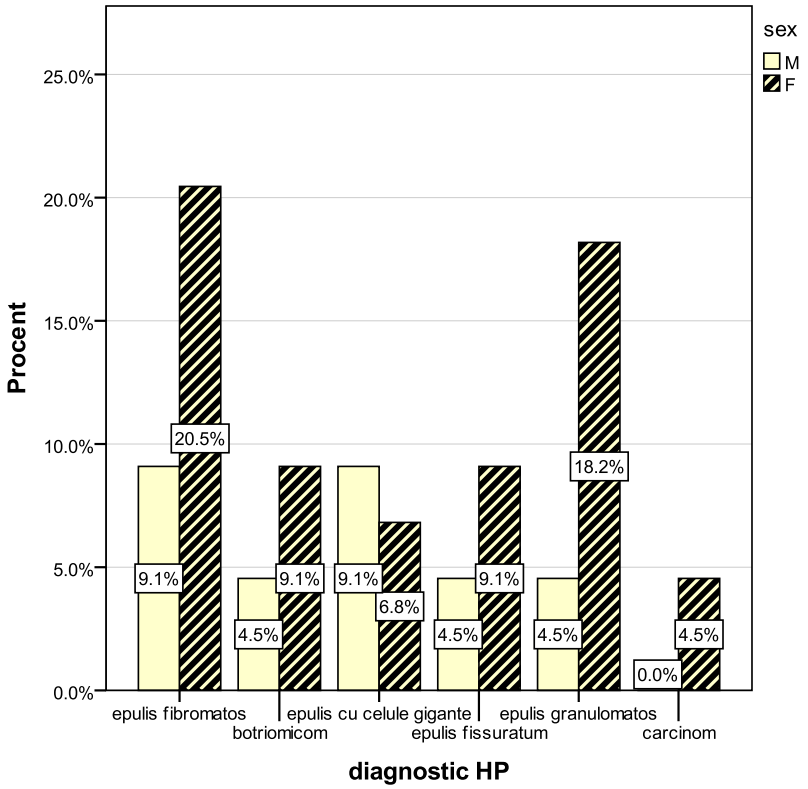

Figure 4. Distribution of oral hyperplastic lesions by gender

The squamous cell carcinoma lesions were localized, one at the maxillary alveolar mucosa level and the other at the labial gingiva of lower anterolateral teeth. Figures 5 and 6 show the tumors at their initial presentation.

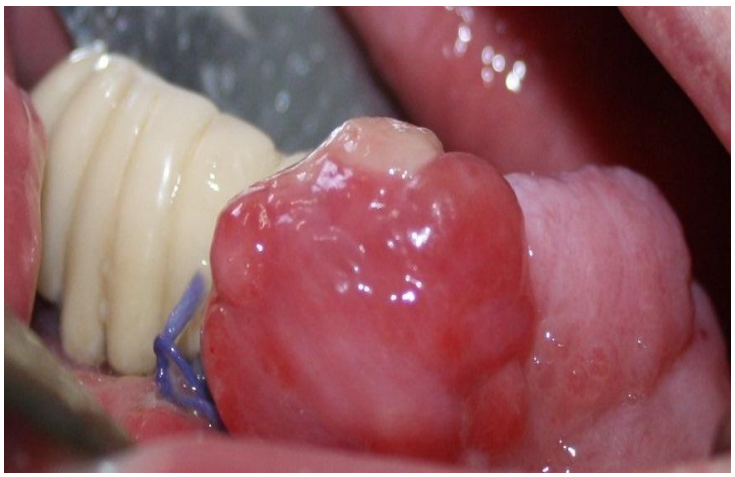

Figure 5. Squamous cell carcinoma of the gingival and alveolar mandible mucosa

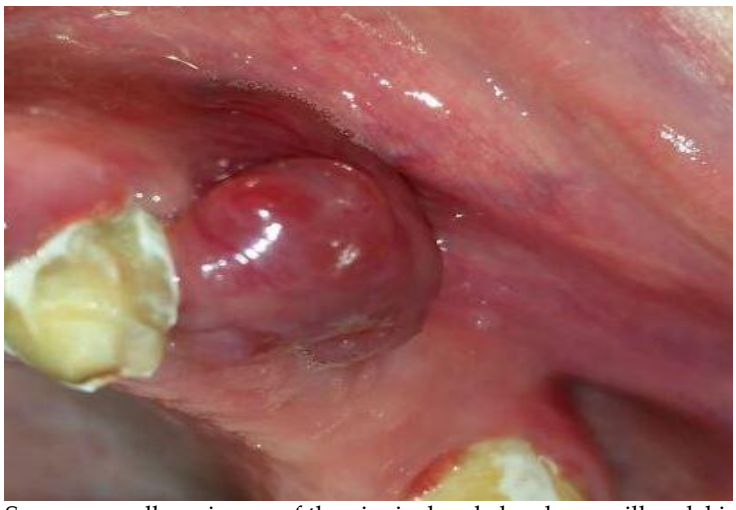

Figure 6. Squamous cell carcinoma of the gingival and alveolar maxillary labial mucosa

DISCUSSIONS

Oral mucosa is a field for external and internal stimuli. It reacts trough a wide spectrum of diseases with a diverse etiology: developmental, inflammatory, reactive or even neoplastic changes [6]. Reactive lesions constantly present clinically and histopathologically as hyperplasic deformity that increase in response to chronic recurring tissue injury which stimulates an exuberant or extreme tissue response [7]. Gingival and alveolar mucosa hyperplasic lesions are tumor-like proliferations with diverse form (sessile or pedunculated), color (from pink to intense red), size (from millimetres to centimetres). The surface could have a non-ulcerated smooth appearance or could be ulcerated [8].

In the present study, a total of 44 oral mucosa hyperplasic lesions were clinically and microscopically examined. The most common lesions were epulis fibromatous, followed by epulis granulomatosa, giant cell granuloma, epulis fissuratum and granuloma pyogenicum. An incipient form of squamous cell carcinoma was found in two cases. With a benign appearance as could be seen in the above pictures, these two cases of squamous cell carcinoma must draw attention to the hyperplastic form of the early stages of malignant gingival and alveolar tumors.

CONCLUSIONS

Gingival and alveolar mucosa could be affected by a diverse group of pathologies. Chronic inflammation associated with dental plaque, trauma, dental restaurations or dental appliances are the most common etiological factors which could lead to hyperplastic lesions. An early diagnosis and elimination of such lesions may minimize further dento-alveolar complications.

Even the most common initial form of oral squamous cell carcinoma is the chronic ulceration, the hyperplastic form of oral cancer must be taken into account. Teamwork in healthcare promotion is important in the management of the early stages of the malignant oral tumors.

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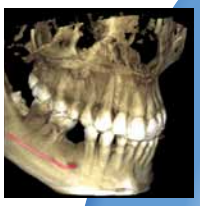

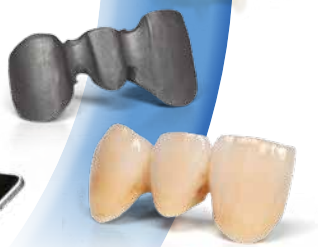

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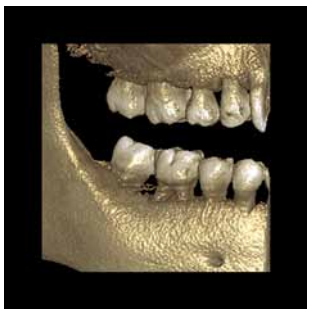

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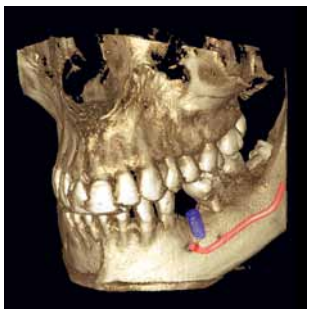

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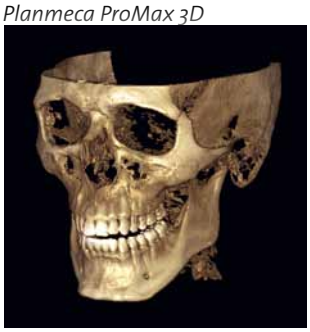

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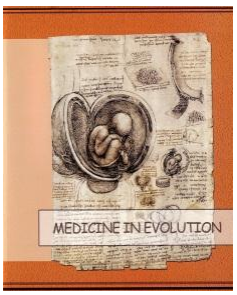
Study about the bacterial prevalence from periodontal pockets in pacients with diabetes and cronical periodontitis



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Abstract

Hypothesis: Diabetes aggravate periodontal disease, by fostering specific bacteria from periodontal pockets.

Material and method: 60 subjects were divided in three groups: 20 with diabetes and cronical periodontitis DP, 20 with diabetes without cronical periodontitis DFP and 20 with periodontitis and without diabetes GC(control group). The bacterial load from periodontal pockets or subgingival plaque was evaluated by PCR, eleven periodontal pathogens were analysed.

Results: Bacteria that presented differences in prevalence between groups were: Eikenella corodens, Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Treponema denticola, Prevotella intermedia, Peptostreptococcus micros, Fusobacterium nucleatum.

Conclusion: In our study, diabetes had a clear contribution for a more severe periodontal disease. Between periodontitis-diabetes and non-diabetes groups there were more differences especially of prevalence of bacteria, and less of types of bacteria involved. The hypothesis that the relationship diabetes mellitus - periodontal disease could be improved by treating one of the two pathological entities seems to be sustained by the results of this study.

Key words: diabetes, periodontitis, bacteria

AIM

To examine the influence of diabetes on the bacterial load from periodontal pockets in persons with cronical periodontitis.

MATERIAL AND METHODS

Our study included 60 people, 28 men and 32 women, aged between 25 and 49, medium age 38,1. They were divided in 3 groups: 20 people with diabetes mellitus and periodontitis DP, 20 with diabetes and without periodontitis GC(control group), and 20 without diabetes and with periodontitis DFP. All of the members of periodontitis groups presented cronical periodontitis, with no less then 2 periodontal pockets of 4 mm depth or more.

Periodontitis was diagnosed by clinical and radiological signs, like congestion, oedema, bleeding, existence of periodontal pockets and gingival atachment loss, mobility and bone loss.

There were excluded those that treated themselves with antibiotics during last year, those with leukemia, neutropenia, genetic and kidney diseases, because of the influence on periodontal simptoms that could modify the results of the study.

People with less than 25 years old or older than 50 years old were not accepted because of too short time from beginning of diabetes or too many complications of this disease. Groups had similar oral hygiene. Patients did not benefit of periodontal treatment during last 6 months.

For each patient was recorded the time of appearance, type of diabetes mellitus and treatment folowed.

The bacterial load of periodontal pockets was measured at 4 mm or more. The tooth was isolated with cotton rolls, wiped with a sterile cotton roll, then a sterile paper point was introduced in the periodontal pocket, and maintained 30 seconds. The paper point was introduced in a sterile tube, sent in the analysis kit, and then sent by post to the laboratory. The technique used was PCR- polymeraze chain reaction which in this case permited the evaluation of eleven bacteria: Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythensis, Treponema denticola, Prevotella intermedia, Peptostreptococcus micros, Fusobacterium nucleatum\periodonticum, Campylobacter rectus, Eubacterium nodatum, Eikenella corodens, Capnocytophaga species (gingivalis, ochraceea, sputigena).

Finally the prevalence of bacteria was calculated, all the results being statistically processed.

RESULTS

Bacteria with differences of prevalence between groups were:

Table 1. Bacteria with differences of prevalence between groups

Bacteria	**Index p**
Eikenella corodens	0.0026
Actinobacillus actinomycetemcomitans	0.0097
Porphyromonas gingivalis	0.0035
Treponema denticola	0.0074
Prevotella intermedia	0.0093
Peptostreptococcus micros	0.0005
Fusobacterium nucleatum	0.0011

Bacteria with no differences of prevalence between groups (Chi-square test) were:

Table 2. Bacteria with no differences of prevalence between groups (Chi-square test)

Bacteria	**Index p**
Campylobacter rectus	0.2140
Capnocytophaga species	0.7489
Tannarella forsythia	0.2719
Eubacterium nodatum	0.0588

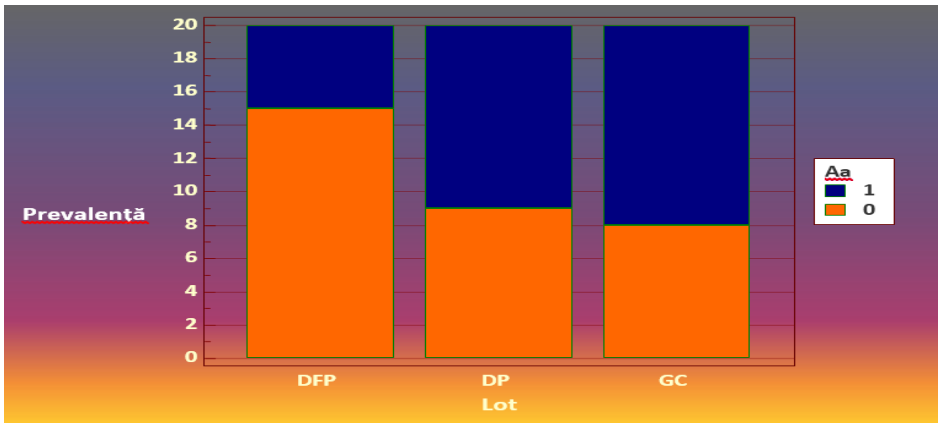

Figure 1. Differences between groups regarding prevalence of Actinobacillus actinomycetemcomitans

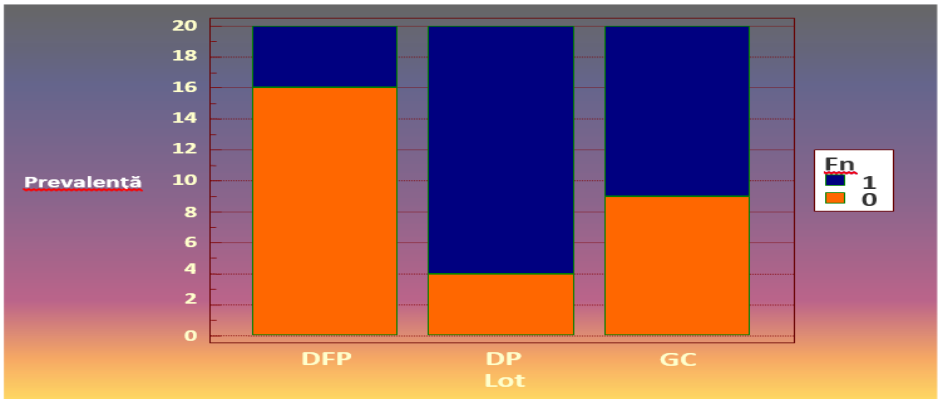

Figure 2. Differences between groups regarding prevalence of Fusobacterium nucleatum

Actinobacillus actinomycetemcomitans has aproximately the same prevalence in periodontitis groups –GC and DP, the values being lower in diabetes group without periodontitis. In this case diabetes seems not to have influence.

Fusobacterium nucleatum had the highest prevalence in DP group, folowed by periodontitis without diabetes group GC and the last DFP.

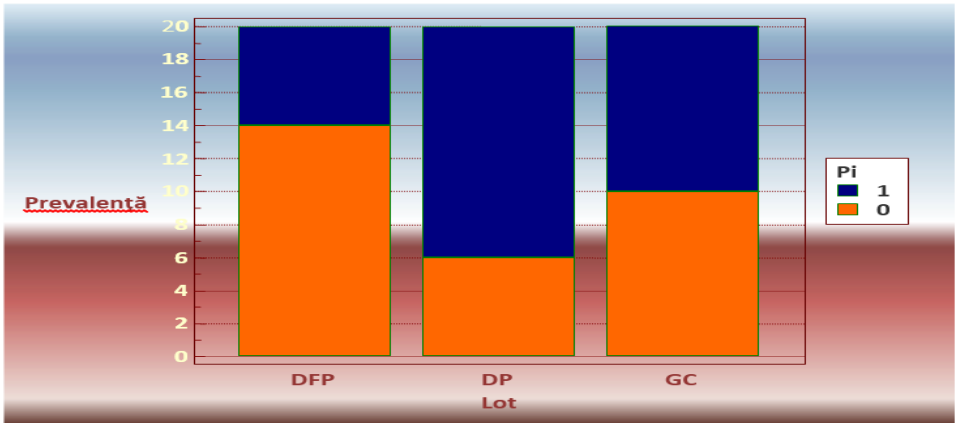

Figure 3. Differences between groups regarding prevalence of Prevotella intermedia

Prevotella intermedia was most represented in DP group, and less in DFP.

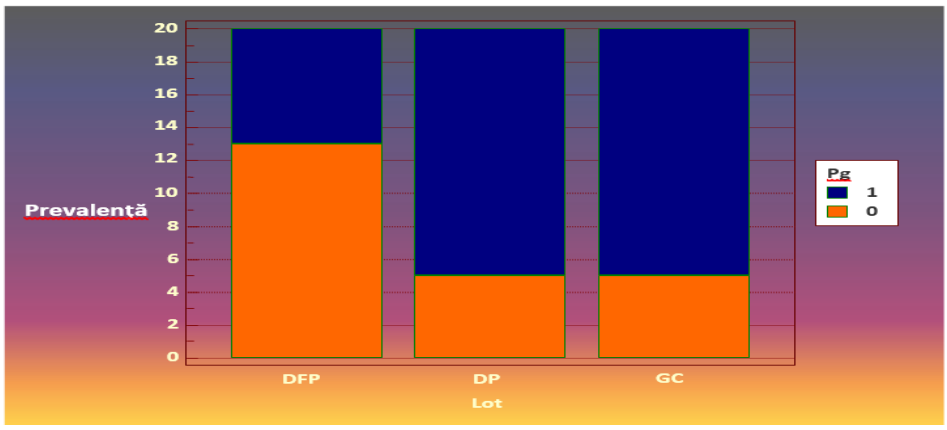

Figure 4. Differences between groups regarding prevalence of Porphyromonas gingivalis

Porphyromonas gingivalis had close prevalence in periodontitis groups, and smaller results in diabetes without periodontitis group.

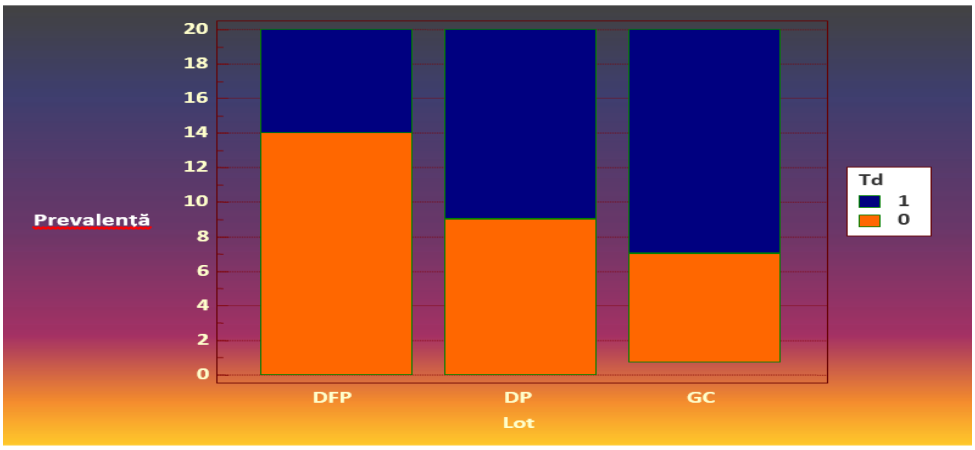

Figure 5. Differences between groups regarding prevalence of Treponema denticola

Treponema denticola had close prevalence in periodontitis groups, a little higher in GC group, and the smallest prevalence in DFP group.

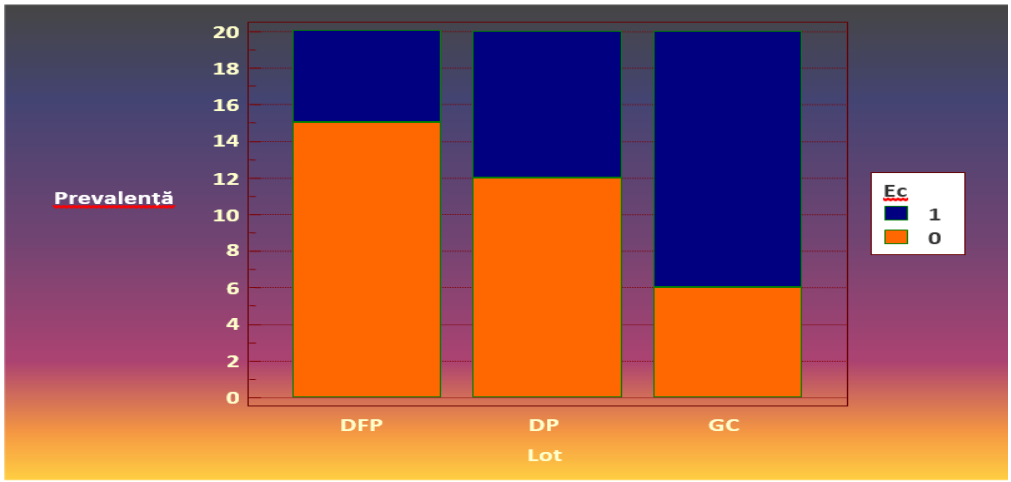

Figure 6. Differences between groups regarding prevalence of Eikenella corodens

Eikenella corodens is most represented in control group GC,smaller values beeing obtained in DP group and the smallest in DFP group.

DISCUSSIONS

Several studies reached the conclusion that people afected by diabetes mellitus had a higher prevalence and severity of periodontitis. Beginning from the idea that a more developed bacterial microflora could be associated with a higher severity of periodontitis, gaining knowledge about it would permit a better explaining of the effects of diabetes mellitus on marginal periodontium.

Research was done on subgingival plaque composition comparing diabetics with non-diabetics.A large number of periodontal pathogens were isolated from periodontal pockets of people with diabetes mellitus, though specific differencies between people with diabetes and periodontitis and those only with periodontitis are not clear enough.[1, 2, 3, 4, 5]

Our study examined the prevalence of 11 periodontal pathogens at three groups, one with periodontitis without diabetes mellitus type II, one with diabetes without periodontitis, and one with diabetes mellitus and periodontitis.The aim of the study was to explore the way diabetes mellitus influences periodontitis. The groups were balanced in terms of age and sex.

Regarding the bacterium Porphyromonas gingivalis, some authors found more of it at diabetics than non-diabetics.[4] Others failed in doing such associations.[6] A more precise comparison, betweend subjects with or without diabetes and periodontitis reached the same conclusion as our study, finding a higher prevalence at those with periodontitis regardless of the presence of diabetes.[2]

For Tannarella forsythia the prevalence was higher in periodontitis groups, yet the difference from control group was not as high as for the other bacteria. Treponema denticola in our study had same values in periodontitis groups, higher than in diabetes without periodontitis group, showing the association with this disease. Though, some authors are sugesting a closer association of this bacterium with diabetes.[3]

Prevotella intermedia and Fusobacterium nucleatum had the highest prevalence in DP group, folowed by GC group. It seems that their presence is periodontitis related, beeing emphasised by diabetes.

Eubacterium nodatum and Campylobacter rectus were weak represented, yet Eubacterium nodatum had higher values in periodontitis without diabetes group.

More frequent, the investigations found similar periodontal pathogens in subjects with periodontitis with and without diabetes. After Ebersole et al. [4] the periodontitis sites in diabetes showed a higher frequency of Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, and Campylobacter spp. Serum antibody to Campylobacter rectus was elevated in type 2 diabetes, whereas antibody to P. gingivalis and C. rectus were elevated in subjects with periodontitis, irrespective of diabetes status.

Lalla et al. found among the 12 investigated species, only levels of Eubacterium nodatum higher in diabetic patients type Iîn schimb a obținut rezultate similare pentru majoritatea patogenilor, cu excepția Eubacterium nodatum, care a foat mai bine reprezentat la diabetici.[5]

Hintao et al. evidenced that type 2 diabetes patients had significantly more severe periodontitis, a higher plaque index and a higher prevalence and magnitude of root surface caries than non-diabetic subjects. Significantly more diabetic subjects had higher levels of Treponema denticola, Prevotella nigrescens, Streptococcus sanguinis, Streptococcus oralis and Streptococcus intermedius in their supragingival plaque than non-diabetic, but unsignificant differencies for salivary and subgingival bacteria.[7]

Usualy, gram negative bacteria were associated with insulin resistance. Gram negative bacteria generate LPS toxins which probably interfere insulin action and are responsible for the maintenance of insulin resistence at periodontitis subjects. [8]

Mashimo et al. showed that the cultivable microflora at subjects with insulin dependent diabetes was predominated by Capnocytophaga and anaerobic vibrios. In some patients, Actinobacillus actinomycetemcomitans were also found. This distinguishes the subgingival flora from that of adult periodontitis patients. In periodontitis lesions from nondiabetic adults, black-pigmented Bacteroides such as B gingivalis or B melaninogenicus subspecies intermedius are often found. [9]

Another study compared the detection rates of 5 putative periodontal pathogens: Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Eikenella corrodens, Treponema denticola, and Candida albicans by PCR between non insulino dependent diabetes mellitus and non-diabetes mellitus adults. The results suggested that P. gingivalis, T. denticola, E. corrodens and C. albicans may play important roles in the periodontitis of both NIDDM and non-DM individuals, however the etiology of periodontitis in both groups may not be different from each other. [10]

Other authors compared a japanese population of T1DM patients with and without periodontitis.T he periodontitis group had a significantly longer mean duration of diabetes and a higher percentages of subjects harbouring P. gingivalis and P. intermedia than the periodontally healthy group. [11]

Sardi et al found that diabetics had a higher prevalence of Candida spp., mainly Candida albicans and Candida dubliniensis, and a lower frequency of Tannarella forsythia, when compared to non-diabetic patients.[12]

On study that compared chinese cronical periodontitis subjects with another group with diabetes mellitus type II and cronical periodontitis. The diabetes and periodontitis patients were more likely to be urban residents and generally had higher incomes, higher mean BMI, and poorer periodontal health status. Higher levels of Treponema denticola and Tannerella forsythia and lower levels of Prevotella intermedia were identified in the subgingival plaque of diabetic group.[13]

CONCLUSIONS

1. Bacteria with difference of prevalence between groups were: Eikenella corodens, Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Treponema denticola, Prevotella intermedia, Peptostreptococcus micros, Fusobacterium nucleatum.
2. DFP group exposed a low level of all bacteria.
3. Close prevalence in DP and GC group had: Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Treponema denticola.
4. Higher prevalence in GC group had Eikenella corodens.
5. Higher prevalence in DP group had: Prevotella intermedia, Fusobacterium nucleatum.

In conclusion, the opinions regarding the influence of diabetes on peiodontal microbiota are multiple, ranging from similar bacteria to various species that could be found in periodontal pockets with greater prevalence. In our study, diabetes had a clear contribution for a more severe periodontal disease. Subjects with periodontitis and diabetes had higher bleeding index and atachment loss. Between periodontitis-diabetes and non-diabetes groups there were more differences especially of prevalence of bacteria, and less of types of bacteria involved. The hypothesis that the relationship diabetes mellitus-periodontal disease could be improved by treating one of the two pathological entities seems to be sustained by the results of this study.

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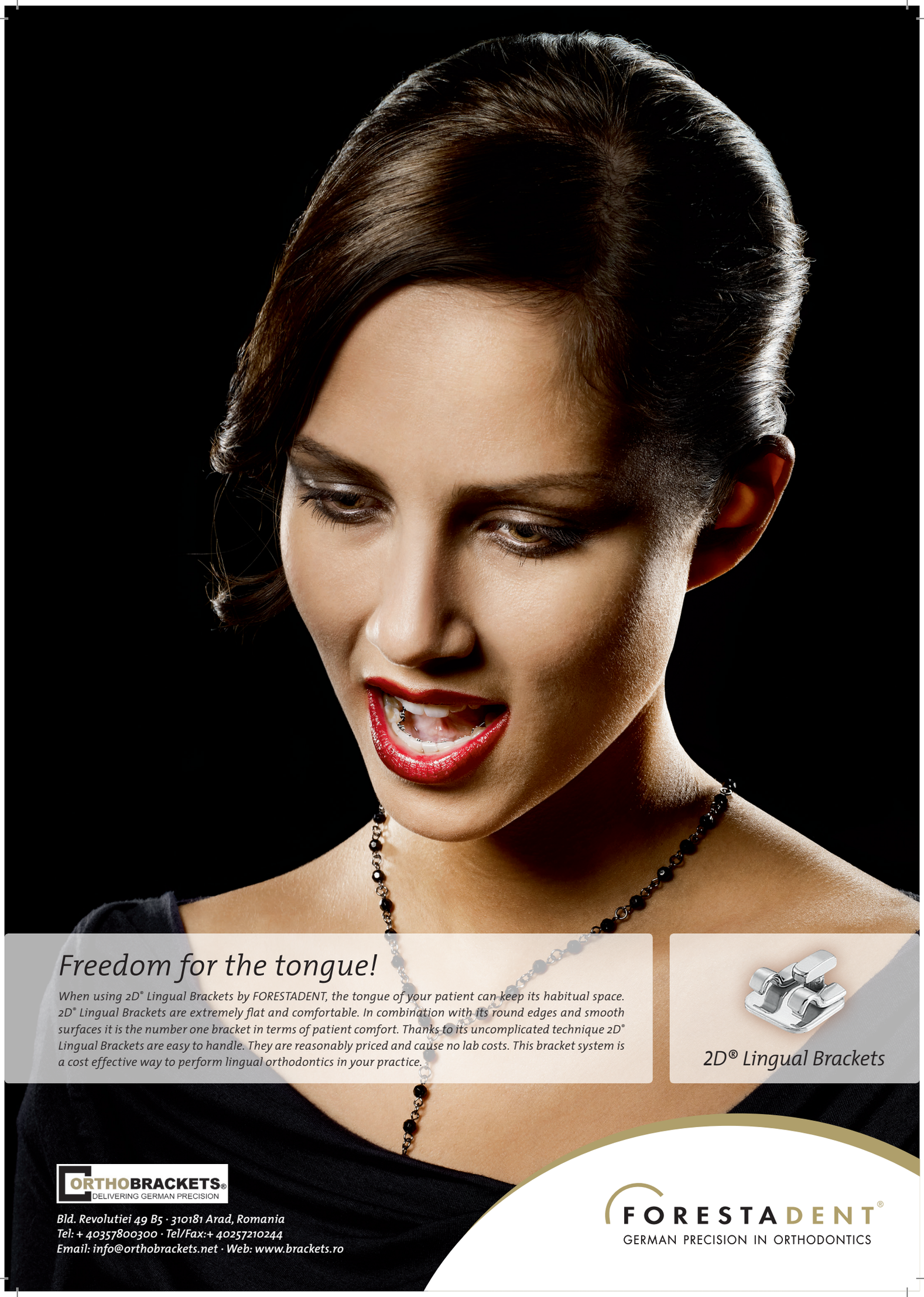
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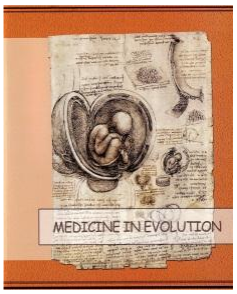

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