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THE ROLE OF VITRECTOMY IN THE TREATMENT OF PROLIFERATIVE DIABETIC RETINOPATHY

УЛОГАТА НА ВИТРЕКТОМИЈАТА ВО ТРЕТМАНОТ НА ПРОЛИФЕРАТИВНА ДИЈАБЕТИЧНА РЕТИНОПАТИЈА

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Abstract

Diabetes mellitus and the complications that occurduring this disease are important social and health problem. Diabetic retinopathy is the leading cause for the decrease in visual acuity in the population between 25 and 65 years of age. It is partly due to vitreous hemorrhage and changes in vitreoretinal mutual relationship in the course of proliferative diabetic retinopathy. Visual deterioration significantly contributes to the change of life-style in these patients and a burden to the social environment. Vitrectomy is a surgical intervention by which the changed vitreous gel and the pathological substrate in it are eliminated and the anatomic relations of referral structures are re-established, which facilitates recovery or improvement of visual acuity in affected patients.

The aim of the study is to present to the ophthalmology specialists the essence and the importance of this surgical intervention, which is of great significance for the patients with proliferative diabetic retinopathy, that is, advanced proliferative diabetic retinopathy.

The emphasis is put on the necessity of this surgical intervention to establish clear optical media and anatomic relations, but also, on the "timing" as particularly important fact for performing the intervention in order to achieve effectiveness.

Conclusion. This surgical intervetion allows improvement of visual acuity in many patients with visual impairment as well as possibility for their normal functioning in social environment, which is very important for these patients with many comorbidities. The recent and permanent achievements in vitreous surgery decrease the risk of complications in this complex and demanding surgical intervention.

Keywords: proliferative diabetic retinopathy, vitreous hemorrhage, vitrectomy

Апстракт

Дијабетес мелитуси компликациите, кои се јавуваат во тек на заболувањето, претставуваат значаен социјален и здравствен проблем. Дијабетичната ретинопатија е водечка причина за намалување на видот кај популацијата меѓу 25-65 години. Значаен дел се должи на крварење во витреалното тело и промени на витреоретиналниот сооднос, во тек на пролиферативната дијабетична ретинопатија. Визуелната попреченост значајно придонесува во промена на животниот стил на таков болен, како и оптоварување на социјалната средина. Витректомија е оперативен зафат со кој се отстранува изменетиот витреален гел и патолошкиот супстрат во него, се воспоставуваат анатомски односи на референтните структури, што овозможува враќање или подобрување на видната острина на афектираните болни.

Цел на трудот е доближување до офталмолошката јавност за суштината и за важноста на оваа хируршка интервенција, која е од големо значење кај болните со пролиферативна дијабетична ретинопатија, односно напредната пролиферативна дијабетична ретинопатија. Во трудот, авторите ја потенцираат неопходноста од овој хируршки зафат во воспоставување проодност на оптичките медиуми и нормализација на анатомските односи, но и го истакнуваат, што е посебно важно „тајмингот" на изедување на интервенцијата, кој е есенцијален за нејзината ефективност.

Заклучок. Со овој оперативен зафат, кај голем број болни со визуелна попреченостсе овозможува подобрување на видната острина, и можност за нормална функција во друштвена средина, што е од неспорно значење за оваа популација болни, која е со голем број коморбидитети. Поновите и перманентните достигнувања во витреалната хирургија го намалуваат ризикот од компликации кај овој сложен оперативен зафат.

Клучни зборови: пролиферативна дијабетична ретинопатија, витреална хеморагија, парс плана

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витректомија

Introduction

Diabetes mellitus (DM) and the complications that occur during the disease are a significant health problem in contemporary world community. One of the microvascular complications of the disease is the onset of diabetic retinopathy (DR), which is a leading cause for decreased visual acuity in the population between 25 and 65 years of age.
In patients with diabetes mellitus retinopathy appears in 13% of those who have had DM longer than 5 years, while in patients that have had DM longer than 10-15 years retinopathy is foundin almost 90% [1].
The vision loss most frequently happens as a result of the damagein macular region where macular edemaor another type of change of the macula appears as a consequence of the underlying disease [2]. The development of proliferative retinopathy, whose occurrence is due to the poor glycemic control and significantly correlated with disease duration, is characterized with the appearance of new fragile blood vessels. As a result, there is bleeding in the vitreous body and modification of thevitreous jelly-like substance, its condensation and onset of retinal tractions, the result of whichis a significantdecrease in visual acuity.
Vitrectomy is a surgical method by whichthe alteredvitreous gel and its pathological content are removed. Vitrectomy is also utilized in a significant number of pathological eye conditions, retinal diseases or changes in the vitreous body.
Robert Mechamer is a pioneer of the modern closed pars plana vitrectomy (PPV), who started to implement this type of surgical method in 1972. It should be pointed out that the very beginnings as well as the later development of the method depended on many other newly developed technological innovations and the application of new surgical techniques.
The aim of the study is to bring to the attention to the specialists in ophthalmology the less abstract intervention, which is of great importance to patients with proliferative retinopathy, especially the more advanced proliferative diabetic retinopathy. One of the goals is to stress the significance of this surgical procedure in establishing clear optical media and anatomical relations as well as to point out that the “timing” of the intervention is crucial for the efficiency of the procedure.

Discussion

A long-term metabolic imbalance during diabetic disease causes changes in microcirculation. The changes in the eye fundus are manifested with the onset of diabetic retinopathy which shows progressive course in the clinical expression. These microcirculatory changes which are determined by the disturbed glycolytic pathway and the accumulation of glycolysis products that damage the retinal capillary endothelial cells as well as the other cells in the retinal tissue, induce retinal ischemia and initiate a cascade transduction intracellular reactions, that is, induce transcription and generate a large number of substances, cytokines that have a proangiogenic influence (VEGF, PIGF, PGF) [3].
They have crucial role in the progression of diabetic retinopathy, which in the proliferative retinopathy stage is characterized by growing of new blood vessels outside of the retinal tissue [4]. The posterior hyaloid membrane has the role of scale which allows these new blood vesselsto permeate in the vitreous body [5].
The appearance of these newly formed extra retinal blood vessels with gentle fibrovascular proliferation represent precautionary signal for hemorrhage in vitreous cavity.
Although small and unremarkable in the beginning, these extravasations provoke macrophage transformation of hyalocytes and pigment cells which leads to collagen modification of the vitreous jelly-like substance and correspondingly, creation of more expressed collagen fibrous structure with newly created capillaries. These changes, their traction or vitreous detachment, predispose tearing of thesmall vessels and extravasation of the newly formed blood vessels, i.e. recurring bleedings into the vitreous space.
The hemorrhage depending on the place of the blood vessels bleeding and the size of hemorrhage as well as depending on the condition of the vitreous gel and the posterior hyaloid membrane occupies different location and volume in the vitreous cavity and can significantly affect the visual acuity. However, bleeding into the vitreous gel is just one of the reasons for decreased visual acuity in proliferative retinopathy [4,5].
The condensation of collagen fibers in the vitreous gel and the vitreoretinal proliferations may produce retinal traction with consecutive retinal detachment from the pigmented epithelium, that is, onset of fractional detachment or onset of retinochisis or even combined rhegmatogenous-tractional detachment. The tractions of these membranes are especially important in the region of arcadesand between them, where dragging or even detachment of macula lutea appears, which is correlated to a significant decrease of visual acuity.
In some cases, the region betweenthe arcades can be bypassed by a thickened posterior hyaloid membrane creating an opacification of the vitreous membrane, which obstructs visual observation of the macula but equally decreases the vision of the patient. Combined with the ischemic macular changes in that area, the macular function is considerably deteriorated. The creation of proliferative membranes in the region of the optic disc papilla or the papillomacular bundle, their traction and compromised blood flow, can also lead to decrease in visual acuity.

The beginnings of vitrectomy as a surgical procedure

Vitrectomy is a surgical procedure, which was introduced by Robert Mechamer and developed in the early 1980s. In the beginning, indications for using vitrectomy were limited to cases with proliferative diabetic retinopathy with vitreous hemorrhage which does not clear up within one year or in patients who have tractional retinal detachment with involved macula.

The expansion of its use initiated establishing of clinical examination regarding the application of this method by the National Eye Institute, through DRVS (Diabetic Retinopathy Vitrectomy Study) [6]. The study showed the advantages of vitrectomy application in patients with type 1 diabetes, where vision improvement was achieved in 35.6%, in comparison to conventional treatment with 11.7%, while postponement of the vitrectomy procedure resulted in good vision in 1, that is, 9% of the patients.

The study suggested that vitrectomy had to be performed with the onset of the first profuse bleeding in these patients, especially if the existence of massive fibroproliferations was evident from the previous exams while the macula lutea was with good potential. Postponed vitrectomy is recommended in older adults so that spontaneous resorption of bleeding is allowed, especially if the vision in the other eye is good.

However, the advancement of vitreous surgery techniques as well as the latest technological achievements that have decreased the complications in this complex surgical procedure, the indications for vitrectomy have been expanded as related to the traction in the optical disc area, peripapillary region and macula, extensive pre-retinal hemorrhage and vitreous retinal proliferations, with aim to remove the pulling of the retinal and papillar region.

Indications for vitrectomy in proliferative diabetic retinopathy

With the extensive use of vitrectomy as a procedure and with theimprovement of the working techniques and technical capabilities as well as the availability of the equipment and instruments, the indications for using this procedure with diabetic proliferative retinopathy have expanded as well as the timing for its use [4,7].

Indications for vitrectomy are the following:

- Persistent or recurrent bleeding in the vitreous body;
- Existence of premacular membrane or premacular bleeding;
- Fibroproliferations with traction in the macular region and its distortion;
- Detachmentof the retina which threatens macular dislodging, or tractional-regmatogenous detachment;
- Refractory edema in macula lutea;
- The latest views include: neovascularization of the frontal segment with opacification of posterior segment, frontal hyaloid proliferation or ghost cell glaucoma [4,7].

The goal of vitrectomy is to remove the bleeding and the altered vitreous body which disturbs the normal process of permission andreceipt of light rays. However, vitrectomy also has therapeutic importance in removing many substances, such as hemosiderin, by which macular toxicity is reduced, i.e. the proteins and cytokines which have favorable role in the development of diabetic retinopathy [8].

In addition, the removal of the posterior hyaloid membrane and vitreous retinal membranes reduces the possibility of further proliferation of blood vessels and recurring bleeding. Vitrectomy allows anatomical stability of the retina and macula, providing better physiological potential and function of those structures [9].

The surgical procedure, though specific and in correlation with pathological findings, generally consists of: [7,10].

1. Removal of vitreous opacification.
2. Excision and dissection of fibro vascular membranes with elimination of traction.
3. Positioning of the retina with the use of intraocular tamponade.
4. Effective homeostasis.
5. Endolaser photocoagulation.
6. Taking care of eventual iatrogenic ruptures and prophylaxis of complications.

Besides the expansion of vitrectomy indications in sense of pathological conditions, technically better conditions for performing the surgical procedure and accepting new techniques and working methods, the time space for vitrectomy performance has been expanded as well. In patients with type 1 DM, the use of vitrectomy procedure with advanced proliferative retinopathy has been elaborated in the DRVS study.

Now vitrectomy is implemented earlier with type 2 DM, that is, before classically accepted attitude for the period of 6 months, the period that would allow resorption of the bleeding. It is mostly related to patients in whom removal of advanced diabetic retinopathy and vitreous hemorrhage significantly reduces the quality of life. Although in many patients the vision is improved, yet the preoperative prediction is not recommended, because the visual results of the surgical procedure are conditioned by the pathological substrate and actual retinal function, where the blood flow and the oxygennation are very important. However, even a slight improvement in the vision of these patients is of great significance.

Conclusion

The proliferative diabetic retinopathy is a considerable complication of the chronic metabolic imbalance in diabetes, which involves the visual acuity and consequent effects on the lifestyle of the patient.

With implementation of vitrectomy, when by intervention on the level of vitreous body and the retina the

pathological substrate and opacification of the vitreous body are removed, the anatomical relations of the tissues are established.

This surgical procedure gives opportunity to many patients with visual disturbances as a result of the disease, to function normally in the social environment which is of great importance to this type of population suffering frommanycomorbidities. The latest and permanent achievements in the vitreous surgery reduce the risk of complications with this complex and demanding surgical procedure.

Conflict of interest statement. None declared.

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ZIRCONIA-DENTAL BIOMATERIAL. A LITERATURE REVIEW

ЦИРКОНИЈА-ДЕНТАЛЕН БИОМАТЕРИЈАЛ. ПРЕГЛЕД НА ЛИТЕРАТУРА

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Abstract

The aim of this study is to present the use of zirconia and its meaning as a biomaterial with outstanding biocompatibility, strength, excellent aesthetic, which promises revolution in dentistry, for crowns, dental bridges and posts in prosthetics and for implants in oral surgery. As new materials and processing techniques are steadily being introduced, the technological evolution of ceramics for dental applications has been remarkable. The interest of dental research in metal-free restorations has been rising following the introduction of innovative all-ceramic materials in the daily practice. In particular, high strength ceramics and related CAD/CAM techniques have widely increased the clinical indications of metal-free prostheses, showing more favorable mechanical characteristics compared to the early ceramic materials. Zirconia has been recently introduced in prosthetic dentistry for the fabrication of crowns and fixed partial dentures, in combination with CAD/CAM techniques.

Key words: zirconia, dentistry, all-ceramic materials, CAD/CAM

Апстракт

Целта на овој труд е презентирање на употребата на циркониумот и неговото значење како биоматеријал со извонредна биокомпатибилност, цврстина, одлична естетика, што ветува револуција во стоматологијата, во протетиката за изработка на коронки, дентални мостови и колчиња за надградби, а во оралната хирургија за импланти. Со воведувањето нови материјали, обработка и техники, значително се зголемува и технолошката еволуцијана керамиката за стоматолошка примена. Воведувањето иновативни, целосно керамички материјали во секојдневната практика ги поттикнува истражувањата на полето на целосно керамичките изработки. Поточно, керамиките со висока цврстина и соодветните CAD/CAM техники ја зголемуваат клиничката индикација за безметални изработки, покажувајќи подобри механички карактеристики, споредено со првичните керамички материјали. Цирконијата, во комбинација со CAD/CAM техниките е од неодамна воведена во стоматолошката протетика за изработка на коронки и на мостови.

Клучни зборови: цирконија, стоматологија, целосно керамички материјали, CAD/CAM

Introduction

An ideal all-ceramic dental material should exhibit excellent esthetic characteristics, like translucency, natural tooth color, outstanding light transmission and, at the same time, optimal mechanical properties, like flexural strength, fracture toughness and limited crack propagation at the functional and parafunctional load conditions, in order to ensure long-term service. Up to date, zirconia has been considered a suitable choice for dental restorations due to its good mechanical properties, tooth colored and natural appearance and low plaque accumulation [1-3]. Zirconia (zirconium oxide) was introduced by Martin Heinrich Klaproth in 1789 [4].
The name ‘zirconium’ comes from the Arabic word ‘Zargon’ which means ‘golden in color’. Zirconia was discovered by the German chemist Martin Heinrich Klaproth in 1789 [5-6]. Its mechanical properties are very similar to those ofmetals and its color similar to tooth color. Hence it has been called as ‘Ceramic Steel’ by Garvie [7].The mechanical properties of zirconia are the highest ever reported for any dental ceramic.
This material is a non-cytotoxic metal oxide, is insoluble in water and has no potential of bacterial adhesion. In addition, it has radio-opacity properties and exhibits low corrosion [8-9].

Phases of zirconia

Three crystalline shapes of this material at different

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temperatures are as follows: cubic (c) (from 2680°C to 2370°C); tetragonal (t) (from 2370°C to 1170°C); monoclinic (m) (from 1170°C to room temperature). Monoclinic (m) phase is a more stable phase. Incorporation of cubic oxides like MgO, CaO, Y2O3 and CeO2 to zirconia can delay creation of the transformation phase. Subsequently, the zirconia crystals in their tetragonal or cubic shape at room temperature remain stable. These materials are referred to as stabilizers [8].

One of the most important properties is a remarkable increase in fracture toughness of the material by hindering, but not preventing, the propagation of a crack; tensile stress concentration converts the transformation from (t) phase to the (m) phase [10].

Increasing the crystal volume, constrained by the surrounding ones, leads to a favorable compressive stress. This limits growth of cracks [10]. Transformation toughening or "phase transformation toughening" (PTT) is the reported mechanism for exceptional flexural strength and fracture toughness of zirconia among all the other ceramics [12]. Heating the material at a low temperature (900-1000°C) for a short time changes the phase from monoclinic back to tetragonal form and generates a relaxation of the advantageous compressive stress at the surface, resulting in a decrease in the material toughness [13].

The grain size influences the mechanical behavior of zirconia. It means that higher temperatures and longer sintering times produce larger grain sizes. The critical crystal size is approximately 1 μm and zirconia with larger crystals are more prone to spontaneous PTT due to lower stability, whereas a smaller grain size generates favorable properties. It is reported that with grain sizes below 0.2 μm, PTT does not increase and fracture toughness decreases. However, the sintering conditions are important because they affect the crystal size, the mechanical properties and the stability of zirconia [14].

Types of zirconia ceramic available for dental application

Although, many types of zirconia-based ceramics are available, three zirconia-containing systems have been used in dentistry. Two of them are bi-phasic materials: glass-infiltrated zirconia-toughened alumina (ZTA) and the magnesium partially-stabilized zirconia (Mg-PSZ); the third type is the yttria partially-stabilized tetragonal zirconia polycrystal (3Y-TZP), a mono-phasic material which is used commonly [15].

In-Ceram zirconia is a glass-infiltrated zirconia-toughened alumina (ZTA), in which, for the first time, zirconium oxide was used as a dental ceramic. Due to its metastable nature, zirconia is a high-performance ceramic material. High-strength cores are composed of 67 % of aluminum oxide and 33% of 12 mol% cerium-partially stabilized zirconium oxide; therefore, zirconia crystals (grain size <1 m) are embedded in an alumina matrix (larger grains <2-6 m, high elastic modulus) in such a composition that yields the highest tenacity and flexure strength inside this class of ceramics (400-800 MPa): micro cracks may trigger the so-called "transformation toughening" of zirconia, so that a crack tip is more often seen to propagate through the alumina matrix surrounding the transformed crystals [1,4]. ZTA can be manufactured according to two different processes: soft machining or slip casting.

The latter presents the advantage of a more limited shrinkage but, at the same time, higher porosity and poorer mechanical properties than yttrium partially-stabilized tetragonal zirconia polycrystal (3Y-TZP) [16], the strongest and most commonly used zirconia-based ceramic. Moreover, stabilization by cerium oxide provides better thermal stability and resistance to low temperature degradation (LTD) than Y-TZP [17,18].

The microstructure of magnesium partially-stabilized zirconia (Mg-PSZ) consists of clusters of tetragonal crystals within a cubic stabilized zirconia matrix. The added stabilizer is MgO (8-10% mol). As regards dental applications, with some exceptions (Denzir-M-Dentronic AB), such a material has not been extensively used, neither has it encountered large popularity due to its remarkable porosity, large grain size (30–60 μm), low stability, tendency to framework wear, and overall poor mechanical properties, especially when compared to 3Y-TZP [19,20].

The third common zirconia is yttrium partially-stabilized tetragonal zirconia polycrystal (3Y-TZP). This type of zirconia is made of transformable, t- shaped grains stabilized by the addition of 3 mol% yttrium-oxides (Y2O3). It is placed in category 4-polycrystalline solids (alumina and zirconia) and has no glassy components. All the atoms are packed into a regular pattern making it dense and stronger. Procera system is a computer-aided designing and computer-aided manufacturing system (CAD-CAM). This ceramic is the frequently used form of zirconia commercially available for dental use [21].

Mechanical properties

Mechanical properties of zirconia have been reported to be higher than other ceramics for dental applications. Fracture resistance of 6-10 MPa/m1/2, a flexural strength of 900-1200 MPa and a compression resistance of 2000 MPa have been reported for it [22]. Zirconia restorations bear an average load of 755 N. Fracture loads of 706-4100 N have been reported; all the studies have demonstrated that in dental restorations zirconia yields higher fracture loads than alumina or lithium disilicate [23].

Zirconia ceramics yield superior wear behavior and lower antagonistic wear compared to porcelains. A trend to higher ceramic and antagonistic wear was shown after grinding treatments [24,25]. Degradation of zirconia

happens in low temperatures and without mechanical load application. This condition, so-called "aging", is a transformation of the tetragonal phase to monoclinic phase which is a stable form. Aging decreases the physical properties of the material and increases risk of failure in zirconia restorations. Presence of mechanical stresses and moisture accelerates zirconia aging. Grain size, temperature, vapor, the presence of surface defects, type, percentage and distribution of stabilizing oxides and processing techniques influence this process. Meanwhile, there is evidence in relation to the long-term evaluation of effects of aging of zirconia on dental restorations. Aging leads to changes in the behavior of the material, weakening it, and subsequently, to material degradation, with micro cracks decreasing strength properties [26].

Manufacturing

Two commonly used different techniques are available for prefabrication of zirconia frameworks: “soft machining” of pre-sintered blocks or “hard machining” of fully sintered blocks [27].
The soft machining process is the most common manufacturing system for 3Y-TZP, based on milling of pre-sintered blocks that are fully sintered at a final stage. The process of production of these blocks consists of compacting zirconia powder in the presence of a binder through a cold, isostatic pressing process; this leads to homogeneous distribution of the components inside the block [17]. Processing at a proper pre-sintering temperature of zirconia is an important factor because this parameter influences hardness, machinebility and roughness of the blocks. Hardness and machinability properties act as reverse factors; this means if hardness of block is adequate, manipulation of blocks is performed safely, but, high hardness is unsuitable for machinability. Moreover, an increase in pre-sintering temperatures generates rougher surfaces [1].
Usually, CAD software programs design the enlarged framework to compensate shrinkage. In CAM procedure, the framework is machined according to the designed form. After this step, the sinterization is performed. Since linear volume shrinkage of restoration is about 25%, the zirconia framework reverses previous dimensions. Performance of these steps provides cores with high stability [1]. However, a certain amount of cubic zirconia may be present due to an uneven distribution of yttrium oxide. The cubic phase has stable oxides than the tetragonal crystals which may provide an unstable material [14]. Addition of metal oxides to zirconia powder or immersing cores in metal salt solutions might yield colored cores. This coloration does not affect mechanical properties of zirconia cores [27]. Many manufacturers prefer this technique i.e. Procera Zirconia (Nobel Biocare AB, Goteborg, Sweden), Lava (3MESPE, Seefeld, Germany) and Cercon (Dentsply Degudent, Hanau, Germany).
In the hard machining technique, the so-called "hot isostatic pressing", the 3Y-TZP blocks are sintered and condensed at high temperatures (1400-1500°C) and under high pressure in inert gas medium. These blocks are very hard, dense and homogeneous [28].
Selection of each one of these two techniques as suitable technique is a matter of controversy. Mean while, the most important problem in soft-machining is the difference in the sintering shrinkage of the framework and the enlargement values [4]. The major disadvantage of the hard machining technique is more time-consuming and requires very tough and wear-resistant cutting devices. Provision of these pieces of equipment renders the production procedure more costly [11].
Milling zirconia blocks at thin sections provides various types of surface micro crack and defects. It seems that factors such as the grain size of the diamond burs or the rotation speed are effective [29].
Surface treatments provide more roughness but decrease toughness and the strength resulting in the exposure of the processing defects. It has been reported that it induces aging potential and decreases serviceability of the restoration [30,31].
The hard machining procedure leads to the production of monoclinic zirconia that is a weak phase in terms of aging and micro cracking [14]. There is controversy about the results of studies on the surface treatments of zirconia [1].
It appears that residual stress due to processing the restoration, especially coefficient of thermal expansion (CTE) difference between the fired zirconia and the veneering material, plays a more important role than surface treatments in aging potential [31].
Recently, cerium oxide has been introduced as a stabilizer for dental applications. The ceria-stabilized zirconia (Ce-TZP) exhibits more suitable thermal stability and LTD resistance than Y-TZP. Ce-TZP demonstrates the highest bending strength in dental ceramics. Presence of yellow-brownish color and future discoloration of ceria-containing zirconia restorations to dark gray is a limitation for dental applications [11,31].
Other factors such as framework thickness, connector shape and size, coefficient of thermal expansion differrence between the coping and veneer affect mechanical properties of zirconia frameworks. Minimum framework thickness (0.5 mm) is necessary for copings to support veneering material and avoid core deformation. CTE of coping must be close to veneering ceramic to reduce stress in restorations [19,32].

Fitness

Various studies have reported different values for precision of fit of zirconia restorations, which is attributed to differences in experimental designs and evaluation

procedures. In these studies, the marginal gaps ranged between 9.0 and 148.8 μm, with an average value of 73.8 μm [18,33]. Higher discrepancies have been detected at the internal gap (i.e. the internal distance measured between the coping and the abutment), ranging between 68.8 and 215 μm in the occlusal direction and between 52.3 and 192 μm in the axial direction [22].
Single crowns milled with dense zirconia copings have exhibited better fit (0-74 μm) [33]. Comlekoglu et al [34] reported values of marginal gap for feather-edge, mini-chamfer, shoulder and chamfer finish lines: 87±10, 114±11, 114±16 and 144±14 μm, respectively. Marginal opening is dependent on the extension and shape of zirconia frameworks. Long-span and curved zirconia frameworks have exhibited less marginal fit [35,36]. Hard-machining has been advised for complex restorations by some studies [22].

Luting of zirconia

A major clinical problem associated with use of zirconia-based components is the difficulty in achieving suitable adhesion with intended synthetic substrates or natural tissues. Resin-based composite cements are the standard material used in luting a ceramic prosthetic to tooth structures. The non-silica composition of zirconnia makes it difficult to bond zirconia to tooth structures using traditional resin composite cements. In some instances, high strength ceramic restorations with ideal retention can be placed using conventional cements which rely only on micromechanical retention [37].
However, a resin bonding is desirable in many clinical situations such as short or tapered prepared tooth structure. Strong resin bonding relies on micromechanical interlocking and adhesive chemical bonding between the cement and the ceramic surface. Retention of zirconia-based ceramic restorations depends on mechanical roughening of the surface and chemical bonding with adhesive monomer in special primers or resin cements. An acidic adhesive monomer such as MDP bonds to zirconia-based ceramics. The phosphate ester group of the acidic monomer results in chemical bonding to metal oxides, zirconia-based ceramics and other ceramics. Therefore, it is recommended to use self-adhesive or adhesive resin cement containing an adhesive monomer (MDP) or application of ceramic primer containing an acidic adhesive monomer as pre-treatment before cementation of zirconia [38].
Chemical-cured phosphate monomer-containing resin-based cements, Panavia Ex (10-methacryloyloxydecyl-dihydrogenphosphate or MDP) and Panavia 21 Ex, exhibited high bond strength. They showed no signifycant difference in bond strength after artificial aging as they formed a water-resistant chemical bond with zirconia [39].
The addition of a MDP-containing bonding/silane coupling agent to enhance bonding of MDP resin cements has produced positive results. It was shown that particle air-abrasion or tribochemical coating, followed by the application of MDP-containing bonding/ silane coupling agent, resulted in increased bond strength compared to MDP-containing cements alone [40].

Bonding of veneering material to zirconia

Zirconia copings for crowns or multi-unit frameworks require application of veneering ceramic, usually specialized porcelain, to achieve suitable esthetics. A high percentage of clinical failures of zirconia-based restorations are attributed to debonding and/or fracture of veneering ceramic [41].
The bond strength between zirconia and veneering ceramics is influenced by many factors. Bonding mechanisms include chemical bonding, mechanical fitting, and shear stress based on the difference in the coefficient of thermal expansion between the TZP and the veneering ceramics. However, no conclusion has been reached regarding the bonding mechanism itself. Factors influencing the bond strength include surface roughness, heat treatment of the TZP and the use of liner porcelain [42].
Since ceramics are extremely susceptible to tensile stresses, achieving a slight compressive stress in the veneering ceramic is preferred, as in metal-ceramic (PFM) restorations. For this to occur, the veneering material must have a thermal expansion coefficient lower than the core material. Zirconia ceramics have coefficients of thermal expansion (CTE) ranging from approximately 9 to 11μm/ m K while specialty porcelains can have CTE values ranging from 7 to 13 μm/ m K [43].
The use of zirconia surface modifiers to achieve strong primary bonding between coping and veneering ceramic could improve the clinical failure rates observed to date. Application of a silicate intermediate layer, applied on the zirconia surface via a tribochemical approach has been studied. A vapor deposition approach could also enable conformal silicate surface modification without use of an aggressive physical process, which might result in damage to the coping surface [44].
The application of a liner, used to modify the color of white zirconia for esthetics, has shown mixed results in bond strength when used on veneers. Aboushelib et al. showed that addition of a liner increased bond strength in Cercon Base/Ceram S core-veneer system but decreased bond strength when used in the Cercon Express core-veneer system.
The bond strength of veneer to Zirconia is comparable to that of veneer to metal and is thought to be sufficient for dental applications [12].

Conclusion

Zirconia-based restorations exhibit excellent esthetic characteristics and optimal mechanical properties (flexu-

ral strength, fracture toughness). Literature confirmed high success rates of these restorations.

Zirconia applications seem to consolidate awell-established position in clinical dentistry, due tothe improvements in CAD/CAM technology and tothe material's exceptional physical properties. Thebiocompatibility of zirconia has been well documentedand in vitro and in vivo tests on Y-TZP have revealedgood biocompatibility with no adverse reactions withcells or tissues. Existing clinical studies demonstrated apromising survival potential regarding tooth-supported restorations but also revealed significant complicationssuch as high incidence of early fractures of either the veneering or the core materials. Longitudinal studies will help to determine the degree of clinical benefitor severity of complications. Basic research should beconducted in the fields of aging, veneering, framework design, bonding, surface modification and esthetic performance to further illuminate the observed complications and provide solutions that will accelerate expected clinical outcomes. As many new trends and applications for zirconia are being discovered, the futureof this biomaterial appears to be very promising.

Conflict of interest statement. None declared.

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RISK FACTORS AND MANAGEMENT OF MECONIUM ASPIRATION SYNDROME

ФАКТОРИ НА РИЗИК И ВОДЕЊЕ НА МЕКОНИЈАЛНИОТ АСПИРАЦИОНЕН СИНДРОМ

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Abstract

Meconium aspiration syndrome (MAS) is an important factor for morbidity and mortality among term newborns. An incidence over 12% of MAS remains to be a serious problem. Aspiration of meconium stained amniotic fluid (MSAF) during antepartum or postpartum period causes respiratory distress, hypoxia, acidosis and need of oxygen or respiratory support by ventilation. Although ventilation is the first choice for treatment of severe MAS, there are other supportive management such as surfactant, inhaled nitric oxide, and high-frequency ventilation (HFV) leading to decreased use of extracorporeal membrane oxygenation (ECMO).
The present study highlights the complex pathophysiology and adequate approach for treatment of MAS.

Key words: meconium aspiration syndrome, mechanical ventilation, asphyxia, infants

Апстракт

Меконијалниот аспирациски синдром (МАС) е важен фактор за појава на морбидитетот и морталитетот меѓу терминските новородени. Со инциденца од 12% претставува сериозен проблем.
Аспирацијата на меконијална обоена амнионска течност за време на антепарталниот или постпарталниот период предизвикува респираторен дистрес, хипооксија, ацидоза, и потреба од кислородна поддршка-механичка вентилација. Иако, механичката вентилација е прв избор за третман на тешките форми на МАС, постојат и други процедури, како апликација на сурфактант, инхалирачки натриум оксид, и високо фрекфентна вентилација (HFV), кои ја намалуваат употребата на екстракорпоралната оксигенација.
Овој труд ја истакнува сложеноста на патофизиологија и адекватниот пристап за третман на МАС.

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Клучни зборови: меконијален аспирационен синдром, механичка вентилација, асфиксија, новородени

Introduction

Meconium aspiration syndrome (MAS) is the aspiration of stained amniotic fluid, which can occur before, during or immediately after birth. MAS is a disease of the term and near-term infant and is associated with significant respiratory morbidity and mortality [1].
Meconium is the first intestinal discharge from newborns, a viscous, dark-green substance composed of intestinal epithelial cells, lanugo, mucus, and intestinal secretions. About 85-95% of meconium is water; the remaining 5-15% consist primarily intestinal secretions, mucosal cells, and solid elements of swallowed amniotic fluid, such as proteins and lipids [2].
Meconium is sterile without containing bacteria. Several factors can cause MAS; intrauterine distress can cause passage of meconium into the amniotic fluid, placental insufficiency, oligohydramnios, genitourinary infection, maternal hypertension and diabetes.
Cleary and Wiswell in 1998 [2] proposed a severity criteria to define MAS: mild MAS is a disease that requires less than 40% oxygen for less than 48 hours, moderate MAS requires more than 40% oxygen for more than 48 hours, and severe MAS requires assisted ventilation for more than 48 hours and is often associated with persistent pulmonary hypertension of the newborn (PPHN) [3].
In the United States the incidence of MAS decreased nearly fourfold from 5.8% to 1.5% between 1990-1992 and 1997-1998. A review by Katz and Bowes in the 1990s confirmed that the incidence of MAS in all births was in a range from 7 to 22%. In 2000-2007 in 132,884 French newborns (37-43 weeks gestational age) was 8%, the incidence of MAS was 0.2% and the incidence of severe MAS with a need for respiratory support was 0.067% [4,5].
According to the unofficial database in Macedonia the incidence of MAS in the last few years is about 18-19%. MAS remains a serious problem in developing countries, and it accounts for about 10% of all cases of respiratory failure with 39% mortality rate.

Pathophysiology of MAS

The pathophysiology of MAS is complex, and it consists of several pathophysiological conditions such as airway obstruction, atelectasis, and pulmonary hypertension. The common disturbances of lung function in MAS include hypoxemia and decreased lung compliance. Poor oxygenation is attributed to a combination of decreased perfusion in lungs, intrapulmonary shunting related to regional atelectasis and extrapulmonary shunting related to PPHN.

The exact mechanisms for meconium-induced inactivation of pulmonary surfactant are not very clear. It is considered that several components of meconium (free fatty acids, cholesterol, and triglycerides), and water-soluble (containing bilirubin, bile acids, enzymes, etc.) ones impair lung function. Meconium can decrease the level of pulmonary surfactant by a combined action of cholesterol and bile acid present in meconium [6].

Meconium may also change the viscosity of the surfactant, decrease the levels of surfactant proteins and cause leakage of plasma protein and proteolytic enzymes through an injured alveolar-capillary membrane, released from inflammed cells.

During the prolonged delivery, meconium is inhaled, producing one of the worst forms of aspiration pneumonitis. Meconium has many adverse properties; high tenacity (stickiness), high surface tension, and inhibition of surfactant function [7,8].

Meconium is toxic to the alveolar epithelium [9] causing disruption of the alveolar-capillary barrier and an exudative edema. To the pulmonary epithelium it causes hemorrhagic alveolitis with high concentrations of protein and albumin in the alveolar space and thus disturbs the ventilation. Meconium contains substances that activate the immunology system, neutrophils, interleukins IL-1, IL 6, and IL 8, and tumor necrosis factors. Thus, it may induce inflammation through the stimulation of neutrophils and alveolar macrophages and may injure the lung parenchyma or lead to vascular leakage causing toxic pneumonitis and hemorrhagic pulmonary edema [3,10]. This is the mechanism of causing atelectasis of the lung and increases the need of mechanical ventilation [11].

In 15-20% of neonates with MAS severe PPHN is revealed. PPHN in neonates may be caused by pulmonary vasoconstriction, hypoxia, hypercarbia, and acidosis, hypertrophy of the alveolar capillaries as a result of chronic intrauterine hypoxia, and pulmonary vasoconstriction as a result of pulmonary inflammation.

The extent of lung destruction is not closely correlated to the quantity of meconium in lung tissue but rather to the degree of hypoxia and acidosis present at delivery. Thus, in the study of Ghidini and Spong was confirmed that severe MAS is caused of pathologic processes occurring in utero, such as chronic asphyxia, infection, or persistent pulmonary hypertension [12].

Diagnosis of MAS

In the first 24 hours after delivery it is important to monitor neonates born through MAS for any signs of respiratory distress. Diagnosis of MAS is based on the presence of respiratory distress in neonates born through MAS, without other causes for respiratory distress. The information about antepartum and intrapartum period is very important for adequate follow-up and treatment of neonates.

If we have information of suspected neonate with MAS, chest radiograph and blood gas analysis should be performed immediately. Because of different etiological mechanisms causing this disease, radiographic findings are different. The classic radiographic findings in MAS are overexpansion of the lungs with widespread coarse, patchy infiltrates. However, the severity of chest radiograph does not always correlate with the clinical picture. MAS is more dependent on the presence and severity of PPHN than on meconium obstruction and parenchymal lung damages.

Treatment of MAS

The management of MAS is indispensable, because MAS is a life threatening condition that needs expert care from experienced neonatologists. The follow-up of mothers is started early in the antepartum period with suggestion for elective induction of labor for pregnancies at or beyond 41 weeks, for reduction of neonatal deaths.

Intrapartum monitoring has been recommended to screen for early signs of fetal hypoxia. Also, fetal blood gas and fetal pulse oximetry will improve decision making in timing of delivery and may reduce the incidence of MAS [13].

In postpartum period if the newborn through MAS has a normal respiratory effort, normal muscle tone, and a heart rate over than 100/ min., then direct endotracheal suction is not recommended. Only suctioning of mouth and nose using a bulb syringe or large bore suction catheter is indicated. After delivery of nonvigorous neonates born through MAS with depressed respiratory efforts, poor muscle tone, heart rate less than 100/min. intubation and direct endotracheal suction is recommended. Cochrane meta-analysis of four randomized studies did not show a difference in the incidence of MAS between intubated and nonintubated vigorous infants [14].

Supplemental oxygen administration for treatment of MAS in many less severe cases is the only therapy required. Some ventilated neonates with MAS receive high inspired oxygen concentration for long periods. SpO_2 is preferable to be higher than 90%.

In ventilated neonates, oxygen therapy can also be monitored by blood gas. Suggested target pO2 range is 60-100 mm Hg. Of all neonates requiring mechanical respiratory support because of MAS, approximately 10-20% are treated with continuous positive airway

pressure (CPAP) [15]. CPAP can be effectively delivered by binasal prongs, typically with a CPAP pressure of 5-8 cm H_2O.
Approximately one-third of all neonates with a diagnosis of MAS require intubation and mechanical ventilation. Ventilator management is challenging because of the complicated pulmonary pathophysiology resulting from areas of atelectasis and areas of hyperinflation, in association with ventilation perfusion mismatch and airway compromise. Indications for intubation include: high level of oxygen support, respiratory acidosis (arterial pH less than 7.25 and PaO2 <50 mm Hg, PaCO2 >60 mm Hg, FiO2 > 0.6, pulmonary hypertension, and circulatory compromise, with poor perfusion and low systemic blood pressure. Intubation of neonates with MAS should be performed with premedication [16,17].
Once intubated, the neonate will require continuous sedation with opiates. In neonates with MAS without associated PPHN, it is sufficient to maintain a pH of 7.3-7.4, with a PaO2 between 60-80 mmHg and a PaCO2 of 40-50 mmHg. The ventilation may be started with a moderate peak inspiratory pressure (PIP)-25 cm H2O, ventilator frequency-40-60/min., (Positive end-expiratory pressure (PEEP)-4-6 cm H20, and an adequate expiratory time (0.5-0.7 sec.) to prevent gas trapping and air leaks. If gas trapping is noticed, expiratory time may be increased and PEEP should be decreased (3-4 cm H2O) [17].
In neonates with MAS and PPHN, mild hyperventilation and higher FiO2 can be considered. Unfortunately, this condition can cause adverse effects such as cerebral vasoconstriction leading to long-term neurologic disorders. In such situations other modalities like inhaled nitric oxide and high frequency ventilation should be considered early.
High frequency ventilation (HFV) has become an important means of providing respiratory support for neonates with severe MAS. Several neonatal databases suggest that 20-30% of all neonates with MAS are treated with high-frequency ventilation [16].
HFV minimizes the barotrauma and may reduce air leak syndrome in MAS. In a pilot studies using inhaled nitric oxide (iNO), Kinsella and Abman confirmed that the combination of HFV and iNO caused the greatest improvement in oxygenation in some neonates with severe PPHN. Probably the main reason for that is the response to iNO by decreasing intrapulmonary shunting and improving iNO delivery to the pulmonary circulation [18].
Several randomized clinical trials have demonstrated that iNO therapy decreases the need for extracorporeal membrane oxygenation (ECMO) in full-term and near-term neonates with hypoxic respiratory failure and PPHN. The neonates with severe MAS responded well to combined therapy with iNO and HFV as compared to either treatment alone [19].
The pathophysiology of MAS has influence over inhibition of surfactant in the alveoli, both by meconium and exuded plasma protein. Four randomized controlled trials of bolus surfactant therapy have been conducted [20-23], which confirmed the benefit in reduction of the need for ECMO but not duration of ventilation, duration of hospital stay, duration of oxygen use, no significant difference in mortality, or other pulmonary outcomes (pneumothorax, pulmonary interstitial emphysema, or chronic lung disease) [24].
Similarly, the study of Dargaville *et al.* has confirmed that lung lavage with dilute surfactant (Survanta) in ventilated infants with severe MAS does not decrease the duration of respiratory support, but may reduce mortality, especially in units not offering ECMO [25].
In the developed world, bolus surfactant therapy is currently used in 30-50% of ventilated neonates with MAS [34,36]. Bolus surfactant therapy should be used judiciously in MAS, choosing neonates with severe disease, and treating early and, if necessary, repeatedly [26].
Infants with severe MAS have been treated with ECMO since 1976, and MAS has been the leading diagnosis amongst neonates referred for this therapy [27].
In severe and refractory hypoxemia associated with MAS, when all therapy resources are without any improvement, ECMO is used as a final rescue therapy. Use of ECMO has decreased significantly in developed countries with the availability of iNO and HFV. 35% of neonates who have need of ECMO are with surviving rate of 95% [28].

Conclusion

There is still no effective treatment or prophylactic measure for MAS. All efforts should be aimed at early prophylaxis and prevention in the antenatal period and intrapartum monitoring for early and appropriate treatment of MAS. Available modes of conventional ventilation and adjunctive therapies are the main guidelines for appropriate treatment of severe MAS.
Only in this way we can influence on the reduction of mortality and morbidity in early neonatal period caused by MAS.

Conflict of interest statement. None declared.

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Original article

ACCELERATED AND DELAYED GASTRIC EMPTYING OF SOLID MEAL IN PATIENTS WITH DIABETES MELLITUS TYPE 2

ЗАБРЗАНО И ЗАБАВЕНО ЖЕЛУДОЧНО ПРАЗНЕЊЕ НА ЦВРСТ ОБРОК КАЈ ПАЦИЕНТИ СО ДИЈАБЕТЕС МЕЛИТУС ТИП 2

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Abstract

Introduction. Gastric motility in diabetes mellitus type 2 can be disturbed in very high proportion of patients. The condition can be accompanied by gastrointestinal symptoms or can be asymptomatic.
Methods. Retrospective analysis of the files of 38 patients with diabetes mellitus type 2 without any other gastrointestinal, renal, hepatic or other endocrinelogical diseases scanned with the same protocol for gastric emptying with a solid meal was performed. All patients had morning glycemia on the day of the scanning less than 15 mmol/L. The duration of diabetes and the values of glycosilated hemoglobin were recorded.
Results. Delayed and accelerated gastric emptying in our study was present in 41% and 24% patients, respectively, while 35% had normal GE. Patients with accelerated emptying had normal starting index reflecting normal duration of the phase when grinding, mixing and digestion of the food in the stomach occurs before it starts to enter the duodenum and accelerated emptying rate. Patients with delayed GE had prolonged starting index and slower emptying rate. Patients with accelerated and delayed GE had higher fasting glycemia compared to patients with normal GE. The fasting glycemia before scanning is an important factor that should always be taken into account during the interpretation of the results from gastric emptying studies.
Conclusion. The aim of this study was to evaluate gastric emptying (GE) of a solid meal in patients with diabetes mellitustype 2 (DM2) employing the scintigraphic technique and to analyze the pattern of disturbances of different parameters of gastric emptying and other factors that can influence gastric motility in these patients.

Key words: accelerated gastric emptying, delayed gastric emptying, diabetes mellitus type 2.

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Апстракт

Вовед. Желудочниот мотилитет е нарушен кај голем број пациенти со дијабетес мелитус тип 2. Нарушувањето може да биде придружено со гастроинтестинални симптоми, но и дабиде сосем асимптоматско.
Методи. Направена е ретроспективна анализа на резултатите од сцинтиграфско одредување на гастричното празнење на цврст оброк, работено по ист протокол кај 38 пациенти со дијабет тип 2, кои немале гастроинтестинално, хепатално, ренално или друго ендокринолошко заболување. Кај сите пациенти гликемијата пред снимањето била под 15 mmol/L. Анализирани се и податоците за времетраење на дијабетот и вредности на гликозилиран хемоглобин.
Резултати. Забавено желудочно празнење беше пронајдено кај 41% од болните, забрзан кај 24%, а 35% од нив имаа нормална брзина на желудочно празнење. Пациентите со забрзан транзит имаа нормален почетен индекс, кој одразува уредно траење на фазата кога храната се меша, ситни и дигестира во желудникот пред да почне да се празни во дуоденумот. Ратата на празнење беше забрзана кај овие пациенти. Кај пациентите со забавено празнење почетниот индекс беше продолжен, а ратата на празнење забавена. Гликемијата пред скенирањето беше повисока кај пациентите со нарушен транзит, споредено со тие со нормален транзит. Гликемијата пред скенирање треба секогаш да се има во предвид при интерпретирање на резултатите од желудочно празнење.
Заклучок. Целта на оваа студија е да се евалурира нарушеното желудочно празнење на цврст оброк, одредено со сцинтиграфски метод кај пациентите со дијабет тип 2 и да се анализираат нарушувањата на различните параметри на желудочното празнење, како и други фактори, кои можат да влијаат на гастричниот мотилитет кај овие пациенти.

Клучни зборови: забрзано желудочно празнење, забавено желудочно празнење, дијабетес мелитус тип 2

Introduction

Diabetic gastroparesis is a complication that is estimated to be encountered in 1% of patients with diabetes mellitus type 2 and around 5% in patients with diabetes mellitus type 1 [1]. This disorder may be accompanied by symptoms like nausea, bloating, vomiting, early satiety and epigastric pain. The condition is often asymptomatic, and therefore its frequency underestimated. The studies that were assessing gastric motility in patients with diabetes reported gastric dysmotility in as high as two thirds of the patients and different patterns of disturbed gastric emptying. Few studieshave reported not only delayed, but accelerated gastric motility in patients with diabetes mellitus as well [2]. The etiology and pathophysiology of gastric dysmotility, especially the accelerated gastric emptying is still unclear.

Materials and methods

A retrospective analysis of the files of 38 patients with diabetes mellitus type 2 without any other gastrointestinal, renal, hepatic or endocrinological diseases scanned with the same protocol for gastric emptying was performed. The group consisted of 27 women and 11 men, with average body mass index of 29.02 kg/m^2. All patients had morning glycemia on the day of the scanning less than 15 mmol/L. The duration of diabetes was recorded, and for some patients the values for glycosilated hemoglobin were available.

Gastric emptying study

The gastric emptying study of the solid meal with radionuclide method was performed at the Institute of Pathophysiology and Nuclear Medicine (IPNM), Medical Faculty in Skopje. The study was performed in the morning before patients had any food. Standardized test meal consisted of one egg labeled with 18.5 MBq 99mTc sulfur colloid, 25gr of toast bread, and 120 ml of water. The test meal standardized in this way is composed of proteins, fats and carbohydrates with energy value of 1000KJ.The radioactive test meal was consumed within 5 minutes, and immediately after the ingestion of the meal the first sequences were taken. The scanning was performed on a computerized planar gamma camera (Siemens-ZLC750). A series of 60 seconds static scans were obtained on an 8 bit matrix with format of 256x256 pixels. The scans were obtained every 5 minutes in the first 30 minutes, at 10-minute interval for the next 30 minutes, and at 15-minute interval until 120 minutes. Every set of scans was obtained in AP and PA position.

Data processing

A region of interest (ROI) was drawn around the tracer activity in the stomach. The integral amount of registered radioactivity (IAR) in the region was calculated as a geometric mean from the IARs in AP and PA position. From the IARs at all scanning time points the time-activity curve was produced. From the time-activity curve the following parameters were calculated: starting index (SI) as representative of the lag phase, gastric emptying half-time (T/2) and gastric emptying rate (ER). The method of calculation of these parameters has beenpreviously published in more details [3].The lag phase represents the movement and redistribution of the meal from the fundus to the distal stomach. This phase ends when the first amounts of the meal enterthe duodenum.The GE T/2 represents the time point when 50% of the starting radioactivity is emptied from the stomach, while the ER is presented as a percent of emptied radioactivity per minute. The normal range established in healthy persons at our Institute for gastric emptying half time is between 48 and 76 minutes, for starting index between 8 and 22 minutes and for emptying rate between 1.4 and 2.1%/minute [3].

Statistical analysis

The statistical analysis wasperformed using the methods of descriptive statistics and the Mann Whitney test for testing the significance of the difference between groups. A p-value less than 0.05 was considered as statistically significant.

Results

Normal gastric emptying half time was found in 35% of patients, while the rest of the patients exhibited disturbances of gastric motility. Patients with DM type

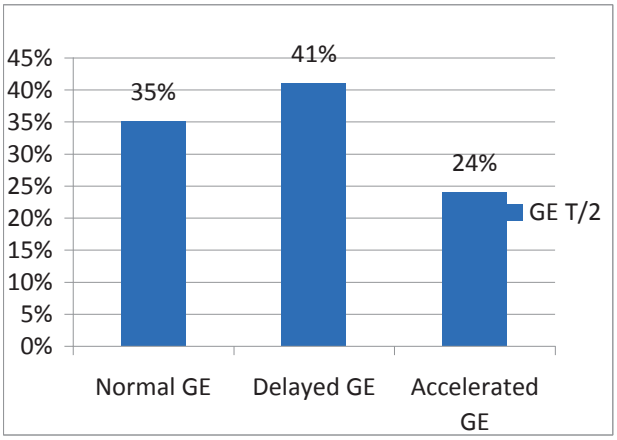

Fig. 1. Gastric emptying half time in patients with DM2

2 in this study have shown two patterns of gastric emptying disturbance-delayed and accelerated gastric emptying. Delayed GE T/2 was recorded in 41%, and accelerated GE T/2 in 24% of patients. These results are presented in Figure 1.

The other parameters derived from the time-activity curve generated from the IAR in the stomach are represented in Table 1.

Table 1. Mean values +/- SD of gastric emptying half time, starting index and emptying rate in three groups of patients with DM2

	Normal GE	Delayed GE	Accelerated GE
GE T/2 minutes	61 +/- 6.7	108.7+/- 48	36.77+/- 5.58
SI minutes	12.5+/- 8.4	29.6+/-16.8	10.44 +/- 5.6
ER %/min	1.4 +/- 0.36	1.07+/- 0.41	2.8 +/- 1.52

Patients with delayed gastric emptying had longer starting index, and slower emptying rate per minute. Patients with accelerated emptying had starting index within the normal range and accelerated emptying rate per minute.

Analysis of the other data available from patients' files did not find any significant difference between the 3 groups of patients according to age or duration of the diabetes. There was no difference in HgbA1c between the group with normal GE and delayed GE. A significant difference was observed only in glycemia values before scanning between patients with normal GE and delayed GE (8.8+/- 1.49 *vs*. 10.6+/-2.29, $p< 0.05$) and normal GE and accelerated GE (8.8+/- 1.49 *vs*10.5+/- 3.1, $p <0.05$).These data is presented in Table 2.

Table 2. Mean values +/-SD for age, BMI, duration of diabetes, glycemia before scanning and HgBA1c in patients with normal and disturbed GE

	Age	BMI	Duration of DM in years	Glycemia mmol/L	HgbA1c %
Normal GE	60.4+/- 8	29.02+/-3.6	11.2+/-7.7	8.8+/- 1.49	8.4+/- 1.75
Delayed GE	54.6+/- 8.9	28.2+/- 4.17	13.9+/- 7.7	10.6+/-2.29	8.1+/- 4.4
Accelerated GE	60+/- 6.7	26.28+/-4.72	12.05+/-5.23	10.5+/-3.1	NA

Discussion

Gastroparesis in patients with diabetes mellitus was reported a long time ago in many studies. The condition is thought to be caused by autonomic neuropathy and is accompanied by symptoms like abdominal discomfort, early satiety, bloating, nausea, vomiting and epigastric pain [4]. However, many asymptomatic patients can have disturbed gastric motility. Delayed gastric emptying was reported in diabetic patients without any significant gastrointestinal complaints [5]. Accelerated gastric emptying of a solid meal wasdescribed many years ago by Swartz *et al*. in a study that revealed this kind of disturbance in patients with short duration of the disease and without complications [6]. Our study reports delayed gastric emptying in 41% of patients and accelerated gastric emptying in 24% of patients. Our findings are in concordance with the study of Bharucha *et al*. [7] performed on a series of 129 patients with diabetes mellitus type 1 and type 2 that reportednormal gastric emptying in 42% of patients, delayed in 36%, and accelerated in 22%.The disturbances in the motility in this study were not related to the duration of diabetes, glycosilated hemoglobin or extraintestinal complications. Similarly in our study we did not find any difference between the groups with normal or disturbed GE in regard to the duration of the disease, age, BMI or glycosilated hemoglobin. It was postulated that the acceleration of the gastric motility may be one of the factors in the development of diabetes mellitus type 2. The studies that report this kind of disturbance in patients shortly after the diagnosis support this hypothesis. Our study did not confirm this hypothesis considering the lack of difference between patients with disturbed gastric emptying and patients with normal gastric emptying in regard to the duration of the disease. Accelerated or delayed gastric emptying in our study was only related to the fasting glycemia before the study. There was a significant difference in the glycemia before the study between patients with dismotility and patients with normal GE. Patients with normal GE had lower glycemia before scanning (8.8+/- 1.49 mmol/L) compared topatients with accelerated GE (10.6+/-2.29), and in patients with delayed GE (10.5+/- 3.1). Hyperglycemia has been recognized in many studies as a factor that retards the gastric emptying [8,9]. Therefore it is accepted in the guidelines that glycemia before gastric emptying scintigraphy should aim to be bellow 11.5 mmol/L [10]. The results from our study show that variations bellow this threshold can influence the results as well. The influence of the fasting glycemia on accelerated gastric emptying is not well established. Recent study in patients with poorly controlled DM2 has reported accelerated gastric emptying in 20% of patients that had higher fasting glycemia [2]. Patients with accelerated GE in our study had higher levels of fasting glycemia similar to those with delayed GE.

Patients with accelerated gastric emptying in our study showed an interesting pattern of emptying. The starting index in this group wasnormal which reflected the normal first phase of gastric motility when the food enters the stomach and is grinded and mixed before it starts to enter the duodenum. The acceleration in this group wasdue to the faster emptying rate of the radiolabeled meal from the stomach. The group with delayed gastric emptying showed disturbances in both parameters, prolonged starting index and slower emptying rate. These findings point to the fact that more complex disturbances of the neuro-endocrine regulation of the gastric emptying are involved in patients with diabetes mellitus type 2.

Conclusion

Gastric emptying in diabetes mellitus type 2 can be highly variable. Delayed and accelerated gastric emptying in our study was present in 41% and 24% of patients, respectively. Patients with accelerated emptying had normal starting index reflecting normal duration of the phase when grinding, mixing and digestion of the food in the stomach occurs before it starts to enter the duodenum and accelerated emptying rate. Patients with delayed GE had prolonged starting index and slower emptying rate. Patients with accelerated and delayed GE had higher fasting glycemia compared to patients with normal GE. The fasting glycemia before scanning is an important factor that should always be taken into account during the interpretation of the results from gastric emptying studies.

Conflict of interest statement. None declared.

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Original article

VITAMIN D INSUFFICIENCY AMONG CHILDREN WITH OVERWEIGHT AND OBESITY

ВИТАМИН Д ИНСУФИЦИЕНЦИЈА КАЈ ДЕЦА СО ПРЕКУМЕРНА ТЕЖИНА И ДЕБЕЛИНА

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Abstract

Aim. The purpose of this study was to find out the prevalence of vitamin D deficiency and insufficiency in overweight and obese children from Kosovo. To the best of our knowledge, this is the first study investtigating the relationship between the body mass index (BMI) and vitamin D status in overweight and obese children in our country.
Methods. A cross-sectional study was conducted including primary school children during the spring of 2016. A total of 130 children, all overweight or obese, aged 9-13 years, were included. Of them 79 (60.7%) were male.
Results. According to BMI for age percentile, overweight and obese were 33.8% and 66.1% of children, respectively. Vitamin D deficiency (<20 ng/ml) was present in 103 (79.2%) children, 23 (17.7%) had insufficiency (20-30 ng/ml) while only four children had normal level (30-100 ng/ml). There was a significant negative linear correlation between BMI for age and vitamin D status with r=-0.4795, p<0.000. Children with higher BMI had lower vitamin D level.
Conclusion. A high prevalence of vitamin D deficiency and insufficiency was found among overweight and obese children from Kosovo. Routine screening and treatment of vitamin D deficiency in these children should be considered.

Keywords: children, overweight, vitamin D insufficiency, Kosovo

Апстракт

Цели. Целта на оваа студија е да ја истражи преваленцата на дефициенција и инсуфициенција на витамин Д кај прекумерно тешки и обезни деца во Косово. Според нашите сознанија, ова е прва студија, која ја истражува врската меѓу индексот на телесна тежина (ИТТ) и статусот на витамин Д кај прекумерно тешки деца, како и деца, кои се обезни во нашата земја.
Методи. Пресечна (cross sectional) студија беше направена на деца од основно образование, во тек на пролетта во 2016 година, со вкупно 130 деца, сите со прекумерна телесна тежина и обезност. Во неа беа вклучени деца на возраст од девет до 13 години. Од нив, 79 (60.7%) беа машки.
Резултати. Според ИТТ за соодветните возрасни перцентили, со прекумерна тежина и обезни беа 33.8% и 66.1% од децата. Дефициенција на витамин Д (<20 нг/мл) беше присутна кај 103 (79.2%) деца, 23 (17.7%) имаа инсуфициенција (20-30 нг/мл), додека само четири деца имаа нормални нивоа (30-100 нг/мл). Најдовме сигнификантна негативна линеарна корелација меѓу ИТТ по возраст и витамин Д статус со r=-0.4795, p<0.000. Деца со повисок ИТТ имаа пониски нивоа за витамин Д.
Заклучок. Висока преваленца на дефицит и инсуфициенција на витамин Д беа пронајдени кај деца со прекумерна телесна тежина и обезност од Косово. Треба да се земе во предвидрутински скрининг и третман за дефицит на витамин Д кај овие деца,

Клучни зборови: деца, прекумерна телесна тежина, инсуфициенција на витамин Д, Косово

What is already known on this topic?

Vitamin D is recognized as a group of fat-soluble prohormones with multiple roles in maintaining optimal overall health. Association of excess body weight in adults and children with decreased serum 25(OH)D concentrations were found in many investigations.

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What does this study add?

To our best knowledge, this is the first study performed in our country to evaluate the serum vitamin D levels in children with overweight and obesity. Consistent with other studies, we found a high prevalence of vitamin D insufficiency among children with overweight and obesity. Furthermore, vitamin D deficiency was more common in children with obesity than in overweight children.

Introduction

As with obesity, vitamin D (VD) deficiency is reaching epidemic proportions worldwide in both pediatric and adult populations. Obesity is defined as a complex, multifactorial chronic disease with abnormal or excessive body fat accumulation. It is a result of the interaction between both genotype and environment factors including behavioral, social, cultural, physiological and metabolic [1]. To assess obesity multiple measures are performed [2]; most often it is defined by the body mass index (BMI), which is calculated by dividing a person's weight in kilograms by the square of height in meters, (kg) / [height (m)]**.** BMI is strongly correlated with fat content in adults (where BMI corresponding to 25–30 is defined as overweight and BMI >30 is considered obese). Given the large variations in BMI due to pubertal status, age and gender, an expert committee recommend the 95th BMI centile for age and sex (or BMI 30 kg/m2) as cut-offs for 'overweight', and the 85th centile as 'at risk of overweight' for screening purposes [3,4]. BMI does not measure body fat directly, but is moderately correlated with more direct measures of body fat as well as with concurrent health risks, especially cardiovascular risk factors [5]. High BMI predicts future adiposity, as well as future morbidity and death. For identifying the fattest children the sensitivity of BMI of the 85th percentile is good, hence, health care providers can assess weight and height routinely in contrast to more precise measures of body fat (such as dual-energy x-ray absorptiometry) [6,7].

Medical Consequences of Childhood Obesity

Overweight children are at an increased risk of earlier onset of many diseases including type 2 diabetes, dyslipidemia, atherosclerosis, hypertension, left-ventricular hypertrophy, sleep apnea, asthma, non-alcoholic fatty liver disease, orthopedic problems and others [8]. Many studies show that they have poor school performance, poor self-esteem, difficulties with peer relationships, and various psychosocial problems. They also often become obese adults with a greater risk of chronic disease and disability [9]. Recent evidence suggests that vitamin D deficiency increases the risk of some of these conditions [10].

Vitamin D, definition

Vitamin D is recognized as a group of fat soluble prohormones; it has multiple roles in maintaining optimal general health and is crucial for normal bone growth during the early years of life. Vitamin D in human body usually can be found as vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) [11,12]. Usually, between 50% and 90% of vitamin D in the body comes from the production in the skin (depends on sunshine exposure) and the remainder is from the diet [13].

Metabolism of vitamin D

Ingested vitamin D (D represents D2, or D3, or both) incorporate into chylomicrons, then absorbed into the lymphatic system, through it enters the venous blood and transported to the liver. The first hydroxylation in the liver, is done by the vitamin D-25-hydroxylase (25-OHase) to produce 25-dihydroxyvitamin D3 (25-OHD3) or 25-OHD2. Further, these products metabolized in the kidney (second hydroxylation) by the enzyme 25-hydroxyvitamin D-1αhydroxylase (CYP27B1) to its active forms, 1,25-dihydroxyvitamin D; 1a,25-(OH) 2D-3 and 1a,25-(OH)2D-2. As a result, 1,25(OH)2D is the biologically active form of vitamin D responsible for maintaining calcium and phosphorus homeostasis by interacting with its nuclear receptor, the vitamin D receptor (VDR) in the small intestinal cells. [14,15]. The renal production of 1,25-dihydroxyvitamin D is tightly regulated by plasma parathyroid hormone levels, serum calcium and phosphorus levels [16]. The bioactive form of VD3, 1a25-dihydroxyvitamin D3 (1a,25 (OH)2D3), functions as a pleiotropic hormone controlling gene expression in numerous cell types and tissues, including inhibiting cellular proliferation and inducing terminal differentiation, inhibiting angiogenesis, stimulating insulin production, inhibiting renin production, and stimulating macrophage cathelicidin production and cell survival [16,17]. These activities are achieved principally via the cytosolic/nuclear vitamin D receptor (VDR) found in more than 40 tissues including pancreatic beta-cells, smooth muscle cells, monocytes, and adipocytes and several immune cells, all of which are associated with obesity and its associated metabolic complications [18-20].

Vitamin D, measure methods, optimal level, deficiency

The serum 25-hydroxyvitamin D (25OHD) is the most common measured indicator of vitamin D status because it reflects dietary intake from vitamin D2 and D3 together with cutaneous synthesis of vitamin D3 [21]. The optimal level of 25-OH vitamin D is a subject of many debates, but the most advantageous serum concentrations of 25(OH)D begin at 75 nmol/L (30

ng/mL), and the best are between 90 and 100 nmol/L (36-40 ng/mL) [22]. Different guidelines also exist regarding the proper definitions of vitamin D deficiency in clinical practice. The Endocrine Society and Society for Adolescent Health and Medicine has suggested that 25(OH)D levels of 75-250 nmol/l (30-100 ng/ml) are sufficient, 52-72 nmol/l (21-29 ng/ml) are insufficient and less than 50 nmol/l (20 ng/ml) are deficient [17,23]. There are several methods for measurement of vitamin D [24] the choice of those depends on the availability of equipment, technical expertise, as well as purpose to quantitate both the D3 and D2 forms of the vitamin D metabolites [25].

Obesity, vitamin D deficiency, consequences

Many researchers consider a reduced vitamin D concentration as a potential risk factor for bone disease, diabetes, metabolic syndrome, cardiovascular diseases, hypertension, cancer, multiple sclerosis, rheumatoid arthritis, infectious diseases resulting from decreased immunity [26-28]. Fractures, Blount disease, and slipped capital femoral epiphysis are more common in children with obesity, and thus, many researchers suggest that vitamin D deficiency increases the risk of development of these conditions [29,30]. There are several observational studies comparing the vitamin D status in adolescents with obesity and multiple metabolic health measures including insulin resistance. Majority, although not all, show significant associations between circulating 25(OH)D concentrations and insulin sensitivity/ resistance indices [31,33]. A recent study has found a high prevalence of vitamin D deficiency in pediatric overweight or obese patients, which was significantly associated with an increase in several atherogenic lipids and may be a modifiable risk factor for CVD. Non-HDL cholesterol, TC/HDL, TG/HDL, TC, and TG levels were all significantly higher in the vitamin D deficient patients compared to patients without vitamin D deficiency [10].
Given that children with obesity are already at higher risk of several comorbidities, in the present study initially we aimed to investigate the prevalence of vitamin D deficiency and to highlight the importance of vitamin D screening in overweight or obese children to reduce those risky comorbidities.

Materials and methods

This is a cross-sectional study that involved 130 children, overweight or obese, aged 9-13 years, referred to the Pediatric Endocrine Service from different primary schools across the capital city of Kosovo, during the spring of 2016. The measurement of the children (weight and length) was done in the examination room during physical examinations, by applying standardized protocols and calibrated instrument. Children were barefoot, wearing only underwear. The weight was measured using a classic balance (Gima: range 1-150 kg, precision 100 g). Height was measured using a telescopic height measuring instrument (Seca 225 stadiometer, seca, Birmingham, UK) to the nearest 0.1 cm. BMI was calculated as weight in kilograms divided by height in meter squared. BMI percentiles were determined by using age- and gender-specific CDC growth charts. The BMI at the 85th to less than the 95th percentile is considered overweight, and BMI at or above the 95th percentile is considered obese [34]. Inclusion criteria were overweight children or obese children without history of acute or chronic disease, endocrine pathology, or suspected syndromes associated with obesity, and without history of taking vitamin D or other medications. The permission for conducting the research was obtained from the Ethics Committee of the Medical Faculty in Prishtina (no. 8384). Written informed consent was obtained from parents of children. The quantitative determination of total 25hydroxyvitamin D concentration in the serum was measured by using the vitamin D Assay Elecsys Roche. Vitamin D status was classified according to the Endocrine Society, as deficient, insufficient, or sufficient (serum 25-OHD: <20 ng/mL, 20-30 ng/mL, and >30 ng/mL), respectively.

Statistical analysis

Data was presented as means ±SD. The compiled data was analyzed with the statistical software SPSS, version 18. The independent sample-*t test* was used to analyze mean difference. A level of significance with p value: $p \leq 0.05$ was considered significant, $p<0.001$ was considered highly significant. Pearson's correlation coefficients {r} were used to determine the correlation between the studied parameters. Analysis of variance (ANOVA) was used to analyze the differences and their associated procedures among and between groups.

Results

From the total number of 130 children, 60.7% were male and 39.2% were female. The most prevailing age group was 10-year-old children, with a total number of 44 children or 33.8% (Table 1).
According to BMI**,** 44 (33.8%) children were over-

Table 1. Number of children according to age and gender

Age (Years)	Gender		Number	Percent %
	Male	Female		
9	10	7	17	13.0
10	24	20	44	33.8
11	21	14	35	26.9
12	11	7	18	13.8
13	13	3	16	12.3
Total	79	51	130	100

weight, of them 21 (47.7%) were male and 23 (52.2%) female. Eighty-six (66.1%) children were obese, most of them 58 (67.4%) were male and 28 (32.5%) were female. The most prevalent group were children aged 10 years, of them 20 (15.3%) were overweight and 24 (18.4%) obese. The smaller group were children aged 13; two (1.5%) of them were overweight, and 14 (10.7%) obese (Table 2).

Table 2. BMI for age percentile according to age and gender

Age (Years)	Overweight BMI between 85th and 95th percentile Number			Obesity BMI at or above the 95th percentile Number		
	Male	Female	n, %	Male	Female	n, %
9	1	3	4 (3)	9	4	13 (10)
10	9	11	20 (15.3)	15	9	24 (18.4)
11	7	5	12 (9.2)	14	9	23 (17.6)
12	3	3	6 (4.6)	8	4	12 (9.2)
13	1	1	2 (1.5)	12	2	14 (10.7)
Total	21	23	44 (33.8)	58	28	86 (66.1)

BMI = body mass index; n= number

The highest mean weight was found in 13-year-old children, 89.46 ±26.5, and the lowest mean weight was found in 9-year-old children, 44.16, ±10.4. Thirteen-year-old group had also the highest mean height, 161.48, ±16.1 meters, while the lowest mean height, with 133.13, ±7.8 meters was found in the group of 9-year-old children (Table 3).

Table 3. Weight and height according to age

Age (year)	Weight (kg)		Height (cm)	
	Mean	SD	Mean	SD
9	44.16	±10.4	133.13	±7.8
10	55.75	±7.2	150.11	±4.9
11	58.79	±8.9	150.46	±6.4
12	64.94	±11.2	152.84	±6.5
13	89.46	±26.5	161.48	±16.1

Among all children, overweight or obese, serum 25 (OH) D concentration ranged between 2.1 and 36.1 ng/ml, with an average of 15.94 ng/ml. The mean serum 25 (OH)D level was higher in 12-year-old group of children with obesity, with 16.69±6.8, while the lowest mean level was found in 13-year-old children, with 12.1±6.0. We found no significant impact of children's age on vitamin D value (Table 4).

Table 4. Vitamin D according to age

Age (years)	Vitamin D (ng/ml)		
	Mean	SD	Range
9	16.05	±5.2	6.7-27.2
10	16.3	±4.9	8.0-29.9
11	16.82	±.7.5	2.1-34.1
12	16.69	±6.8	9.3-36.1
13	12.1	±3.7	5.5-18.7
Total	15.94	±6.0	2.1-36.1

F(Analysis of Variance) = 1.98 p=0.1 ns

Vitamin D deficiency (<20 ng/ml) was found in 103 or 79.2% of children; 23 children or 17.7% had insufficiency (20-30 ng/ml) while only 4 children or 3% had sufficient levels (>30 ng/ml).

There was a correlation between BMI of age percentile and vitamin D status with a statistical significance ($p<0.001$). Vitamin D deficiency was more often present in children with obesity than in overweight children (93% *vs* 52.3%) (Table 5).

Table 5. Vitamin D status in overweight and obese children

BMI for age percentile	Vitamin D status Deficiency < 20ng/ml		Insufficiency 20-30 ng/ml		Sufficiency >30 ng/ml	
	N	%	N	%	N	%
Overweight	23	52.27	19	43.18	2	4.55
Obesity	80	93.02	4	4.65	2	2.33
Total	103	79.2%	23	17.7%	4	3.1%

Chi -square=30.7 df=1 p<0.001 sig

In the group of overweight children, only 2 children, aged 11 years, had sufficient vitamin D level; 19 (43.2%) had insufficient level, and 23(52.3%) had deficient level. There was no statistically significant difference in vitamin D values <20 ng/ml from 20 to 30 ng/ml, depending on the age of the overweight children (Table 6).

Two children with obesity, aged 11 and 12, had sufficient D vitamin level; all other had insufficient and deficient vitamin D (<30 ng/ml) level. Four children with vitamin D insufficiency were aged 9, 10 and 11 years. All children aged 11 years had vitamin D deficiency. There was no statistically significant differentce of vitamin D values <20, from 20 to 30 ng/ml, depending on the age of the obese children (Table 7).

Table 6. Vitamin D status in overweight children according to age

	Vitamin D status					
	Deficiency < 20ng/ml		Insufficiency 20-30 ng/ml		Sufficiency >30 ng/ml	
	N	%	N	%	N	%
9	2	50	2	50	/	/
10	12	60	8	40	/	/
11	4	33.33	6	50	2	16.67
12	3	50	3	50	/	/
13	2	100	/	/	/	/
Total	23	52.27%	19	43.18%	2	4.5%

Fisher exact, two tailed p=0.69 ns

Table 7. Vitamin D status in children with obesity according to age

	Vitamin D status					
	Deficiency < 20ng/ml		Insufficiency 20-30 ng/ml		Sufficiency >30 ng/ml	
	N	%	N	%	N	%
9	12	92.31	1	7.69	/	/
10	22	91.67	2	8.33	/	/
11	21	91.30	1	4.35	1	4.35
12	11	91.67	/	/	1	8.33
13	14	100	/	/	/	/
Total	80	93.02%	4	4.65 %	2	2.33%

Fisher exact, two tailed p=0.69 ns

We found a significant negative linear correlation between BMI for age and vitamin D status, with r=-0.4795, p<0.000. Children with higher BMI had lower vitamin D level (Figure 1). According to gender, we found the negative linear correlation between BMI for age and vitamin D status, with r=-0.525, p<0.000001 at boys, while, r= -0.444, p=0.001 at girls. (Figure 2 and Figure 3).

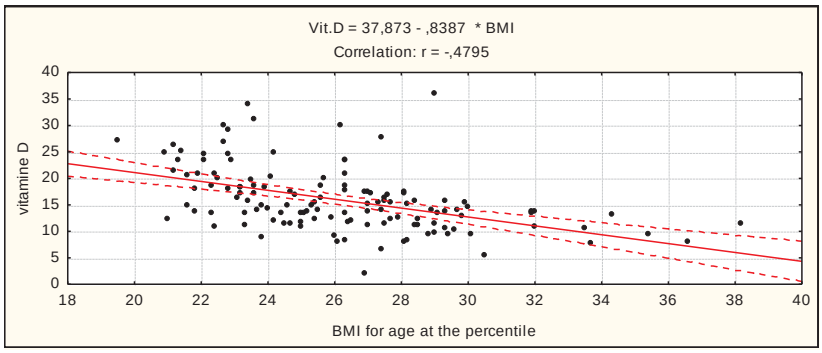

Fig. 1. Correlation between BMI for age percentile and vitamin D
r=-0.4795, r^2=0.22, t=6.18, p<0.00

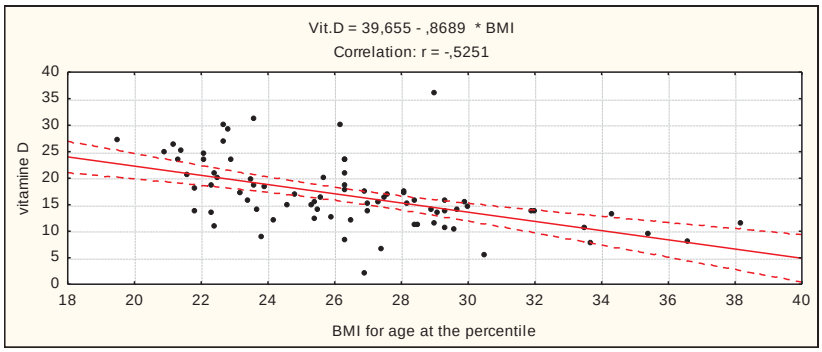

Fig. 2. Correlation between BMI for age percentile and vitamin D in male children
r=-0.525, r^2=0.28, t=5.4, p<0.000001

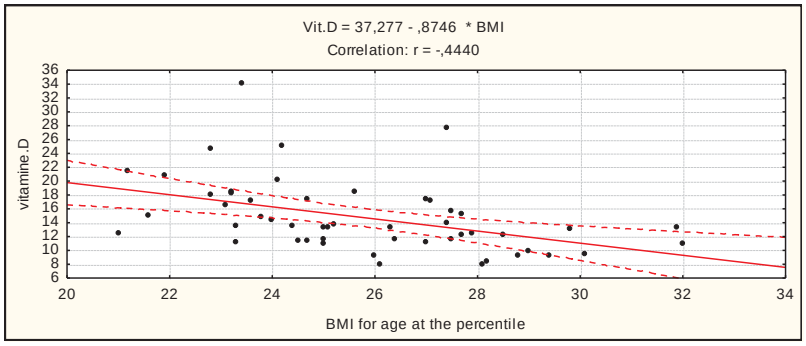

Fig. 3. Correlation between BMI for age percentile and vitamin D in female children
r= -0.444, r^2=0.197, t=3.5, p=0.001

Discussion

To the best of our knowledge, this is the first study performed in our country to evaluate the serum vitamin D levels in overweight and obese children. Association of excess body weight in adults and children with decreased serum 25(OH)D concentrations has been shown in many investigations [35-37]. Obesity was seen as a risk factor for vitamin D insufficiency and severity of obesity was inversely correlated with 25-hydroxy vitamin D [25(OH)D] levels [38]. Low dietary vitamin D intake and insufficient activity, resulting in limited sun exposure also have been cited as possible confounding factors [39]. There might by several reasons for the decrease of vitamin D in children with obesity. Firstly, some researchers have indicated that children with obesity, due to sedentary lifestyle and less outdoor activities, are less exposed to sunlight (ultraviolet light) that is indispensable for vitamin D synthesis [40,41]. Secondly, vitamin D is a fat-soluble micronutrient and is easily stored in the adipose tissue, which reduces the bioavailability of vitamin D [42]. The inverse association between high body fat and low vitamin D levels has been attributed to sequestration of the fat-soluble vitamin within the plentiful adipose tissue [43]. High content of body fat may act as a reservoir for lipid soluble vitamin D and increase its sequestration, determining its low bioavailability. It has also been reported that fat content is inversely related to serum 25(OH)D concentration; this association is stronger than that between 25(OH)D and BMI. In people with obesity, not only fat mass is increased but also lean body mass, as an adaptive response to greater body weight [44]. Excess body fat may disrupt hormonal pathways important for skeletal health like leptin; an adipocyte-derived hormone that binds to osteoblasts, appears to activate a pathway that inhibits renal synthesis of the active form of vitamin D [45]. Using a proteomic approach to identify potential *in vivo* biomarkers that could provide a link between VD deficiency and pediatric obesity, the multimeric forms of adiponectin, was identified as being down regulated in obese pediatric subjects with vitamin D deficiency. Further, a direct effect of 1a,25-(OH)2D3 on adipocytes was demonstrated, with adiponectin and its multimeric forms, as well as the adiponectin interactive protein, DsbA-L, upregulated by 1a,25-(OH)2D3 treatment at low pharmacological concentrations [46].

We found a high prevalence of vitamin D insufficiency and deficiency among overweight and obese children. Children with obesity appear to be particularly at risk.

The measurement of vitamin D was performed in the beginning of spring. Considering the fact that the sun exposure is reduced during winter, we can assume that this is likely to have an impact on the higher prevalence of vitamin D deficiency and insufficiency, found in our study. Similar to the findings reported in a study comprising British children [47], our study demonstrated that serum vitamin D levels were low in overweight and obese children.

Our findings also correspond with a study conducted in a large group of children, 6-18 year olds in the United States, where the prevalence of vitamin D deficiency among children with healthy-weight, overweight, obese, and severely obese were 21%, 29%, 34%, and 49%, respectively [48]. Among those with severe obesity, the prevalence of vitamin D deficiency approached 90% in African American children and exceeded 50% in Latino children, compared to 27% among white children [48]. In a study including overweight and obese children from Norway the prevalence of vitamin D deficiency and insufficiency was 19% and 31%, respectively [35].

Association between BMI and low 25(OH)D concentrations were also found across different age groups of Caucasian populations from North America and Europe, pointing out that higher BMI leads to lower vitamin D status and providing evidence for the role of obesity as a risk factor for the development of vitamin D deficiency [49]. A study based on genetic approach has demonstrated that higher BMI leads to lower 25(OH)D, while any effects of lower 25(OH)D in increasing BMI are likely to be small [27]. An inverse association of serum 25(OH)D and body mass index (BMI) greater than 30 kg/m^2 has been found [50]. Each unit increase in BMI is being associated with 1.15% lower concentration of 25(OH) D [27].

Our findings pointid out to a significant negative linear correlation between BMI for age and vitamin D status, indicating that children with higher BMI had lower vitamin D levels. Those study suggests that national prevention of obesity can lead to a reduction in the prevalence of vitamin D deficiency. The importance of screening, monitoring, and treating vitamin D deficiency as a means of alleviating the adverse influences of excess adiposity on health has been highlighted [27,49].

Some limitations need to be acknowledged regarding the present study. Our study was done in early spring, and duration to sun exposure was not measured. In addition, we did not measure the vitamin D status in children with healthy weight in order to compare them with findings in overweight or obese children.

Conclusion

A high prevalence of vitamin D deficiency was found among overweight and obese children from Kosovo.

Children with higher BMI had lower vitamin D level.

Vitamin D deficiency was more often present in children with obesity than in overweight children.

Early detection of obesity and vitamin D deficiency among young population would have a high impact on decreasing the incidence of many disease processes.

The high prevalence of vitamin D insufficiency among children with obesity suggests that routine screening and treatment of vitamin D deficiency in these children should be considered.

However, further studies are needed to be done in children with healthy weight and conducted in other seasons, to determine the clinical relevance of low vitamin D levels among these children and its association with comorbidities.

Conflict of interest statement. None declared.

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Original article

EARLY AND LATE COMPLICATIONS AFTER ALLOGENEIC TRANSPLANTATION OF HEMATOPOIETIC STEM CELLS – PROSPECTIVE –RETROSPECTIVE STUDY

РАНИ И ДОЦНИ КОМПЛИКАЦИИ ПОСЛЕ АЛОГЕНА ТРАНСПЛАНТАЦИЈА НА ХЕМАТОПОЕТСКИ МАТИЧНИ КЛЕТКИ – ПРОСПЕКТИВНА-РЕТРОСПЕКТИВНА СТУДИЈА

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Abstract

Introduction. Allogeneic transplantation of hematopoietic stem cells (HSCT) represents a curative method for treating patients with malignant and non-malignant hematological disorders. Complications that occur in post-transplantation period significantly affect the outcome of this intervention and the quality of life of these patients. The aim of this study was to evaluate post-transplant complications and to determine the strategy in their management.
Methods. This study was designed as a prospective-retrospective, which included and analyzed 65 patients treated with allogeneic transplantation from HLA identical donor at the University Clinic of Hematology-Skopje, in the period from 25.09.2000 to 31.12.2016. Clinical-laboratory characteristics of patients, disease status, protocol of conditioning regiment were analyzed, and special emphasis was given to the detection, monitoring and analysis of registered post-transplant complications, their diagnosis and treatment.
Results. In the period of the first 60 days after allogeneic HSCT was conducted; in 30 patients early complications were recorded (46.15%). The duration of the infective syndrome was longer in patients with post-transplant complications. Acute GVHD was observed in 28 patients, with the most common localization on the skin (75%). Chronic GvHD was registered in 11 patients. In 16 patients (24.61%) there was a relapse of the underlying disease, of which male patients non-significantly more often had relapse of the disease than female patients - 28.13% *vs* 21.21%. Fatal outcome occurred in 18 patients (27.69%), in whom the most common cause was relapse of the underlying disease and GvHD. Patients with a donor woman for a male recipient (57.14%) significantly more common had a fatal outcome. The difference between patients with and without acute GVHD in relation to lethal outcome was statistically confirmed for a value of p=0.069. With an increase in the EMBT risk for one unit, the chance of fatal outcome increases by 2.5 times.
Discussion. The long survival and/or recovery after allogeneic transplantation leads to increased risk of developing late complications. The multidisciplinary approach is mandatory in monitoring these patients and includes the family, workplace, family doctor and more specialties.

Keywords: allogeneic transplantation, early and late complications, GvHD, immune system, donor-recipient match

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Апстракт

Вовед. Алогената трансплантација на хематопоетски матични клетки (ТХМК) е куративна метода за лекување пациенти со хематолошки малигни и немалигни заболувања. Компликациите, кои се јавуваат во посттрансплантацискиот период, сигнификантно влијаат на исходот на оваа интервенција и квалитетот на животот на пациентите. Целта на оваа студија беше да се евалуираат посттрансплантациските компликации и да се детерминира стратегијата во нивното менаџирање.
Методи. Оваа студија беше дизајнирана како проспективно-ретроспективна, вклучени се и анализирани 65 пациенти, лекувани со алогена трансплантација од ХЛА идентичен донор на ЈЗУ УК за хематологија-Скопје, во период од 25.09.2000 год. до 31.12.2016 година. Анализирани се клиничко-лабораториски карактеристики на пациентите, статусот на болеста, протоколот за кондиционирање, а посебен осврт беше даден на детекција, мониторирање и анализа на регистрираните посттрансплантациски компликации, нивната дијагноза и третман.

Резултати. Во периодот од првите 60 дена по извршена алогена ТХМК, кај 30 пациенти се регистрирани рани компликации (46.15%). Инфективниот синдром подолго траел кај пациенти со посттрансплантациски компликации. Акутна ГвХД беше регистрирана кај 28 пациенти, со најчеста локализација на кожата (75%). Хроничната ГвХД беше регистрирана кај 11 пациенти. Кај 16(24.61%) од пациентите настапи релапс на основната болест, од кои пациентите од машки пол, несигнификантно почесто имаа релапс на болеста, во однос на пациентите од женски пол–28.13% vs 21.21%. Летален исход настапи кај 18 пациенти (27,69%), кај кои најчеста причина беше релапс на основното заболување и ГвХД. Статистички, сигнификантно почесто, егзитираа пациентите со донор-жена за мажреципиент (57.14%). Разликата меѓу пациенти, со и без акутна ГвХД, во однос на леталниот исход беше статистички потврдена за вредност на p=0.069. Со зголемување на ЕМБТ ризикот за една единица, шансата за летален исход се зголемува за 2.5 пати.
Дискусија. Долгото преживување и/или излекување по алогена трансплантација доведува до зголемен ризик од појава на доцни компликации. Мултидисциплинарниот пристап е мандаторен во следење на овие пациенти и ја вклучува фамилијата, работната средина, матичниот лекар и повеќе специјалности.

Клучни зборови: алогена трансплантација, рани и доцни компликации, ГвХД, имун систем, донор-реципиент совпаѓање

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) represents a curative method for treatment of patients with hematologic malignant and non-malignant diseases, immunodeficiency, autoimmune, genetic and other diseases [1]. At the same time, allogeneic HSCT is the most complex biological manipulation in human medicine in which, not only the stem cells, but also the immune system of the patient is replaced with the immune system of the donor [2,3]. Though HSCT has significant curative potential in these diseases, its practical application is limited by complications associated with the transplantation such as infections and graft-versus-host (GvHD) that can lead to a mortality rate of up to 50% in elderly patients or patients that are less compliant in the HLA-DNA system [4-6]. Therefore, a careful assessment of the risk and benefits prior to each transplanttation is required [7], with a special-individual approach for each patient [8-10]. The progressive growth of allogeneic transplantations in recent decades has resulted in a significant increase in long-term survival and/or cure and reduction in transplantation morbidity and mortality [1,11]. Although most patients with allogeneic transplantation have a good quality of life, health care and control of complications is mandatory for their complete recovery and good quality of life. Complications that occur in the post-transplant period significantly affect the outcome of this intervention and the quality of life in the patients [12]. Complications are due to highly aggressive chemotherapy and immune system disorders [13,14]. All these late complications are presented with a wide range of manifestations in terms of frequency, onset time, risk factors, prevention, treatment approaches and outcomes. The risk and type of complications depend on the pre-transplantation measures [7], the age of the patient, timing of allogeneic transplantation, present comorbid conditions, and other factors that are subject of current studies [8,15]. The leading causes of increased morbidity and/or mortality are secondary malignancy, infections, chronic GvHD [9], respiratory and cardiovascular diseases [12]. The long survival line after allogeneic transplantation has been prolonged due to a mandatory high-quality and multi-disciplinary approach [16]. The late effects of HSCT may be due to underlying disease, pre-transplant comorbidity, protocols used before transplantation, type of conditioning regimens [17], acute and chronic GvHD and its treatment [18,19] and/or infectious complications [20,21]. Moderate and severe side effects are easily recognizable and during the first year after allogeneic HSCT, deviations in laboratory findings are common. When it is possible to discontinue the immunosuppressive drugs, most of these parameters tend to normalize [2]. Little attention is paid to the discrete changes in the clinical and biochemical parameters during the post-transplant period. However, the changes that exist over the years and decades can ultimately lead to significant organ dysfunction, so monitoring of these parameters is required [22].
The aim of this study was to analyze and evaluate the most common post-transplant complications in patients treated with allogeneic HSCT in different age groups, disease status, donor type [23], type of conditioning regimen and chemotherapy, and to determine the strategy of their management and treatment [24,25].

Materials and methods

Design of the study

This was a prospective - retrospective study that was conducted at the University Clinic of Hematology in Skopje, and its aim was to analyze the early and late complications after allogeneic transplantation. The study was approved and done in accordance with the Ethics Committee for Human Research, at the UKIM - Medical Faculty in Skopje.

Patient population and selection criteria

Sixty five patients treated with allogeneic HSCT at the Department of Transplantation at the University Clinic of Hematology between September 25, 2000, and December 31, 2016 were included in the study. Transplantation was performed for the treatment of hematological malignancy and non-malignant disease in all patients. All donors were HLA-identical brother and sister. Peripheral blood was used as a source of stem cells in most of the patients. The patients' characteristics are shown in Table 1.

Table 1. Patients' characteristics

Gender	
Male	32
Female	33
Age (range)	
>20	9
20-30	22
30-50	22
<50	12
Underlying disease	
Acute myeloid leukemia (AML)	36
Acute lymphocytic leukemia (ALL)	10
Chronic myeloid leukemia (CML)	5
Myelofibrosis	5
Aplastic anemia (AA)	5
Myelodysplastic syndrome (MDS)	2
Others	2

Stem cell transplantation procedure

All patients included in the study were treated with allogeneic HSCT, but previously they were treated with chemotherapy in several cycles in accordance with primary hematological disease. All patients received appropriate conditioning regimen. A central venous catheter was routinely implanted prior to the infusion of stem cells. Table 2 shows patients and donor characteristics and type of the conditioning regimen.

Table 2. Patients' and donors - transplantation procedure

Donor type	
Matched sibling	63
Identical sibling	1
Mismatched family	1
Donor / recipient sex	
Male / Male (M→M)	19
Male / Female (M→F)	22
Female / Male (F→M)	14
Female / Female (F→F)	10
Type of conditioning	
Busulfan + cyclophosphamide (BuCy)	25
Busulfan + cyclophosphamide + melphalan (BuCy + M)	31
Cyclophosphamide + ATG	5
BEMA	2
Flag-Ida	2

Conditioning protocols were applied depending on the underlying disease and the numerous prognostic parameters that were analyzed before the implementation of this intervention. Day 0 was designated as the day of graft infusion. Care and antimicrobial prophylaxis was performed after transplantation. All of the blood products were filtered, irradiated, and then applied to recipients. In the first 100 days after transplantation, patients were screened for cytomegalovirus reactivation in order to initiate preventive therapy with ganciclovir, if necessary. GvHD is defined in accordance with the Seattle criteria for diagnosis and GvHD setting.

European Group for Blood & Marrow Transplantation Allograft risk score (EMBT risk score)

Earlier analyses on outcome after HSCT for other diseases indicated that age, disease stage, time interval, donor type and donor recipient gender combinations influence survival, non-relapse mortality and relapse risk. The risk score for this analysis used the same 5 pretransplant risk factors as initially defined: age of the patient, disease stage, time from diagnosis to transplantation, donor type, and donor-recipient sex combination, with 0 to 1 or 2 points for each factor. EMBT risk score for our patients is shown in Table 3.

Table 3. EMBT risk score

Score	5 year OS	TRM	patients
0	70%	16%	3
1	62%	23%	29
2	54%	29%	22
3	43%	34%	8
4	33%	41%	2
5	24%	47%	1
≥6	23%	52%	

Graft-versus-host disease (GvHD) prophylaxis and therapy

The majority of patients received cyclosporine A in combination with methotrexate. Both acute and chronic GvHD were diagnosed on the basis of clinical symptoms and/or biopsy from the skin, liver, gastrointestinal tract or oral mucositis. Acute GvHD was diagnosed clinically and evaluated by attending physicians from grade 0 to IV and chronic GvHD was defined as limited *vs*. extensive disease according to the appropriate criteria for diagnosis and therapy.

Care and treatment

Prophylaxis against infection included parenteral and oral antibiotics, antimycotics and virostatics during the phase of neutropenia. Appropriate doses of immunoglobulins were given to all patients during the post-transplant period.

Results

Patients

Sixty-five patients treated with allogeneic HSCT were analyzed in this study. The median age of patients was 33.46 ±12.4, with min-max 16-58 years. The average duration of the disease before transplantation was 8 months (1-15 months). The number of patients in remission was 57 and the number of patients with active disease 8, before allogeneic HSCT was performed. All donors were HLA identical - brothers or sisters.
In the period of the first 60 days after allogeneic HSCT was performed, in 30 of our patients early complication occurred, and the incidence of this post-transplant complications was 46.15% (Table 4).

Table 4. Early complications after allogeneic transplantation

Early complications	**n (%)**
No complications	35 (53.85)
with complications	30 (46.15)

Infections

The most severe infections occurred during the first six months of transplantation due to the slow recovery of the immune system. Recipients of HSCT at different times after transplantation were confronted with various complication from infections resulting from an immune defect in host defense. That is why the patients were treated with additional parenteral antibiotic therapy according to microbiological tests and immunoglobulins after what the patient status was improved. The duration of the infective syndrome was longer in patients with complication post-transplantation (p=1.0).

Acute and Chronic GvHD

Patients received prophylactic therapy for GvHD consisting of cyclosporine A in combination with methotrexate. Acute GvHD was registered in 28 (34.08%) patients. In our patients, 6 patients were reported with an acute GvHD grade I, 16 patients-with grade II, 10 patients-with grade III and 2 patients with grade IV, of which in 21 patients it was on the skin, in 16 patients intestinal GvHD and in 5 patients it was hepatic. In all of these patients, therapy with parenteral corticosteroids and immunoglobulins were additionally given according to the GvHD grade. Chronic GvHD (cGvHD) was developed in 11 (16.94%) patients with involvement of the skin and liver. Among this group of patients, 6 patients were with previous aGvHD, 4 patients with limited cGvHD and 1 patient with extensive character. Steroid refractor GvHD was noted in 2 patients. Three of the patients with cGvHD on the skin received PUVA (psoralen and ultraviolet A) therapy.

Nephrological complications

Complications from the urogenital system, expressed as acute renal failure, were observed in 4(6.15%) patients with allogeneic HCST after 60 days of transplantation. In 2 patients, the diagnosis of the disease was AML, in one patient CML, and in one MM, all with an identical donor. The time from diagnosis to transplantation in 2 patients were 1-3 months, and in 2 patients 4-6 months. EMBT risk score 1 had 2 patients, risk score 3 one patient, and risk score 5 one patient. The underlying disease in 3 patients was in remission, and 1 in the active phase before the transplantation. In 3 patients, Bu - Cy type of conditioning was applied, and in 1 patient type Bu Cy - Mel type of conditioning.

Donor lymphocyte infusion (DLI)

Six of the sixty-five patients received a donor lymphocyte infusion when relapse of the underlying disease occurred, of which 3 were men and 3 were women.

Late complications

In 29 of our patients with allogeneic HSCT late complications occurred, and the incidence of this post-transplant complications was 44.61%. Secondary malignancy occurred in 4 patients, and all of them were females. In 16 (24.61%) patients with allogeneic HSCT, there was a relapse of the underlying disease, of which 5 with a diagnosis of ALL, one with a diagnosis of AA, 8 patients with a diagnosis of AML, one with CML, and in one patient a relapse was registered with non-Hodgkin's lymphoma (Table 5). Male patients were slightly more likely to have relapsed disease than female patients - 28.13% *vs* 21.21%.
Fatal outcome occurred in 18 patients (27.69 %), of which 10 were men and 9 were women. The most common reason for fetal outcome in our patients was relapse of the underlying disease and GvHD (Table 6). The difference between patients with and without acute GvHD in relation to lethal outcome was statistically confirmed for a value of p = 0.069.

Impact of the EBMT Risk Score on overall survival (OS) and treatment-related mortality (TRM)

Overall survival and TRM were significantly influenced by the EBMT risk score. With an increase in EMBT risk score for one unit, the chance of fatal outcome increases by about 2.5 times-OR=2.503 95% CI (1.298-4.825).

Table 5. Relapse after allogeneic transplantation

Characteristics		n	relapse		p value
			no	yes	
Gender	Male	32(49.2)	23 (71.88)	9 (28.13)	[a]0.52 ns
	female	33(50.8)	26 (78.79)	7 (21.21)	
Patient's age	<20 years	9(13.8)	6 (66.67)	3 (33.33)	0.45 ns
	20 – 30 years	22(33.8)	16 (72.73)	6 (27.27)	
	30 – 50 years	22(33.8)	19 (86.36)	3 (13.64)	
	>50 years	12(18.5)	8 (66.67)	4 (33.33)	
	mean ± SD		32.69 ± 13.9	33.71 ± 12.1	0.78 ns
Diagnosis	ALL	10(15.4)	5 (50)	5 (50)	
	AA	5(7.7)	4 (80)	1 (20)	
	AML	36(55.4)	28 (77.78)	8 (22.22)	
	Myelofibrosis	5(7.7)	5 (100)	0	
	MDS	2(3.1)	2 (100)	0	
	Non-Hodgkin' lymphoma	1(1.5)	0	1 (100)	
	CML	5(7.7)	4 (80)	1 (20)	
	MM	1(1.5)	1 (100)	0	
HLA matching	1	63(96.9)	48 (76.19)	15 (23.81)	
	2	1(1.5)	0	1 (100)	0.43 ns
	3	1(1.5)	1 (100)	0	
Donor-recipient	M – M	19(29.2)	14 (73.68)	5 (26.32)	
	M – F	22(33.8)	16 (72.73)	6 (27.27)	0.78 ns
	F – M	14(21.5)	10 (71.43)	4 (28.57)	
	F – F	10(15.4)	9 (90)	1 (10)	
Time from Dg. to transplantation	1 month	1(1.5)	1 (100)	0	
	1 – 3 months	4(6.2)	4 (100)	0	0.73 ns
	4 – 6 months	19(29.2)	15 (78.95)	4 (21.05)	
	> 6 months	41(63.1)	29 (70.73)	12 (29.27)	

Table 6. Fatal outcome after allogeneic transplantation

Characteristics		n	Fatal outcome		p value
			no	yes	
Early complications	No	35(53.8)	26 (74.29)	9 (25.71)	[a]0.7 ns
	Yes	30(46.1)	21 (70)	9 (30)	
aGvHD	No	37(56.9)	30 (81.08)	7 (18.92)	[a]0.069 ns
	Yes	28(43.1)	17 (60.71)	11 (39.29)	
cGvHD	No	55(84.6)	40 (72.73)	15 (27.27)	[a]1.0 ns
	Yes	10(15.4)	7 (70)	3 (30)	
Relapse	No	49(75.4)	38 (77.55)	11 (22.45)	[a]0.12 ns
	yes	16(24.6)	9 (56.25)	7 (43.75)	
Time from transplantation to relapse	1 0-6 months	4(6.2)	1 (25)	3 (75)	0.52 ns
	2 6-12 months	5(7.7)	4 (80)	1 (20)	
	3 1-2 years	3(4.6)	1 (33.33)	2 (66.67)	
	4 2-5 years	3(4.6)	2 (66.67)	1 (33.33)	
	5 > 5 years	1(1.5)	1 (100)	0	

Discussion

Long-term survival and/or cure after allogeneic transplantation leads to an increased risk of late complications [12]. Monitoring of the post-transplant period and clinical follow-up of the registered complications enabled the creation, standardization and acceptance of uniform criteria in the approach of each patient treated with this intervention [8,26]. Our study included 65 patients who were treated with allogeneic HSCT at the University Clinic of Hematology in Skopje. The risk of a late death is not negligible. Our goal was to identify complications that occur in the early and late stages after allogeneic HSCT, their observation, diagnosis, management and timely treatment.

A number of variables related to patient characteristics or transplantation [12,27], such as age of the patient [7], the type and duration of the underlying disease or conditioning regimen [17], may affect the recovery of immunity following HSCT [10,27]. Other complications of post-transplantation, such as GvHD [19] and administration of immunosuppressive drugs as a consequence of GvHD [18,28], may also have an effect [28,29]. The complexity of these interrelated variables, as well as the difficulties in collecting a sufficient number of long-term survivors, is an obstacle to identify the major risk factors that contribute to the immune deficiency of long-term survivors [15]. Acute and chronic GvHD was one of the main causes affecting the immune reconstitution of T and B cells [13,14], and at the same

time the main causes of death that are not related to relapse of the underlying disease [29,30]. GvHD can lead to fatal outcome as a direct complication or is associated with an immune deficiency that increases the susceptibility to infections [10,18]. Careful monitorring of these patients may be of great significance, as infusions of donor lymphocytes (DLI) can control the relapse of the underlying disease after transplantation [24,25]. The EMBT risk score was prognostic about overall survival, the relapse of primary hematological disease, and the lethal outcome of allogeneic transplantation [31,32]. Our results should be interpreted with caution because the protocols for transplantation, the treatment of complications and monitoring were not equal among patients in our group. Transplantation techniques have changed over the two decades of the first patient, and thus the prevention of some complications after transplantation, such as acute GvHD [18, 19] have improved, and the treatment of relapse to the disease is now more effective [16,29]. In addition, transplantation is now more often used in elderly patients and in patients in whom donors are not HLA identical siblings [3,4,6,23,33].

This provided a recommendation for a mandatory interdisciplinary medical and non-medical approach that should provide a solid health status, a social integration and quality life of this category of patients. The integration of clinical and additional laboratory variables enabled the creation of outcome predictors and therapeutic strategies in the post-transplant process [7, 26]. The multidisciplinary approach is mandatory in monitoring these patients which will help us to create our own therapeutic strategy with defined recommenddations for screening and preventive post-transplant complications-a calendar of activities [15,34-36]. Patients, their family, family doctor and other medical specialties must be familiarized with it, all who are proactively involved in managing these serious complications of allogeneic HSCT. Long-term adverse effects are multifactorial, the natural history of late effects will change in the future, as transplantation techniques have changed significantly over the last three decades [12,21]. Chronic GvHD remains the biggest challenge-a risk factor [9,19]. The rapidly growing population of all-transplant patients creates an obligation to educate the sick patients, their family, doctors and other institutional and non-governmental organizations [11]. Since it is higher than the average rate of secondary malignancies, cardiovascular [34], infectious, endocrine, pulmonary and kidney disease, and bone loss indicate that this population requires more examinations and interventions than the general population [22].

Conflict of interest statement. None declared.

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Original article

RECONSTRUCTION OF THE AORTIC ROOTH AND REIMPLANTATION OF THE NATIVE AORTIC VALVE (AORTIC VALVE - SPARING OPERATION SEC. DAVID) IN YOUNG PATIENTS WITH ACUTE STANFORD TYPE A DISSECTION OF THE AORTA (ONE YEAR EXPERIENCE AT THE UNIVERSITY CLINIC FOR STATE CARDIOSURGERY)

РЕКОНСТРУКЦИЈА НА АОРТАЛНИОТ КОРЕН СО ПЛАСТИКА И РЕИМПЛАНТАЦИЈА НА НАТИВНАТА АОРТНА ВАЛВУЛА (AORTIC VALVE - SPARING OPERATION SEC. DAVID) КАЈ МЛАДИ ПАЦИЕНТИ СО АКУТНА СТЕНФОРД ТИП А АОРТНА ДИСЕКЦИЈА (ЕДНОГОДИШНО ИСКУСТВО НА УНИВЕРЗИТЕТСКАТА КЛИНИКА ЗА ДРЖАВНА КАРДИОХИРУРГИЈА)

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Abstract

Introduction. The objective was to report our experience with David procedure (Valve-sparing aortic root replacement) in young patients population diagnosed with Stanford type A acute aortic dissection.
Methods. From March 2017 to April 2018, 3 patients (men, mean age 39.5 years) with acute type A dissecttion, received Valve-sparing aortic root replacement under hypothermic circulatory arrest and selective antegrade cerebral perfusion.
Results. Cardiopulmonary bypass time was 269±17 minutes, and the time of selective antegrade cerebral perfusion was 30.5±9 minutes. The in-hospital mortality was 0 %. Mean intensive care unit length of stay was 2-4 days. No permanent neurologic dysfunction and paraplegia were observed, only one pacient was diagnosed with trancient neurologic deficit tip 2. In the first 72 hours the mean drainage was up to 1400 ml± 120 ml sero-hemorrhagic fluid.
Mean hospital stay was 12.3±4.1 days. At discharge, a properly functioning reconstructed valve with aortic regurgitation grade I or less was documented echocardiographically in all patients.
Conclusions. David procedure (Valve-sparing aortic root replacement) in young patients population is safe and effective in patients with acute type A dissection and provides good quality of life avoiding potential complications of implanted prostetic valves and consecutive use of anticoagulants.

Keywords: surgery, thoracic aorta, dissection, Stanford type A, aortic valve, young patients

Апстракт

Целта на овој труд е да се сподели нашето искуство со операцијата по Давид (замена на коренот на аортата со зачувување на нативната аортна валвула) кај млади пациенти со дијагностицирана Стенфорд тип А акутна дисекција на аортата.
Методи. Во периодот од март 2017 до април 2018, тројца пациенти (мажи, на средна возраст 39,5 години), со акутна,тип А дисекција на аортата, добија замена на коренот на аортата со зачувана аортна валвула во хипотермичен циркулаторен арест со селективна атеградна церебрална перфузија.
Резултати. Времето на кардиопулмонален бајпас беше 269±17 минути, а времето на селективна антеградна церебрална перфузија 30.5±9 минути. Морталитетот, во тек на болничкиот престој беше 0%. Средниот престој во единицата за интензивна нега беше два до четири дена. Не беше воочена никаква трајна невролошка дисфункција или параплегија, само еден пациент беше дијагностициран со транзиторен невролошки дефицит тип 2. Во првите 72 часа, средната дренажа беше 1400 ml±120 ml серохеморагична содржина.
Средниот болнички престој беше 12.3±4.1 дена. При отпуст, ехокардиографски беше документирана уредна функција на реконструираната валвула со регургитација од I степен или помалку.
Заклучоци. Операцијата по Давид (замена на коренот на аортата со зачувана аортна валвула) кај млади пациенти е безбедна и ефективна метода кај пациенти со акутна дисекција, тип А и овозможува добар квалитет на живот, избегнувајќи ги потенцијалните компликации од имплантацијата на механичка валвула и употребата на антикоагулантна терапија.

Клучни зборови: хирургија, торакална аорта, дисекција, Стенфорд тип А, аортна валвула, млади

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пациенти

Introduction

Aortic dissection is one of the most common diagnosed patologies of the aorta, caracterized with extremely high mortality, and with the world prevalence of 0,5 to 3 people on every 100 000 population, per year [1]. 50% of the patients diagnosed with acute dissection of the aorta die in the first 48 hours when they are not operated. For a long period of time, standard operation for treatment of Stanford Type A aortic dissection that involves the aortic rooth, followed with aortic regurgitation is Bentall surgery (Operation sec. Bentall), with wich complete excision and substitution of the aortic rooth together with the aortic valve is made with composite graft with implemented mechanical valve [1,3]. In younger patients, in order to avoid the negative consequences of application of a mechanical valve, and the need for the patient to use anticoagulant therapy for life, in cases when a native aortic valve can be reconstructed, a surgery of preservation of the native valve by re-implantation in the suitable graft (Op. sec. David) is made, an operation that in the long run provides an excellent survival rate and avoids multiple cardiovascular events as a consequence of implanting a prosthetic mechanical valve and lifelong need for receiving anticoagulant therapy [4].

Matherial and methods

In the period from March 2017 till April 2018 at the Clinic for State Cardiosurgery three patients aged 35 to 42 years were treated with acute Stanford type A dissection of ascending aorta and consecutive aortic insufficiency. Aortic root reconstruction technique with was used, with preservation and reimplantation of the native aortic valve in the tubular graft. (aortic valve- sparing operation sec. David) [2]. All patients were admitted and operated as emergency cases with strong haemodynamic instability, and from preoperative trials TTE was performed on which the cardiac fraction was preserved without myocardial kinetics disorder, with a certain degree of aortic insufficiency (from medium to severe) and without verified coronary artery disease (coronarography). In CT, all were verified for type A dissection of ascending aorta. Based on the findings above (dilatation of the aortic ring with expressed insufficiency of the aortic valve and pathologically altered wall of the ascending aorta), indication for performing this type of surgery was set.

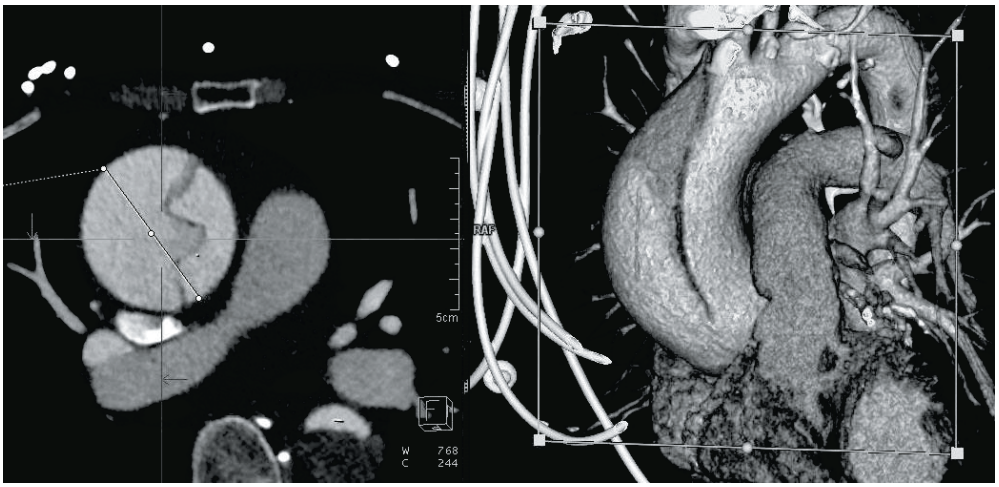

Fig. 1. CT angiography showing the Stanford Type A dissection of the aorta

Surgical procedure

The surgery was performed through medial sternotomy. In two patients, peripheral arterial cannulation was performed by applying an arterial cannula over 8 mm dacrophic grafts sutured to the axillary artery, while in one of them right femoral artery was cannalized due to the absence of pulsations on the right arm, and central venous cannulation in the right atrium with two-stage venous cannulas was made. A vent was placed in the upper right pulmonary vein and a cardio-pulmonary bypass was established, after which patients began to cool to 18^{o}C. Myocardial protection was achieved by the application of anterograde crystalloid cardioplegia. During this cooling period, the supra-aorthal branches were verified and isolated (t.brachiocephalicus, a.carotis comm sin., a.subclavia sin.), as well as identification, isolation and preparation of coronary blood vessels for creating appropriate buttons on them (Carrel patch method). Aortotomy and verification of the initial site of the dissection was performed, wich in two patients was above the level of the ostium of the right coronary artery, and in one of the patients was on the aortic back

wall at the height of the sinotubular aortic joint. The inspection of the aortic valves showed that there are no structural changes in the aortic valves, with good coaptation of the cuspses and no abnormalities.
By attaining the appropriate temperature (18°C), the cardiopulmonary bypass was interrupted and in cardiocirculatory arrest, with partial anterogradal cerebral perfusion of both patients who had cannulas in the axillary arteries and total arrest in the patient with cannula in the femoral artery, distal anastomoses were created with dacron tubular graft 28mm, with pre-prepared lateral grafts for transferring the arterial cannula and establishing a central cardiorespiratory bypass. In one patient replacement of the half of the aortic arch was made, and in the other two only ascending part of the aorta was replaced. In all three patients the duration of the cardiocirculatory arrest was 25-35 minutes with no changes at the level of cerebral perfusion, followed by appropriate monitoring.
After the creation of the distal anastomoses, the patient's heating was started, the aortic clamp was transferred to the proximal part of the graft and the reconstruction of the aortic root began. After the inspection and verification of the aortic valves competences, without appropriate structural disorders, a suspension of the commissures was initiated, and then excising of the aortic wall at a height of 5 to 7 mm from the aortic ring. Circumferently in the length of the entire aorta, 12-14 polyester 2-0 sutures with pleget were placed inner inside out at the height of the basal ring of the aortic valve. The same sutures were lined from inside

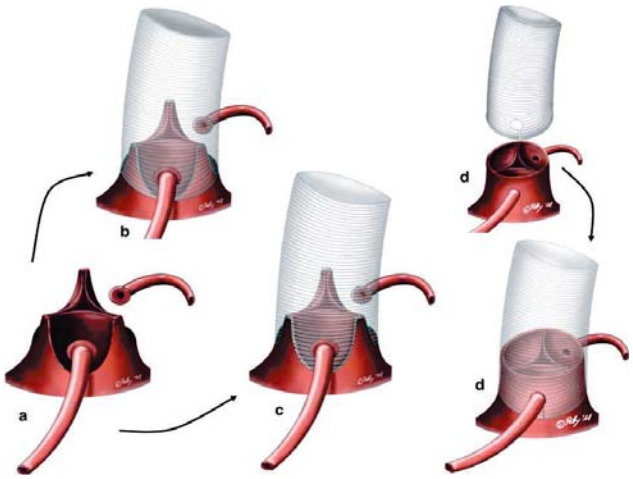

Fig. 2. Reimplantation of the coronary arteries in the tubular Dacron graft

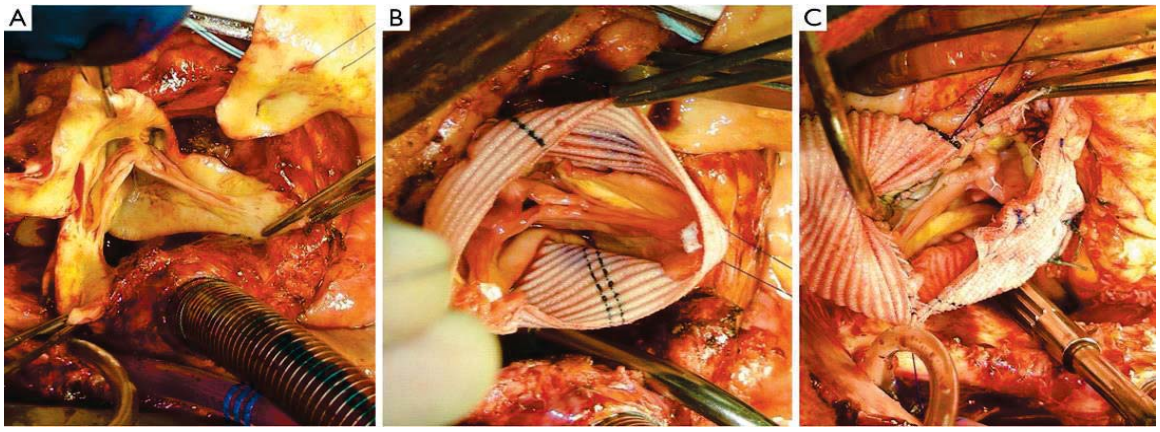

Fig. 3. David Procedure (Valve saving aortic root replacement)

outward to 30 mm dacon graft and the whole aortic ring was incorporated in the graft itself, and the southerers were tied. The commissures were fixed to the appropriate graft height using three 4-0 polypropylene sutures. Using the continuous suture of the three polypropylene joints, the aortic valve itself was re-implanted on the graft. A physiological saline test was performed to verify the competence of the valve after its graft reimplantation. The two coronary arteries were implanted at the corresponding projection sites of the left and right coronary sinus using continuous 4-0 polypropylene sutures. In the end, a primary anastomosis between the two grafts and the deaeration of the heart was made [1,6].

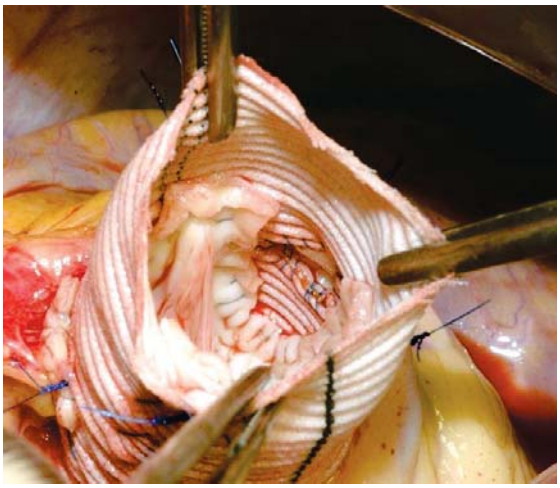

Fig. 4. David procedure(after reimplantation of coronary buttons)

Results

The perioperative competence of the aortic valve in the three cases was confirmed by transoesophageal echocardiography, in two cases there was only trivial aortic regurgitation, and in one of the cases it was not at all. The time spent on an extracorporeal circulation machine was 180 to 350 minutes, while the time of the myocardial ischaemia was from 100 to 150 minutes. The patients were transferred to intensive care with minimal support of inotropic and vasoactive drugs. All were extubated 24-48 hours after surgery without evident neurological deviation, except for one in which a type 2 neurological deficit was verified. On average, patients in the first 72 hours drained from 1200-1600 sero-haemorrhagic contents. The early postoperative course was normal, with normal cardiorespiratory rehabilitation. All patients left the clinic 9-14 days after the surgery. All of them were prescribed appropriate therapy for regulation of arterial hypertension and risk factors reduction. The post-surgical echocardiographic examinations showed that all had a well-balanced and preserved cardiac function with normal contractility without adequate kinetic outbreaks and competent aortic valves without any signs of insufficiency, except for one who had only a trivial trail of regurgitation.

Discussion and conclusion

The advantage of surgery for reconstruction and preservation of the native aortic valve (Op.sec David) in relation to the complete replacement of the aorta with a composite graft (Op. Sec. Bentall) in young patients is the fact that with this operation an excellent survival result is achieved and there is a reduced risk of complications as a result of the absence of a prosthetic valve (a faster structural degeneration of the bioproteases in a particular young adult population or the need for the application of anticoagulant therapy and the conescutive consequences of it such as thrombus-embolic or haemorrhagic incidents when mechanical valve is applyed) [5]. The past experience of monitoring these patients gives us the knowledge that they lead a completely normal, active and quality lifestyle without the appropriate constraints and possible complications.According to our so far modest experience with this acute type of pathology in young patients, whenever possible it is advisable to obtain this way of treatment by preserving the native aortic valve [6].

Conflict of interest statement. None declared.

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ММП

Original article

THE EVALUATION OF SOME MARKERS OF PROXIMAL RENAL TUBULES DAMAGE IN PATIENT WITH PSORIATIC ARTHRITIS

ЕВАЛУАЦИЈА НА НЕКОИ МАРКЕРИ ОД ПРОКСИМАЛНИТЕ РЕНАЛНИ ТУБУЛИ КАЈ ПАЦИЕНТИ СО ПСОРИЈАТИЧЕН АРТРИТ

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Abstract

Introduction. The aim of the study was to compare diagnostic values of alanine-aminopeptidase (microsomale AAP), γ-glutamyltransferase (γ–GT, β2-microglobuline (β2-M), C-reactive protein (CRP) in early diagnosis in previously untreated psoriatic arthritis (Psa). In addition, we determined the effect of untreated-psoriatic arthritis on tubular function, sensitivity of the brush border region as well as the diagnostic value of enzymes originating from proximal renal tubules.
Methods. From the standard methods of the International Federation for Clinical Chemistry (IFCC) we used the kinetic method for determination of alanine – aminopeptidase (microsomal AAP), γ-glutamyltransferase (γ–GT) and MEIA (Microparticles Enzyme Immunoassay (Abbot $A_x$sym system) for determination of β2-microglobulin in urine. We examined samples (serum and urine) from 70 participants (35 Psa untreated, 35 healthy control group). RF and CRP weredetermined with latex agglutination test in the same participants.
Results. From 35 examined patients with Psa, 12 pts showed presence of AAP enzymuria (test sensitivity was 34.28%), 8 pts showed presence of γ–GT (test sensitivity was 22.85%), while the presence of β2-microglobulin in urine was low (test sensitivity 0%).
Conclusion. AAP has better sensitivity than γ–GT and β2-microglobulin in the detection of asymptomatic renal endothelial changes in untreated Psa.

Keywords: alanine-aminopeptidase, γ-glutamyltransferase, β2-microglobulin, psoriatic arthritis

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Апстракт

Вовед. Да се споредат дијагностичките вредности на аланин аминопептидаза (микрозомална ААП), γ-глутамил трансфераза (γ-ГТ), β2 микроглобулин (β2-М), Ц-Реактивниот протеин (ЦРП) во раната дијагноза, кај нетретиран псоријатичен артритис (ПсА).
Цели. Да се одреди ефектот на нелекуваниот просијатичен артритис на тубуларна функција, осетливоста на Brush Border регијата, како и дијагностичката вредност на ензимите со потекло од проксималната ренална тубула.
Методи. Употребувајки ги стандардизираните методи од интернационалната федерација за клиничка хемија (IFCC), употребена е кинетичка метода за одредување на Аланин аминопептидаза (ААП), γ-глутамилтрансфераза (γ-ГТ), како и MEIA (Microparticle Enzyme Immunoassay) (Abbot $A_x$sym system) за одредување на β–2 микроглобулин во урината, испитани се примероци (серуми и урини) на 70 партиципанти, (35 ПсА не третирани, 35 Контролна здрава група). РФи ЦРП е одреден со тест за аглутинација (Латекс тест) кај истите партиципанти.
Резултати. Од вкупно испитаните 35 пациенти со ПсА, 12 пациенти покажаа присуство на ААП ензимурија, (сензитивност на тестот 34.28%), 8 пациенти присуство на γ-ГТ, (сензитивност на тестот 22.85%), додека застапеноста на β-2 микроглобулин во урина беше во низок процент (сензитивност на тестот 0%).
Заклучок. ААП има повисока сензитивност од γ-ГТ и β2-Микроглобулин во детекција на асимптоматски бубрежни ендотелијални промени кај нетретиран ПсА.

Клучни зборови: аланин аминопептидаза, (ААП); γ-глутамил трансфераза (γ-ГТ), β2 микроглобулин (β2-М); псоријатичен артритис

Introduction

Brush borderregion (brush, layer, striated)is composed of microvilli covered with simple cubic and cylindricalepithelium, found in different location of thebody. Diameter of the microvilli is 100 nm, while their length varies from 100 nm to 200 nm. Because microvilli are so small and dense in the brush border epithelium, they could be seen only with electronic microscope. With light microscope they could be usually seen collectively as 'fuzzy fringe' (feathered, fibrillary, edgy, borderline), as a partof the surfice of the epithelium. The appearance of the 'fuzzy fringe' determines the name brush border, because this structure resembles the painter brush.

Brush epithelial cells are found in two main locations in the human body.

1. In intestinum: it is the place where absorption takes place. Brush epithelium in the intestinal cover layer is the place of terminal carbochydrate digestion. These enzymes are located close to the transpoters, which enable absorption of the digested food.
2. In the kidneys: where the brush epithelium is useful to make difference between proximal tubules (that posses brush epithelim) and distal tubules (that do not posses).

Microvilli have the characteristics of PH parturition. It is the tendency of the acid matters to accumulate in the alkaline fluid compartments, while alkaline matters in acid compartments. So, acid drugs are secreted in great quantities when urine is alkaline, and vice versa, alkaline drugs are secreted in great quantities when urine is acid.

The aim of this study wasto determine the effect of untreated psoriatic arthritis on tubular function and sensitivity of the brush border of the proximal tubules. AAP, γ–GT, β–2M are used as indicators for proximal tubular damage.

Renal markers for evaluation of the renal function

Several classes of measurable proteins in urine are used for evaluation of the renal dysfunction.

1. Enzymes with high molecularweight, that are not usually filtered in the glomerulus, originating mainly from the proximal tubules (microsomal AAP, NAG).
2. Intermediate proteins that are usually filtered in the glomerulus in small qantities and are reabsorbed in the tubules in great part (albumin, transferin).
3. Proteins with low molecular weight that are usually filtered in the glomerulus and are reabsorbed in the tubules (β2-microglobulin) [1-6].

Alanine-aminopeptidase (AAP) (aryl amide amino acid, aminopeptidase, α-amino-acyl-peptide-hydrolase (microsomal) AAP, ES 3.4.11.2, previously 3.4.1.2) is a hydrolytic derivative of peptides, amides and p-nitroanilide.

AAP is found in numerous tissues, mostly in the kidney, intestine, lungs and liver. AAP in different tissues has different electrophoretic conductivity. This enzyme has at least five different isoenzymes that could be separated from each other with electrophoresis, ion-changing chromatography or immunologically. In normal serum only one isoenzymeis found, while in hepatobilliar or pancreatic diseases additional fractionsare found. The enzyme is also found in urine.

γ–GT plays an important role in the glutathione metabolism. High enzyme concentrations are found in kidneys (proximal tubule), pancreas (acinarcells), prostate and liver. γ–GT is mostly located on the external part of the plasma membrane [7]. γ–GT isoenzymes in serum are a result of different post-translational modifications as for example complex formations with lipoproteins or modifications of the carbohydrate part of the γ–GT molecule [8]. The possibility of the presence of isoenzymes in different tissues (liver, pancreas, kidney, duodenum) is due to the differences in carbohydrate part of the γ–GT molecule. Although the peptide part of the enzyme molecule is the same no matter the tissue of origin, these isoenzymes differ in kinetic, electrophoretic and immunological features.

The tubular function could be evaluated with mesurements of the excreted low molecular proteins in urine. β2-microglobulin (β2-M) is used as an indicator of the tubular dysfunctions in glomerulonephritis [9] and is often used as a sensitive marker for evaluation of the renal function [10-12]. β2-M is a small polypeptide with low molecular weight (11.815 daltons). β2-M contains light chains of the main histocompatibility antigen (HLA). It influences production of the RF (IgM class). In healthyindividuals, β2-microglobulin is found both in serum and urine. 95% of the free β2-M is ultrafiltrated through renal glomerules and almost completely is reabsorbed in 99.9% with proximal tubular endocytosis and finally is catabolized in amino acids. Due to this mechanism, in urine are usually detected in traces. Imparement in the glomerular filtration leads to increase in serum β2-M, while tubular damage leads to rise in urine β2-M.

Serum concentration of β2-M depends on the glomerular filtration rate (GFR) and shows a significant negative correlation with inulin clearence. These findings show that with determination of the serum level of β2-M one could get an index for dysfunction of the renal gromerulus.

β2-M is used for evaluation of the GFR and renal tubular function, especially for tubulotoxic effect of different substances, such as heavy metals (cadmium and lead) and as a screening test for early detection of Balkan nephritis in regions where it is edemic. In urine β2-M is unstable if Ph<6, and it is recommened to alkalize the urine with bicarbonates before it is tested. β2-M is considered the earliest protein of tubular proteinuria.

Material and methods

Diagnosis of the patients included in the study was based upon revised diagnostic criteria for Classification of Psoriatic Arthritis from 2005, proposed by the American Association for Rheumatic arthritis (ARA) [13]. Clinical evaluation for disease activity and disease diagnosis wasbased on diagnostic criteria of Moll-Wright for Classification of Psoriatic Arthritis [14]. Patients weredermatologically tested, including examination of the psoriatic changes of nails, psoriatic areas and disease activity index (PASI) as well as evaluation of the peripheral and axial joints [15]. Oligoarthritis was taken in consideration when <5 joints were involved and polyarthritis when ≥5 joints wereinvolved. Symmetric arthritis wasconsidered when bilateral joints wereinvolved >50%.

The study included 35 patients (8 women, 27 men) suffering from Psa and 35 patients (23 women, 13 men) as a healthy control group. Median age was 50.18 years (SD±8.09) (35-65 years) in Psa group, while 48.2 years (SD±10.19) (29-65 years) in healthy control group. Median disease duration was 30.17 (SD±40.13) in the interval of 1-60 months. None of the patients included in the study had previous or current history of renal disese. None of them previously used NSAIDs. The others negated use of other drugs before entering the study, especially drugs from the baseline therapy such as methotrexate, antibiotics or diuretics. Samples were collected in the period of two years.

Inclusion criteria: patients suffering from psoriatic arthritis, aged 18-65 years, newly diagnosed and previously untreated.

Exclusion criteria: all patients with diseases or conditions that can directly or indirectly influence the results, such as:

1. Patients <18 and >65 years old.
2. Patients with previous history of diseases of the spleen, thyroid gland, liver damages, renal, hematological, cardiovascular, neurological, lung, autoimmune impairments.
3. Patients with diabetes mellitus, acute infections, AIDS, febrile conditions, malignant diseases.
4. Patients previously treated with antibiotics and salicylates < 6 months before entering the study.
5. Patients with hypertension, uric arthritis, urinary infections, SLE, Sjögren disease, mixed connective tissue disese, vasculitis.
6. Patients treated with antihypertensive, antidiabetic and cardiological drugs.
7. Patrients with previous history for blood transfusion and patients with incresed body mass index.
8. Patients with hypersensitivity on drugs or some of their components.
9. Patients with history for using drugs from the baseline.
10. Patients with acute or chronic renal failure.
11. Patients who in 0-point had glycemia, elevated serum urea and creatinine; hypertension and impared hematological and enzyme status.

All patients participated in the study voluntarily, so the ethic criteria for inclusion in the study werefulfilled.

Laboratory evaluation

For clinical evaluation of the disease one has to examine the following parameters: complete blood count (CBC), reactants of the acute phase such as C-reactive protein (CRP), rheumatoid factor (RF), erythroid sedimentation rate (ESR), aspartate-aminotransferase (AST), alanine -aminotransferase (ALT), creatinine kinase (CK), lactate-dehydrogenase (LDH), serum urea and serum creatinine. The urine samples were taken not only for routine analyses, but also to determine the levels of AAP, γ–GT, β–2M. Due to the urine instability of β–2M <6pH, alkalizination of the urine before testingis recommended.

Serum creatinine wasdetermined according to the Jaffe method. Reference values are: serum creatinine 45-109 μmol/L, urine creatinine 7-17μmol/L.

CRP wasdetermined with the agglutination test (Latex CRP test) (BioSystems S.A. Reagens&Instruments Costa Brava 30,Barcelona, Spain). Reference values are: serum CRP<6mg/L.

RF wasdetermined with the agglutination test (Latex CRP test) (BioSystems S.A. Reagens& Instruments Costa Brava 30, Barcelona, Spain). Reference values are: serum RF < 8 IU/ml.

ESR was determined with theWestergren method. Normal values are: for men 7-8mm, for women 11-16mm.

GFR (creatinine clearance) was estimated by the Cockcroft-Gault Equation.

Determination of the activity of alanine amino – peptidase (AAP): kinetic method.

Referencevalues: urine AAP 0.25-0.75 U/mmol creatinine.

Determination of the activity of γ-glutamyltransferase (γ-GT): IFCC method (17-20).

Reference values: γ-GT (urine) 0.84-1.80 U/mmol creatinine.

Determination of β2-microglobulin (β2-M) concentrationin urine was done according to MEIA (Microparticles Enzyme Immunoassay) method (Abbot $a_x$sym system).

Reference values: β2-microglobulin (urine)-0.02-0.19 mg/L.

Statistical analysis

Testing the significance of differences between two arithmetical means, i.e. proportions wasused to compare certain mean numerical parameters between groups, as well as Willcoxon-matched test for independent samples. Sensitivity and predictivity for positive and negative test of the examined markers weredetermined with the test for sensitivity and specificity. P-value between 0.05 and 0.1 wasconsidered statistically significant. Analysis of the data wasperformed with the statistical package Statistica 7.0.

Results

From the 35 examined patients with Psa, 12 pts (34.28%) showed presence of APP enzymuria, 8 pts (22.85%) presence of γ-GT, while a low percentage (0%) presence of β2-microglobulin in urine. RF was present in

0 pts (0%). AAP, γ-GT β2-microglobulin and other laboratory variables in Psa and heathy control group are showen in Table 1.

Table 1. AAP, γ-GT β2-microglobulin and other laboratory variables in Psa and heathy control group

	Psa untreated group N^{O} 35 Value Positive/negative	**Heathy control group N^{O} 35 Value Positive/negative**
AAP + > 0.75 U/mmol/creatinine)	12/23	1/34
γ-GT + >1.80 (U/mmol/creatinine)	8/27	0/35
β2 M +> 0.19 (mg/L)	0/35	0/35
RF +30 ≥ IU/ml	0/35	0/35
CRP +12 ≥ mg/L	13/22	1/34

Diagnostic value of alanine aminopeptidase (microsomal AAP) γ-glutamyl transferase (γ-GT), β2 microglobulin (β2M) in Psa

Diagnostic performance of AAP, γ-GT, β2M and other laboratory variables in Psa, are shown in Table 2.

AAP had better diagnostic performances than γ-GT and β2M taking in consideration sensitivity and specificity (sensitivity 34.28% *vs* 22.86% *vs* 0%) and almost equal

Table 2. Diagnostic performances of AAP, γ-GT,β2Mand other laboratory variables in Psa

	AAP Psa No 35	γ–GT**Psa No 35**	**β2M Psa No 35**	**RFPsa No 35**	**CRPPsa No 35**
Sensitivity %	34.28	22.86	0	0	37.14
Specificity %	75.56	100	100	100	97.14
Predictive value forpositive test%	52.17	100	0	0	92.86
Predictive value for negative test%	59.65	56.45	50	50	60.71
Accuracy %	65.71	61.42	50	50	67.14

specificity (specificity 75.6% *vs* 100 % *vs* 100%) in detection of renal impairment in untreated Psa.

1. There was astatistical relation using the Wilcoxon -matched test between AAP in Psa and healty control group for p<0.05 (p=0.01). In the Psa group there was astatistical relation between AAP and γ-GT for p< 0.05 (p=0.00); AAP and β2M (p=0.00).
2. There was astatistical relation using the Wilcoxon-matched test between γ-GTin Psa and healty control group for p<0.05 (p=0.40); β2Min Psa and healthy control group for p<0.05 (p=0.06).
3. There was astatistical relation using the Wilcoxon-matched test between AAP in Psa and age, disease duration (in months); PASI index, RF and CRP, serum creatinin, serum urea in the same group for p<0.05: AAP *vs* age p=0.00; AAP *vs* disease duration (in months) p=0.00; AAP *vs* PASI p=0.00; AAP *vs* RF p=0.02; AAP *vs* CRP p=0.041; AAP *vs* ESR p=0.00; AAP *vs* serum creatinin p= 0.00; AAP *vs* serum urea p=0.00.
4. There was astatistical relation using the Wilcoxon-matched test between γ-GT in Psa and age, disease duration (in months), PASI index, RF, CRP, ESR, serum creatinin and serum urea in the same group for p< 0.05: (γ-GT *vs* age p=0.00; γ-GT *vs* disease duration (in months) p=0.00; γ-GT *vs* PASI index p=0.00; γ-GT *vs* RF p=0.02; γ-GT *vs* CRP p=0.042; γ-GT *vs* ESR p=0.00; γ-GT *vs* serum creatinin p=0.00; γ-GT serum urea p=0.00.
5. There was astatistical relation using the Wilcoxon-matched test between β2M in Psa and age, disease duration (in months); PASI index, RF and CRP, ESR, serum creatinin and serum urea in the same group for p<0.05: β2M*vs* age p=0.00; β2M*vs* disease duration (in months) p=0.00; β2M*vs* PASI index p=0.00; β2M*vs* RF p=0.02; β2M *vs* CRP p=0.044; β2M*vs* ESR p=0.00; β2M*vs* serum creatinine p=0.00; β2M*vs* serum urea p=0.00.

Discussion

In the standard medical rheumatology the biggest emphasize is put on rheumatoid arthritis as the most exposed disease, neglecting somehow the other diseases especially seronegative arthropathies, probably due to their lesser extent.

The explanation for the renal tubular enzymes is increased exfoliative turnover of the epithelial cells in Psa, which is adequately present also in proximal tubular epithelial cells.

Of all enzymes, the greatest emphasize is put on NAG as a dominant lysosomal tubular enzyme. Traditional treatment of Psa and RA includes non-steroid anti-inflammatory drugs (NSAIDs), disease modification drugs (DMARDs), steroids and immunosuppressive cytotoxic drugs. Methotrexate in low dose regime is the most frequently prescribed drug from DMARDs, while Ketoprofen (Niflam^{r}, Ketonal^{r}) and Paracetamol from NSAIDs.

Enzymes in urine could originate from plasma, glands from the urogenital tract, epithelial cells of the urinary tract, white blood cells, erythrocytes and kidneys. There are 40 different enzymes in the urine belonging to different groups: oxydo-reductases, transferases, hydrolases, lyases, while isomerases and ligases are not found in urine. Presence of so many enzymes in urine indicates the dominant role of the kidneys in their excretion.

Brush border morphology with the brush epithelium increases the cell surface, especially useful for absorption. The cells that absorb substances have great necessity of contact surface with substances in order to be efficaceous. The luminal surface of the epithelial cells from this segment of the nephron is covered with densely packed microvilli that form border, whish can be seen under light microscope. The microvilli largely increase the luminal surface of the cells which in great measure facilitate their resorptive function.

In some pathological conditions, incresed quantities of β2-M are excreted in urine. It happens when β2-M serum concentration exceeds the renal threshold. The serum level of β2-M depends on the ratio of synthesis and release in serum pool and its relation with clearence. Such conditions are notified in patients with inflammatory diseases (rheunatoid arthritis, SLE, Sy. Sjögren, Crohn disease, cancer, liver damage). β2-M concentration in urine could be increased also when reabsorption is decreased due to renal proximal tubular damage. Proximal tubular dysfunction results inelevated concentrations of urine β2-M, allowing to make distinction between proximal tubular from glomerular renal impairment.

The urine enzyme activity in urine is usually low and increases in renal tubular cell damage. Urinary enzymes, especially NAG, AAP and AF, are very sensitive indicators of renal parenchymal damage in comparison with functional measurements such as glomerular filtration rate and creatinine clearance. Relatively low sensitivity to GFR could be explained with large functional reserves of the kidneys and their great compensatory ability.

AAP sensitivity wasgreater in comparison with γ-GT and β2M (34.28% *vs* 22.85% *vs* 0%), with approximately equal specificity (75.6% *vs* 100 % *vs* 100%).

Statistical relation of disease duration (in months) and AAP and γ-GT and β2M enzymuria (p=0.00) points out that untreated Psa damages the renal tissue as one of the visceral manifestations of the disease [21-29].

Conclusion

AAP has greater sensitivity than γ-GT and β2M in asymptomatic renal lesions in untreated Psa. AAP and γ-GT could be used in everyday clinical practice in diagnosis of early, asymptomatic renal lesions.

Conflict of interest statement. None declared.

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Case report

TREATMENT DILEMMAS AND UNMET NEED IN A PATIENT WITH ACTIVE RELAPSING MULTIPLE SCLEROSIS

НЕЗАДОВОЛЕНИ МЕДИЦИНСКИ ПОТРЕБИ И ТЕРАПИСКИ ДИЛЕМИ КАЈ ПАЦИЕНТ СО АКТИВНА РЕЛАПСНА МУЛТИПЛА СКЛЕРОЗА

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Abstract

Introduction. Multiple sclerosis (MS) is a chronic immune-mediated inflammatory demyelinating disease of the CNS that leads to neurodegeneration. While worldwide more than 2.5 million people, in R. Macedonia more than 1.200 are affected by MS and every day is a continuous fight with the ongoing challenges. Our aim is to describe the patient's treatment dilemmas and unmet medical needs, despite available therapeutic options.
Case report. 25-year-old female with many neurological symptoms and initial EDSS score 2.0 was investigated following the standard diagnostic procedures (neurological exam, evoked potentials, brain MRI). In accordance with the McDonald diagnostic criteria 2010 relapse-remitting multiple sclerosis was diagnosed. Treatment with interferon β-1a was initiated with primary aim to reduce relapse frequency. During the 7-month treatment, patient had an active disease presented with 4 relapses and EDSS increasing to 4.0. Despite the JCV antibody index value of 3.82 and potential high risk for developing PML, the patient was switched to natalizumab. Patient was relapse-free but MRI scans (5 and 18 months after natalizumab initiation) revealed an active disease with demyelinating lesions. After 2 years on natalizumab and willingness to become pregnant, many treatment dilemmas appeared on how to further continue to control the disease, prevent disability progression, sustain patient's wellbeing and quality of life.
Conclusion. Results from phase III clinical trials and real-life routine clinical practice from ocrelizumab, anti-CD20 antibody that targets B-cell, showed high-efficacy, good safety profile and more convenient drug administration in patients with MS.This gives us hope that ocrelizumab potentially may satisfy the unmet medical needs, solve thecurrent treatment dilemmas and decrease disease burden in patients with active relapsing multiple sclerosis.

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Keywords: multiple sclerosis, relapse-remitting multiple sclerosis, relapse, disability, treatment dilemmas

Апстракт

Вовед. Мултипла склероза (МС) претставува хронично имунолошки посредувано, инфламаторно и демиелинизирачко заболување на ЦНС кое води до невродегенерација. Во светот повеќе од 2,5 милиони лица, а во Р. Македонија повеќе од 1200 лица се афектирани од МС и секој ден водат битка со тековните предизвици наболеста. Целта е да ги прикажеме терапискитедилеми и незадоволените медицински потреби кај пациентите со МС и покрај достапност на терапевтски опции.
Приказ на случај. 25 годишна пациентка со мноштво невролошки симптоми и иницијален EDSS скор од 2.0 била испитувана следејќи ги стандардните дијагностички процедури (невролошки преглед, евоцирани потенцијали, MRI). Во согласност со McDonald 2010 критериумите била дијагностицирана релапсна-ремитентна мултипла склероза. Започнат третман со interferon β-1a со цел намалување на фреквенцијата на релапси. Во тек на 7 месечниот период на третман, пациентката имала активна болест со појава на 4 релапси и зголемување на EDSS на 4.0. И покрај вредноста на индекс на антитело JCVод 3.82 и потенцијален ризик за развој на прогресивна мултифокална леукоенцефалопатија бил започнат третман со natalizumab. Не се појавиле нови релапси, но MRI испитувањата (5 и 18 месеци после почетокот на третман со natalizumab) откриле присуство на активна болест со демиелинизирачки лезии. После 2 години на терапија со natalizumab и желба за забременување, голем број тераписки дилеми се јавуваат во смисол како ефикасно да ја продолжиме контролата на болеста, превенција на прогресија на инвалидноста, одржување на благосостојбата и квалитетот на живот на пациентот.

Заклучок. Резултатите од фаза III клиничките испитувања и од редовната рутинска пракса за ocrelizumab, anti-CD20 антитело насочено кон Б-клетките, покажале висока ефикасност, добар безбедносен профил и покомфорен начин на администрација на лекот кај пациентите со МС. Ова ни дава надеж дека лекот ocrelizumab потенцијално може да ги задоволи незадоволените медицински потреби, да ги реши актуелнитетерапискидилеми и да го намали товарот на болеста кај пациентите со активна релапсна мултипла склероза.

Клучни зборови: мултипла склероза, релапснаремитентна мултипла склероза, релапс, инвалидитет, терапискидилеми

Introduction

Multiple sclerosis (MS) is chronic immune-mediated inflammatory demyelinating disease of the central nervous system that leads to neurodegeneration. It's characterised by ongoing disease activity, with profound effects on patient independence and quality of life[1,2].MS is the most common cause of nontraumatic neurological disability [3] and average age of onset is between 20-40 years [4,5] and twice as common in women than men [4].Worldwide more than 2.5 million people are affected by MS [6] with striking latitudinal gradient in MS prevalence [7]. Republic of Macedonia is in area of medium risk with incidence 4/100.000 people, 60-80 newly diagnosed patients each year. More than 1.200 patientsare living and struggling with the challenges that are caused by MS in R. Macedonia [8]. Approximately 85% of patients have relapse-remitting multiple sclerosis (RRMS) [9], while 10-20% have primary progressive multiple sclerosis (PPMS) at disease onset [10-12]. The symptoms are variable and unpredictable in every patient [2, 13-15]. The most common symptoms are fatigue in 80% [8] and mobility impairment and muscle weakness in 90% of the patients [2]. There is no cure for MS and because the condition largely affects people in the most productive stages of their lives, the costs to individuals, families and society are significant.

Case presentation

A 25-year-old female presented to the neurology clinic in 2015 with symptoms suspicious for MS. She had numbness in her hands, difficulties in walking and fatigue. She also reported a need for urgent urination with preserved bladder control. Two months prior hospitalization she experienced weakness in her left limbs with reduced sensation; tremorin both hands; difficult control of her left leg while walking; and fatigue. The performed neurological examinations showed generalized amplification of reflexes in her legs, mild left hemiparesis, and paraesthesia in her hands. Expanded Disability Status Scale (EDSS) score was 2.0.

In her history, in 2014, she experiencednumbness in her fingers with a sense of imprecision in writing and performing on precise movements, but perceived as no need of examination and treatment.

Neurological examinations performed during hospitalization revealedhemi hyperaesthesia on left limbs; bilateral asymmetric left-hand pyramidal symptomatology; motor weakness on left limbs; bilateral ventricular dismetry on arms; and ataxia with positive Romberg to the left. She was admitted for further paraclinical investigations that showed: VEP (Visual Evoked Potential) right latency on the upper limit, left above the upper normal limit; BAEP (Brainstem Auditory Evoked Potential) bilaterally increased left low-grade II wave; SEP (Sensory Evoked Potential) prolonged latency left to the cortical response (Figures 1, 2 and 3). All performed laboratory testsprior diagnosis (blood count, C3C4 complement, anti-HIV, VZV, CMV, EBV, HSV, HBsAg, anti-toxoplasma, RF, AST, ANA HEp2 (IFA), anti-DNA, c-ANCA, anti-SSA, anti-SSB, ACA, LE cells) were in referent and/or normal ranges.

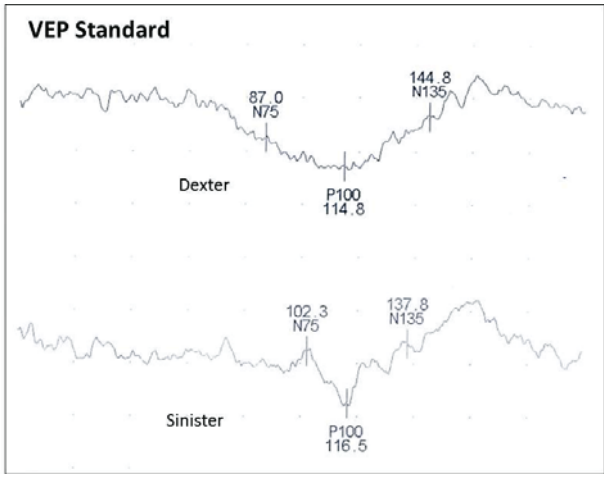

Fig. 1. Standard VEP (visual evoked potentials) prior diagnosis showed right latency on the upper limit, left above the upper normal limit

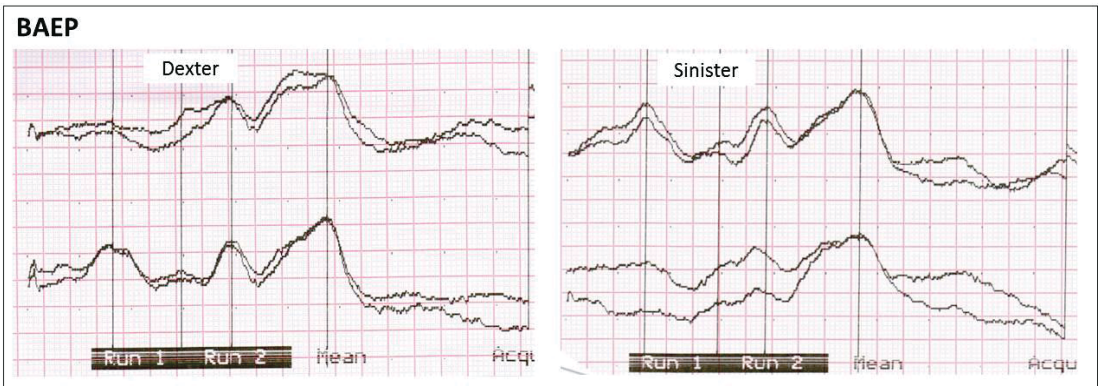

Fig. 2. BAEP (Brainstem Auditory Evoked Potential) prior diagnosis showed bilaterally increased left low-grade II wave

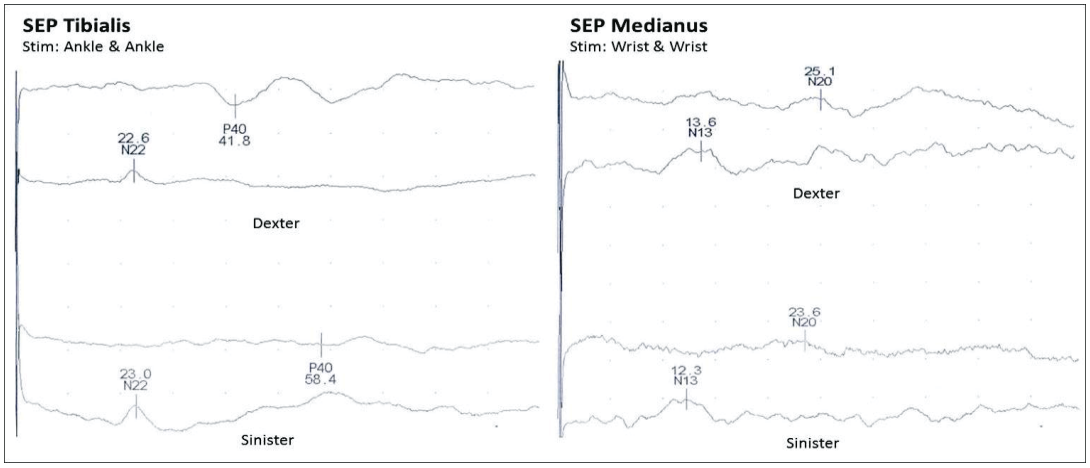

Fig. 3. SEP (sensory evoked potentials) Tibialis and Medianus prior diagnosis showedprolonged latency left to the cortical response

In very short period, her EDSS score increased to 3.5. Treatment with corticosteroids for 5 days in dosing of 1000 mg i.v./daily was initiated for revealing the symptoms. A brain MRI showed abnormalities, few demyelinating lesions in the periventricular, perpendicular to the lateral chambers (Figure 4). The MRI findings were consistent for demyelination. Lumbar puncture and oligoclonal bands examinations were not performed due clear diagnosis of MS. According to the McDonald diagnostic criteria 2010, relapse-remitting multiple sclerosis was diagnosed and treatment with disease modifying therapy(DMT), interferon β-1a 30 mcg i.m. once weekly, was initiated. The primary aim was to reduce the frequency of relapses.

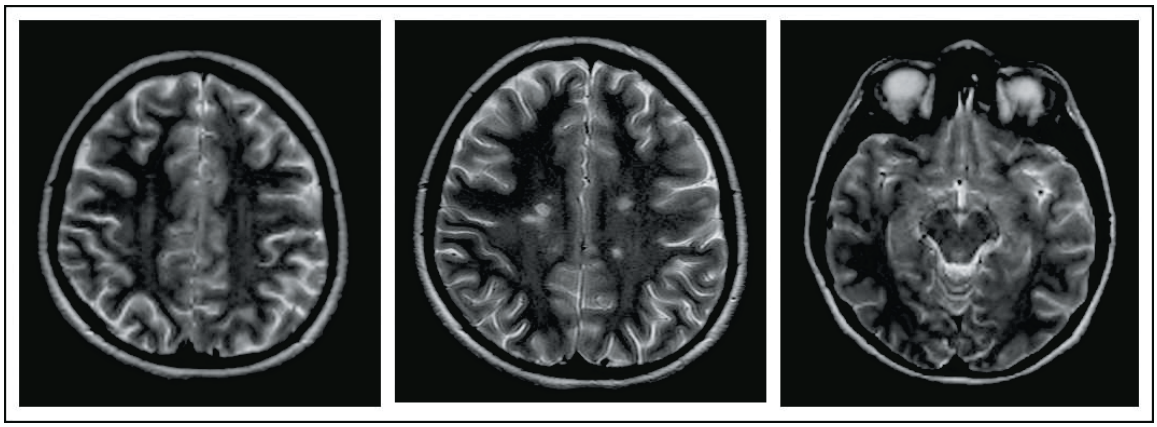

Fig. 4. Initial brain MRI scans showed abnormalities with few demyelinating lesions in the periventricular, perpendicular to the lateral chambers suspected for MS

Despite treatment with IFN β-1a during 7 months, her disease was active; she was hospitalized at the clinic due to 4 relapses (Figure 5*)*. She reported weakness in her limbs, need ofurgent urination, fatigue, and significant changes in the neurologic functions (ataxia, bilateral pyramidal symptomatology, hemiparesis and hemihypaesthesia).

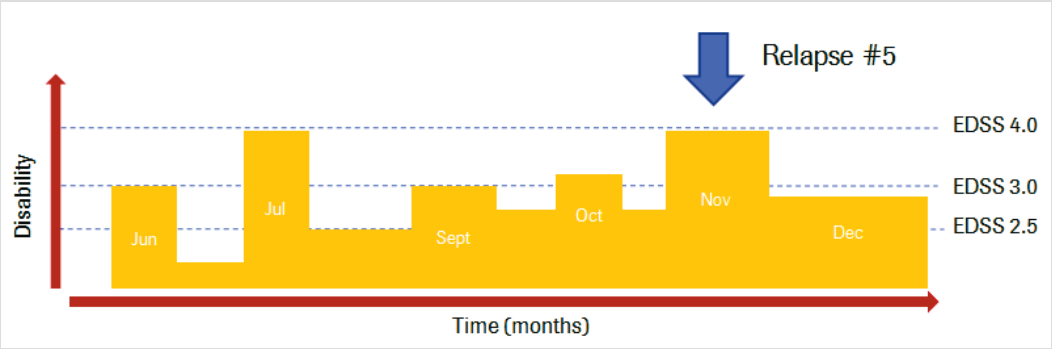

Fig. 5. EDSS score and occurrence of relapses in 7 months period while on treatment with IFN β-1a

Her EDSS score increased to 4.0 while brain and spinal cord MRI scansrevealed multiple demyelinating lesions in acute phase (Figure 6 and 7*)*. Relapses were treated with corticosteroids for 5 days in dosing of 1000 mg i.v./dailyand her symptoms settled down over the following month.

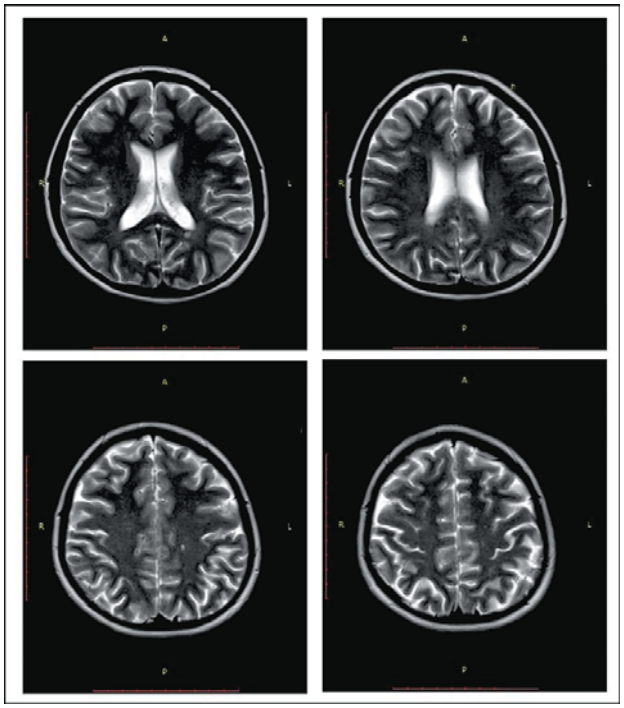

Fig. 6. Brain MRI scansshowed multiple demyelinating lesions in acute phase

Taking into consideration the high disease activity, more than 5 relapses and disability progression (EDSS from 2.0 to 4.0), decision to switch the treatment to more efficacious DMT was made. Despite the positive anti-JC virusantibody test (J Cvirus antibody index value 3.82) and potentialhighrisk of developing PML (progressive multifocal leukoencephalopathy), treatment

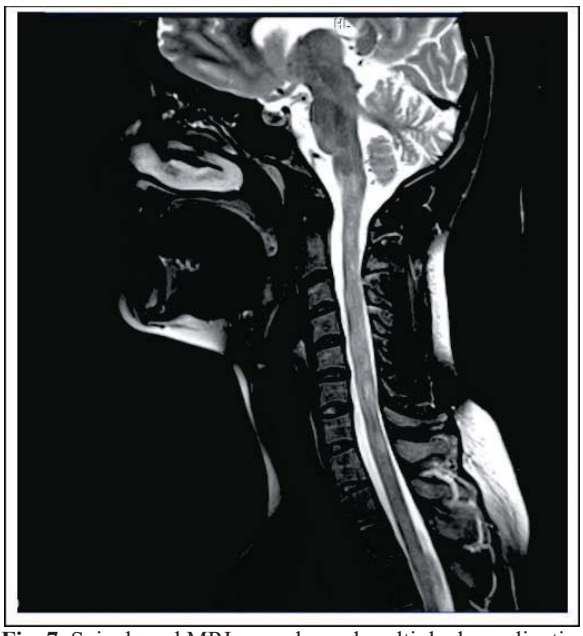

Fig. 7. Spinal cord MRI scan showed multiple demyelinating lesions in acute phase

with natalizumab 300 mg i.v. once monthly was initiated. While on treatment she remained relapse-free but her MRI scans, 5 and 18 months after initiation of natalizumab, revealed right ponto mesencephalic discrete peripheral signal amplification in favour of subacute lesion, discrete signal intensification in lesions at the height of the neck (Figure 8); and discrete ring-shaped signaling of plaque at the level of the corona radiate supraventricular to the right with a hypersignal and diffusion in addition to a subactive zone, accordingly. The patient is still on treatment with natalizumab, but now there are several treatment dilemmas thathave to be considered, in order to continue effectively controlling her disease, preventing disability progression and sustaining herwellbeing.

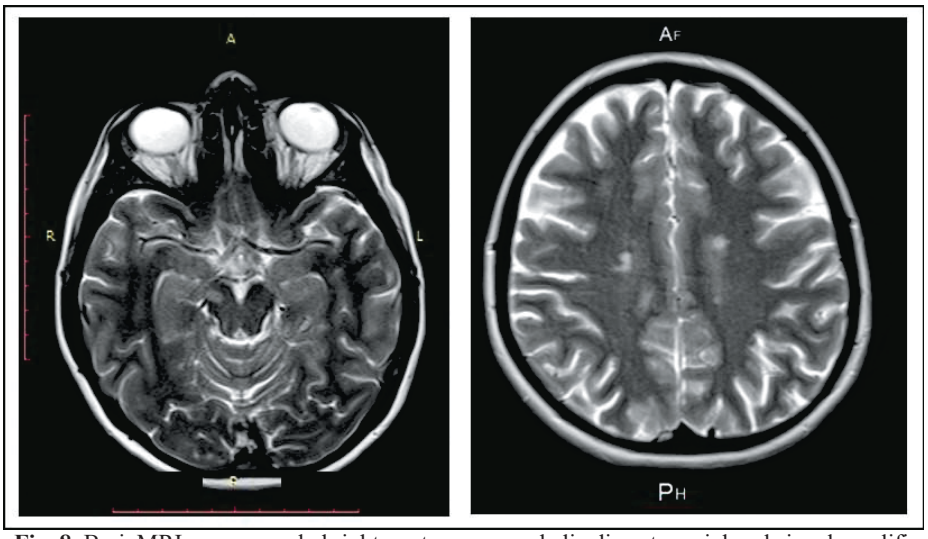

Fig. 8. BrainMRI scans revealed right ponto mesencephalic discrete peripheral signal amplification in favour of subacute lesion and discrete signal intensification in lesions at the height of the neck 18 months after initiation of treatment with natalizumab

The dilemmas are following:

- willingness to become pregnant in near future
- activity disease while on treatment
    - beside absence of clinical symptoms (relapse) the disease is active within the first 2 years of treatment initiation with natalizumab
- high risk of developing progressive multifocal leukoencephalopathy after 2 years on treatment with natalizumab in patient with high anti-JC virus antibody index [16].

Discussion

As large proportion of MS patients are women of reproductive age and as the knowledge on the effects of DMTs on the immune system is incomplete, pregnancy outcomes in patients exposed to DMTs are important to understand. Several publications became available years ago recommending treatment with interferon ß or glatiramer acetate (GA) as long as possible in pregnant women with active disease. A prospective cohort study from German MS and Pregnancy Registry showed that interferon ß is safe during the first trimester of pregnancy [17]. According to the modified European marketing authorization 2016 [18], GA is no longer contraindicated during pregnancy because pregnancies were not at higher risk for congenital abnormalities compared to what is expected in general population. GA can be used during pregnancy as bridging therapy or throughout pregnancy [19-21]. Monoclonal antibodies are classified as a pregnancy category C drug. Results of pregnancy outcomes are limited because of small number of pregnancies occurred, limiting the ability to make proper conclusions. Pregnancy outcomes, including information about child health up to 1 year after birth, have to be collected in ongoing clinical studies and post-marketing experience have to continue to be collected and assessed [22]. The current medical attitude on using monoclonal antibodies during pregnancy istaking them only if the potential benefit to mother overcomes the potential risk to the fetus. Final decision which medicines should be used during pregnancy has to be made interdisciplinary between neurologists, gynecologists, psychologists and the patient as well.

The aims of usinganeffective medication in MS patients with active disease areto control the disease, prevent disability progression, sustaining patient's wellbeing and improve quality of life.No evidence of disease activity (NEDA), also referred to as freedom from disease activity, is a new goal that is emerging in multiple sclerosis treatment because appearance of only one new MRI T2 lesion can increase a patient's risk of disability progression up to 15-fold [23]. Similarly, apublication of Tremlett *et al.* showed that achieving disease-free status may predict a long-term reduction in the accumulation of disability [24]. Natalizumab is a highly effective medication, but its use is generally limited to 2 years because of the increasing risk of PML (progressive multifocal leukoencephalopathy), a potentially fatal brain infection. This creates a difficult situation: it is typically started in people with high active disease. We have to be very careful when it's time to stop, because discontinuation of natalizumab treatment may trigger a severe rebound with marked clinical and radiological worsening [25] andanother medication may not be able to minimize the flare-up that commonly occurs after switching off natalizumab. The Observational Program (TOP) has examined this issue [26] and the data showed that most patients (58%) were switched to fingolimod, and about 10% switched either to dimethyl fumarate, interferon, or glatiramer acetate. After switching, there was an in-

creased risk of relapse. However, relapses were not as frequent as before the start of treatment (i.e. before natalizumab was started). People were less likely to show improvement in their disability after switching to another medicine, but 17% did show some improvements, suggesting that there are less effective options once it's time to stop natalizumab. However, caution will be needed to ensure that the patient stopping natalizumab doesn't already has a PML before he/she startswith anothermedication. Frequent MRIs would be needed while patient is taking natalizumab, after he/she has stopped natalizumab and before he/she has started with anothermedication, and while on it. TOP didn't include anyone switching from natalizumab to alemtuzumab or ocrelizumab-perhaps the most potent MS medications. The regulatory approval ofocrelizumab (anti-CD20 antibody) for treatment of RMS in more than 60 counties worldwide, was based on two identical phase III clinical studies in patients with relapsing forms of MS [27]. Clinical studies data indicated that ocrelizumab cut the relapse rates by 47%, reduced disability by 43%, and decreased inflammation by 95%, compared to the current standard treatment (IFN ß-1a) [28]. The marketing authorizationgave the opportunity to develop a real-life clinical experience with ocrelizumab outside of the frame of clinical studies whereby >50.000 patients have been treated in the post-marketing setting worldwide [29]. The experience of the previously mentioned routine clinical practice showed that switching from natalizumab to ocrelizumab is possible in patients with relapsing forms of MS, providing an efficient control of the disease with a more tolerable safety profile. The outcome of the treatment experience gained until now (>50.000 patients) [29] showed that targeting B-cells with ocrelizumab can be an evolutionary treatment strategy that might be a potential treatment approach in MS, an opportunity to decrease the patient's disease burden and meet the unmet medical needs:

- High-efficacious medicines to stop or possibly reverse disability progression [30-32];
- Safe and tolerable high-efficacious medicines that might improve the benefit/risk balance [33]; and
- More convenient drug delivery that might improve the patient treatment persistence and adherence [30].

Conclusion

Results from phase III clinical trials and real-life routine clinical practice from ocrelizumab, anti-CD20 antibody that targets B-cell, showed high-efficacy, good safety profile and more convenient drug administration in patients with MS. This gives us hope that ocrelizumab potentially may satisfy the unmet medical needs, solve the current treatment dilemmas and decrease disease burden in patients with active relapsing multiple sclerosis.

Conflict of interest statement. None declared.

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Case report

AN ADULT PATIENT WITH AORTIC COARCTATION REPAIR, A COMPLEX MEDICAL ENIGMA AND CHALLENGE: CASE REPORT

ВОЗРАСЕН ПАЦИЕНТ СО ОПЕРИРАНА АОРТНА КОАРКТАЦИЈА, КОМПЛЕКСНА МЕДИЦИНСКА ЕНИГМА И ПРЕДИЗВИК, ПРИКАЗ НА СЛУЧАЈ

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Abstract

Introduction. Aortic coarctation (CoA) is considered not only a circumscript narrowing of the aorta, but a part of a generalized vascular disease. Complications include early CAD, heart failure, CVI, Ao aneurism/ dissection and early death (in the III-IV decade).
Case report. A 42-year-old woman, who has undergone surgical correction of the coarctation at the age of 20 months, complains of fatigue, vertigo, instability, intermittent claudication, frequent chest pains associated with BP above 130/80mmHg, tachycardia, extrasystoles, and headaches. She also complains of memory loss and inability to concentrate when her BP is lowered. Physical examination revealed a systolic murmur 2/6 (heard between the scapulas), left arm BP: 90/70mmHg, right arm BP: 130/80 mmHg. ECG: sinus rhythm, HR 85/bpm, QS form in V2-V5. CT angiography and heart ultrasound revealed restenosis with the narrowest part of the thoracic aorta being 10x12mm, with max gradient of 33mmHg and a mean gradient 18,3mmHg. Medical history notable for hypertension, hyperlipidemia, paroxysmal supraventricular tachycardia (HR of 180/min); SVES; paroxysmal atrial fibriloflutter (rapid ventricular conduction, HR of 180/min), generalized atherosclerosis, angina pectoris (positive treadmill test), circulatory insufficiency of the left upper extremity and bilateral lower extremities (ABI right 0,75; ABI left 0,90), hypoplastic left vertebral artery with grade IV Steal Sy, TIA with dysarthria and patent foramen ovale showed by TEE. Coronarography revealed no significant stenosis of the coronary and carotid arteries, the left subclavian artery and left vertebral artery 100% occluded. The patient is not a candidate for cardiovascular surgery or a vascular intervention due to the high probability of complications. Medications: Propafenone 300 mg t.i.d, Rivaroxaban 20 mg once a day, Rosuvastatin 20 mg once a day, Cilostazol 100 mg b.i.d.
Conclusion. Our aim was to highlight the complexity of this entity-coarctation of aorta, with it's variety of presentation in the clinical setings, especially in the postoperative course that significantly decrease patient's quality of life. This represents challenge on medical tretman in adult patient with operated aortic coarctation.

Key words: Aortic recoarctation, adult patient

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Апстракт

Вовед. Аортната коарктација (CoA) се смета дека не е само циркуларно стеснување на аорта, туку е дел од генерализирано васкуларно заболување. Компликациите вклучуваат рана КАБ, срцева слабост, ЦВИ, Ао аневризма/дисекција и прерана смрт (во III-IV декада).
Приказ на случај. 42 годишна жена, која имала хируршка корекција на аортна коарктација на возраст од 20 месеци, се жали на замор, вртоглавица, нестабилност, интермитентна клаудикација, чести градни болки при крвен притисок (КП) над 130/80 mmHg, тахикардија,екстрасистоли и главоболки. Таа, исто така, се жали на губење меморија и неспособност да се концентрира, кога КП е намален. Физикалниот преглед открива систолен шум 2/6 (интерскапуларно), КП на лева рака: 90/70 mmHg, десна рака: 130/80 mmHg. ЕКГ: синус ритам, СФ 85/мин, QSформа во V2-V5. КТ ангиографија и срцев ултразвук откриваат рестеноза на најтесниот дел на торакална аорта 10x12 mm, со максимален градиент 33mmHg и среден градиент 18,3 mmHg. Медицинската историја укажува на постоење хипертензија, хиперлипидемија, пароксизмална суправентрикуларна тахикардија (со СФ од 180/мин); предкоморни предвремени удари; пароксизмален претkоморен фибрило-флатер (со брзо коморно спроведување, со СФ од 180/мин), генерализирана атеросклероза, ангина пекторис (позитивен treadmill test),

циркулаторна инсуфициенција на левиот горен екстремитет и двата долни екстремитета (АБИ десно 0,75; АБИ лево 0,90), хипопластична лева вертебрална артерија со степен IV Steal Sy лево, ТИА со дизартрија и отворен foramen ovale прикажан на ТЕЕ. Коронарографијата открива дека нема сигнификантни стенози на коронарните и каротидни артерии, како и дека левата артерија супклавија и левата вертебрална артерија се 100% оклудирани. Пациентката не е кандидат за кардиоваскуларна хирургија или за васкуларна интервенција, заради голема можност за компликации.

Терапија. Тбл. Propafenone 300 mg двапати дневно, Тбл. Rivaroxaban 20 mg еднаш дневно, Тбл. Rosuvastatin 20 mg еднаш дневно, Тбл. Cilostazol 100 mg двапати дневно.

Заклучок. Наша цел беше да се потенцира комлексноста на клиничките наоди во постоперативниот тек на аортна коарктација, кои значајно го намалуваат квалитетот на животот на пациентот. Тоа, воедно, претставува предизвик во лекувањето на оперирана коарктација на аорта кај возрасен пациент.

Клучни зборови: аортна рекоарктација, возрасен пациент.

Introduction

According to Guidelines for the management of GUCH (2010) [1], aortic coarcation (CoA) is considered as part of a generalized arteriopathy, and not only as a circumscript narrowing of the aorta. Coarctation is the third most prevalent form of congenital heart disease [2,3]. CoA accounts for 5-8% of all congenital heart defects. The prevalence of isolated forms is about 3 per 10000 live births. There is a morphological spectrum of abnormalities, ranging from a discrete stenosis distal to the left subclavian artery to a hypoplastic aortic arch and isthmus, or long tubular stenosis of the descending thoracic aorta.

Coarctation can be considered a primary (native) phenomenon, or a recurrent event, secondary to previous repair. Although there are many parallels in the management of native and recurrent coarctation, the pathophysiological processes responsible for secondary coarctation are different, and this may affect the approach and outcomes of management. Furthermore, the outcome data following repair suggest that coarctation is far from cured in a significant proportion of cases. Restenosis is a potential consequence of any type of repair, and late hypertension is relatively common, even in the absence of residual or recurrent coarctation.

We can find (re)coarctation across the very wide age range and in variety of presentation, that is why our goal was to show a case report with operated aortic coarctation, but with very limited quality of live.

Case report

The patient is a 42-year-old female, who has undergone a surgical repair of the CoA at the age of 20 months in Ljubljana (1976) (sec.Clagett). She has a BSA of 1,9m^2 and hyperlipidemia. In the last two years, more notably in the last year, she complains of fatigue, vertigo, instability, difficulty with walking and prolonged standing, intermittent claudication at 200 m and numbness in the bilateral lower extremities.

She has frequent chest pains associated with BP above 130/80 mmHg, dyspnea, tachycardia, extrasystoles, headaches and left ocular palsy. She also complains of memory loss and inability to concentrate when her BP is lowered with a subjective feeling of drowsiness and nausea, which interfere greatly with her day to day activities.

She had her first hypertensive episode during her first pregnancy 17 years ago, with a BP of 180/120mmHg. She was hospitalized due to preeclampsia, associated with proteinuria and leg edema. She was prescribed antihypertensive medicine. The kidney ultrasound showed no abnormalities. The BP Holter showed poorly regulated hypertension with maximal values of 185/125 mmHg and an average BP of 150/95mg. In 01/2016 she suffered a transient ischemic attack with dysarthria and a BP of 170/105 mmHg. She was prescribed amlodipine, nebivolol and enalapril, but she states that she felt unwell with the medications.

Physical examination revealed a systolic murmur 2/6 (heard between the scapulas), left arm BP: 90/70 mmHg, right arm BP: 130/80 mmHg. Systolic BP left leg (a. tibialis post.) 85 mmHg, systolic BP right leg (a. tibialis post.) 90 mmHg. ECG: sinus rhythm, HR 85/bpm, QS form in V2-V5, with low-voltage R waves in all standard and precordial leads.

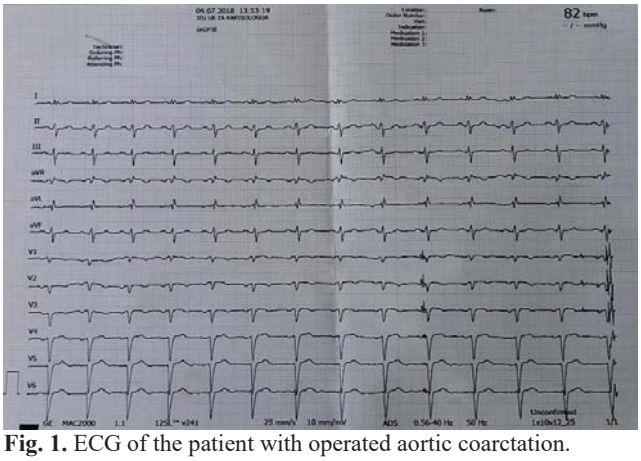

Fig. 1. ECG of the patient with operated aortic coarctation.

The rhythm holter showed frequent episodes of PSVT with a HR of 180/min; frequent SVES, singles, in pairs or often in continuous runs; paroxysmal atrial fibriloflutter with rapid ventricular conduction, HR of 180/min.

The exercise test was highly indicative of CAD, with a short duration of just 3 mins, only 30% of the car-

diovascular capacity was reached, with a horizontal ST depression in the inferior leads, maximal HR of 166/min, BP did not rise accordingly.

The heart ultrasound showed normal global systolic left ventricular function, with hypokinesis of the apical and basal segment of the inferior wall. The GLS was -14,8%. The left atrium was enlarged. There was sclerosis of the aortic valve with fusion of the right coronary cusp and the noncoronary cusp, pointing to a functional bicuspid valve. There was mild aortic and mitral regurgitation noted. The narrowest part of the thoracic Ao was 11-12mm. The flow speed was increased, with a maximal gradient of 33,7mmHg and a mean gradient of 18,3mmg, with a high likelihood of restenosis. The IAS was thinner at the level of fossa ovalis.

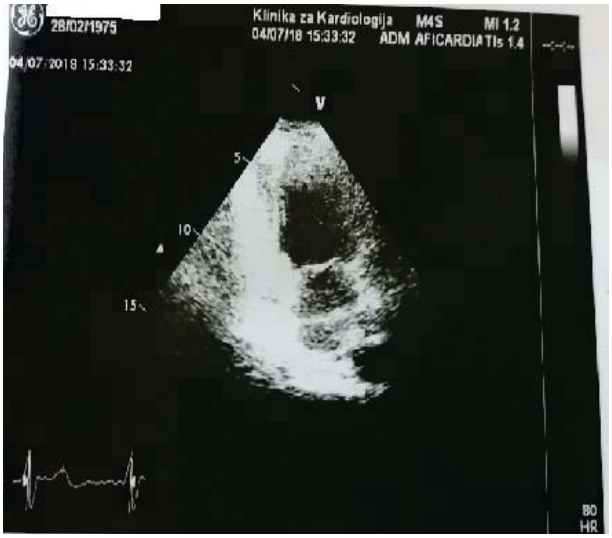

Fig. 2. Hypokinesia of the inferior wall

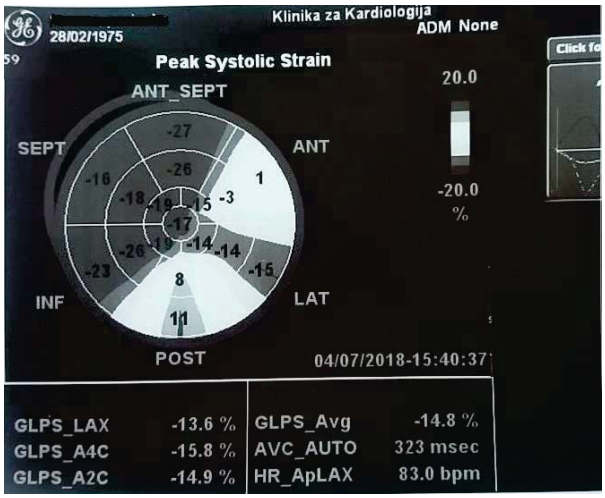

Fig. 3. Reduced Global Longitudinal Strain -14,8% (2-CH view)

CT angiography revealed that the Ao descendens is narrower (15-16 mm) and tortuous distal to the origin of the left CCA, with restenosis on the narrowest part of the thoracic aorta-10x12 mm and a dilatation distally to the narrowing-22 mm. The ascendant aorta is 30 mm, and the arch 20 mm, both with borderline dimensions, hypoplastic. The left subclavian artery cannot be visualized from the standard points of view, but can be seen from the level of the left vertebral artery, appearing grossly hypoplastic and fragile, with retrograde filling from the left ECA. The left vertebral artery is also hypoplastic and fragile, with a diameter of 1mm. A prominent right vertebral artery with a diameter of 4mm.

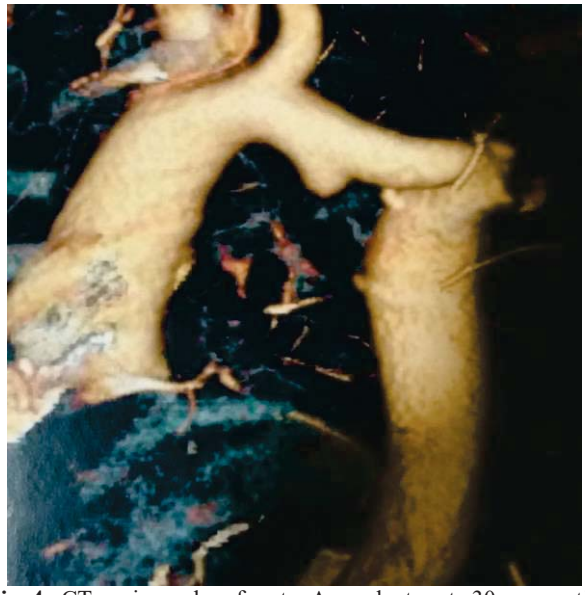

Fig. 4. CT angiography of aorta: Ascendant aorta 30mm, aortic arch 20mm, both hypoplastic
Ao descendens narrower (15-16 mm) distal to the origin of the left CCA, restenosis on the narrowest part of the thoracic aorta-10x12 mm, dilatation distally to the narrowing -22 mm. Left arteria subclavia missing.

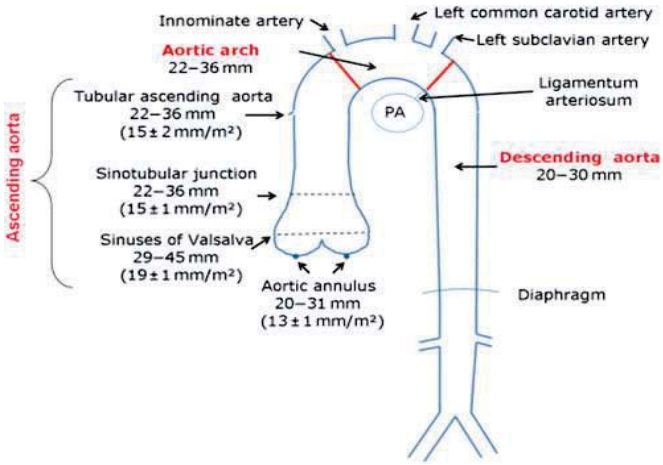

Fig. 5. Normal values of the aorta

Carotid Doppler: shows a hypoplastic and fragile left vertebral artery, with a diameter of 1mm, grade IV steal phenomena is noted. The right vertebral artery is dominant, with a diameter of 4mm with anterograde filling, tortuous. Mild atherosclerotic lesions on both carotid arteries. CCA with a thickened IMT.

Doppler of the upper and lower extremities: circulatory insufficiency of the left upper extremity (abnormal signals of the left brachial artery) and bilateral lower extremities (ABI right 0,69; ABI left 0,90), supporting the intermittent claudication.
CT of the peripheral blood vessels: showed very fragile arteries of the bilateral lower extremities.
Transesophageal echocardiography: revealed patent foramen ovale.
Coronarography: No significant stenosis of the coronary and carotid arteries. The left subclavian artery and left vertebral artery are 100% occluded.The patient is not a candidate for cardiovascular surgery or a vascular intervention due to the high probability of complications.
Neurological examination: Vertigo, with abnormal conduction through the peripheral auditory pathways and a positive Romberg test.
The orthopedic surgeon concluded that the difficulty standing and walking are not of spondylogenic or neurogenic origin.
In the course of the treatment, due to hypermenorrhea, we discontinued the baby aspirin. Since the diagnosis of AFF episodes, we put the patient on Rivaroxaban 20 mg once a day. The patient was also prescribed Propafenone 300 mg t.i.d. for rhythm control (the patient has stated that she feels unwell when on β-blockers). Additionally, she was prescribed Rosuvastatin 20mg once a day and Cilostazol 100 mg b.i.d. She was recommended regular follow ups for management of the hypertension and other CV risk factors, reassessing of the aortic restenosis and monitoring for the complications such as aortic dilatation and dissection and early onset of CAD.

Discusion

CoA is typically located at the insertion site of the ductus arteriosus, but it often varies. The most important notion is, if the ductus arterious is opened or closed, and it's location-proximally or distally of the coarctation. With preductal coarctation, the narrowing is proximal to the ductus arteriosus, it typically presents in infancy (infantile form) and if severe, usually presents in the first three weeks of life. In ductal coarctation the narrowing occurs at the insertion of the ductus arteriosus and usually appears when the ductus arteriosus closes. In postductal coarctation (adult form) the narrowing is distal to the insertion of the ductus arteriosus. This latter form is most common in adults and may be diagnosed incidentally for the presence of a cardiac murmur, hypertension, headache and lower limb muscle weakness.
In most cases, the coarctation is located distal to the origin of the left subclavian artery, thus the patients experience the typical symptoms with high BP in the upper limbs and low BP in the lower limbs. In certain instances, the coarctation may involve the left subclavian artery or lie proximal to it. This rare occurrence of a presubclavian coarctation was first described by Theron Clagett (1957), and the surgical protocol for the repair of this type of coarctation, is named after him. In his research paper, out of the 223 patients he included with surgical repair of coarctation at the Mayo Clinic, only six had presubclavian coarctation [4]. In these 6 patients it was surgically warranted that the left subclavian artery was removed along with the ligamentum arteriosum and the coarctation. With the exception of only one patient who had a patent ductus arteriosus and a right-left shunt and expired shortly after surgery, the other 5 patients had a good outcome from the surgery. Due to the presubclavian localization of the coarctation, our patient underwent the same surgery at the age of 20 months.
Aortic coarctation is part of a complex vascular disease. 'Cystic medial necrosis' (medial degeneration) with early elastic fibre fragmentation and fibrosis was found in the ascending and descending aorta, resulting in an increased stiffness of the aorta and carotid arteries [5,6]. CoA associated functional anomalies, include lowered baroreceptor activity, reduced arterial reactivity and compliance, and increased arterial stiffness in the vasculature. It is likely that these changes contribute to the pathophysiology of hypertension [7].
Seifert BL. and al. rated the stiffness index of the proximal descending aorta (precoarctation) and its relation to Doppler-derived pressure gradients obtained by continuous wave Doppler, and invasive catheter pressure gradients. They found that increasing the stiffness of the precoarctation segment also increased the degree of acceleration of flow velocity toward the coarctation, so the pressures and gradients in this segment increased also. Continuous wave Doppler instantaneous pressure gradients overestimated the catheter instantaneous pressure gradients [8].
DeGroff CG. and al. show that the degree of antegrade diastolic flow (diastolic runoff) noted on spectral Doppler tracings is dependent on lesion severity, saying that the presence of this spectral Doppler pattern is as much related to the severity of coarctation as it is with changes in aortic compliance. They developed three computational numeric models of coarctation with high, low, and no wall compliance. Flow simulations run representing high and low flow states. In both the low and high-flow states, the degree of diastolic runoff increased with increasing vessel compliance. Increased aortic compliance brings greater dilatation of the precoarctation aorta in systole, resulting in a persistence of stored upstream energy. This stored energy, released downstream in diastole, as the precoarctation aortic walls contract, leads to increased degrees of diastolic runoff [9].
CoA hemodinamicaly contributes to significant after load on the LV, manifested by increased wall stress, compensatory left ventricular hypertrophy, the development of arterial collaterals and finaly LV dysfunction.

Clinical features include upper body systolic hypertension, lower body hypotension, a blood pressure gradient between upper and lower extremities (>20 mmHg indicates significant CoA), radio femoral pulse delay. Cardiac catheterization with manometry (a peak-to-peak gradient >20 mmHg indicates a haemodynamically significant CoA in the absence of well-developed collaterals), and angiocardiography is still the gold standard for CoA evaluation at many centres before and after operative or interventional treatment.

Whereas blood pressure usually normalizes for a time after successful repair, one third of CoA patients develop hypertension (HTN) by adolescence and 90% by middle age. The pathogenesis of the later onset HTN remains poorly understood. Possible explanation may lie with the mechanical obstruction caused by the restenosis, the structural changes in the walls of the central and peripheral blood vessels, the lowered baroreceptor activity, abnormal function of the RAA system, higher catecholamine levels, essential hypertension, hypoplasia of the aortic arch and the occurrence of HTN during physical activity. The likelihood of HTN is higher if the patient was older and had HTN prior to surgery.

According to Guidelines beta-adrenergic receptor blockers have been established for HTN terapy in CoA preoperatively and postoperatively. If no residual arch obstruction exists, ACE inhibitors or angiotensin II antagonists may be added if hypertension persists despite beta-blocker therapy.

What concerns of treatment, aortic coarctation can be repaired surgically or percutaneously (catheter interventional treatment). The decision should be made according to the anatomy and location of the coarctation, age of the patient, presence of other cardiac lesions, and other anatomic determinants (extensive collaterals or aortic calcification). In native CoA with appropriate anatomy, stenting has become the treatment of first choice in adults in many centres. For adults with recurring or residual CoA, angioplasty with or without stent implantation has been shown to be effective in experienced hands if anatomy is appropriate. The operative techniques are still used and are necesery in many situations. Re-CoA repair in adults can be complicated, and ascending-to-descending aorta conduits may be preferable in cases of difficult anatomy. Although the surgical risk in simple CoA may currently be <1%, it increases significantly beyond the age of 30-40 years. Associated problems that may require intervention have to be considered: aneurysm of the ascending aorta with a diameter >50 mm [>27.5 mm/m2 body surface area] or rapid progression; aneurysm at the previous CoA site; aneurysms of the circle of Willis or associated significant aortic valve stenosis or regurgitation [1]. Acording to the Guidelines [1] indications for intervention in coarctation of the aorta as class I C is: All patients with a non-invasive pressure difference >20 mmHg between upper and lower limbs, regardless of symptoms but with upper limb hypertension (>140/90 mmHg in adults), pathological blood pressure response during exercise, or significant LVH should have intervention.

Vimalarani A. and al (2018) reported an 56 year old adult patient, with surgically corrected coarctation with Dacron tube graft (16 mm x 20 mm) at 21 years of age. He was admitted for angina pectoris, hypertension, and exertional dyspnea, so coronary angiogram revealed left anterior descending artery and diagonal disease, which were stented. Because of the severe stenosis at the proximal and distal anastomosis of the Dacron tube graft, they deployed covered stent inside the Dacron graft. The use of covered stents has expanded for native and recurrent CoA, because they can prevent or deal with the complications of aneurysm formation and stent fractures, or tortuous lesions [10]

Despite apparently successful repair of the obstruction, however, individuals with a history of CoA demonstrate excess morbidity and premature mortality (in the III-IV decade) associated with hypertension (HTN), cerebrovascular accident, coronary arterydisease, heart failure and aortic dissection/rupture. These adverse outcomes are independent of the severity of the original obstruction, type of treatment or restenosis. Presbitero *et al*., showed that patients with repaired coarctations still died, on average, at a much earlier age than the general population [11]. Since then, researchers have been trying to examine the cause of this excess mortality. Multiple studies have shown the main cause of death in patients with corrected CoA is coronary artery disease (CAD) [12,13] saying that CoA is associated with accelerated or premature CAD despite repair.

Roifman *et al*. (14) identified 756 individuals diagnosed with CoA and 6471 with ventriculoseptal defect (1983-2005). They compared the rate of cardiovascular diagnoses in age-matched CoA and ventriculoseptal defect cohorts (median age 30 years). The CoA group had significantly greater rates of HTN (45% vs 16%), CHF (15% vs 7%), peripheral vascular disease (13 vs. 2.7%), and stroke (5.5% vs 2.6%; $P<0.0001$ for all) and hyperlipidemia (4.0 vs. 2.4%, p=0.01). CoA patients also had higher CAD (4.9% vs3.5%), but this was not statistically significant after adjusting for the greater prevalence of CAD risk factors: HTN, hyperlipidemia, and male sex in the CoA group. The authors conclude that CoA is not an independent risk factor for CAD. We also saw that prevalence of cardiovascular comorbidities remains so high in CoA patients. So it is emphasized the need for treatment of cardiovascular risk factors such as HTN and dyslipidemia in CoA patients to prevent the late complications, but is not entirely clear that standard risk factor treatment is effective in reducing the occurrence of CAD and stroke in CoA. The 4.9% prevalence of CAD in this analysis (2005) is very similar to historical observations of

5.1%, reviewed by Verheugt *et al*. [14] The 5.5% prevalence of cerebrovascular disease in this study is actually greater than earlier estimates [15]. So we can't conclude that conventional treatment prevents coronary and cerebrovascular disease in CoA patients.

Dendramis G. and al describe a case of a 63-year-old man, admitted for acute coronary syndrome. During the cardiac catheterization with right femoral artery access and aortography they accidentally found significant coarctation at the level of the thoracic aorta. With a transradial right approach they treated the culprit lesion critical stenosis (80%) of the proximal left anterior descending artery and subocclusion of the distal circumflex artery. He pointed that it is possible that CoA can go unnoticed for many years and can be diagnosed accidentally after the onset of its complications [16].

The incidence of CAD in CoA patients, makes a relation to postulated vascular reactivity abnormalities in CoA. Several studies have shown that CoA patients may have higher rates of persistent endothelial dysfunction, increased levels of pro-inflammatory cytokines and vascular stiffness and these intrinsic vascular abnormalities may persist even after repair, so they can potentially predispose to the development of CAD regardless of repair.

Raneem F. and al (2018), reported of total transcatheter approach including stenting of severe coarctation of the aorta (CoA) located 16 mm distal to LSA, transcatheter aortic valve replacement (TAVR) for severe aortic bicuspid valve stenosis, and percutaneous coronary intervention (PCI) to treat significant coronary artery disease (significant proximal left anterior descending (LAD) stenosis) in a high risk elderly patient. They report a 70-year-old female, with significant comorbidities: uncontrolled hypertension and acute decompensated heart failure on admission, type 2 diabetes mellitus, chronic obstructive pulmonary disease, and severe calcifications of the ascending aorta. The procedures were successfully performed and the patient was asymptomatic at follow-up [17].

In the recent years there is a progress in elucidating the genetic origins of CoA and related cardiovascular deseases as a key to identifying individuals at risk for complications.

There are findings that the combination of CoA and bicuspid aortic valve (BAV) ocured in male sex more frequently. Girls and women with a single X chromosome (Turner syndrome) demonstrate prevalence of hypoplastic left heart estimated at 10%, aortic coarctation at 12%, and BAV at 30% [18].

Tagariello A. and al reported mutations in the Y-chromosome allele of transducin ß–like protein 1 (*TBL1Y*) in 2/83 study subjects with CoA [19]. This gene is located in a Yp region and variation in this locus correlates with atherogenic lipid profiles in men [20]. Roifman et al report in his study a significantly higher prevalence of hyperlipidemia in CoA versus ventriculoseptal defect patients. These recent developments indicate that further studies focused on the sex chromosome short arms, could be productive in illuminating the genetic male predisposition to both CoA and CAD.

Conclusion

Our aim was to highlight the complexity of this entity -coarctation of aorta, with its variety in clinical presentation, especially in the postoperative course. Even with a good postoperative outcome, most patients' still have a decrease in the quality of life, making the future medical treatment of these patients a significant challenge.

Conflict of interest statement. None declared.

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УПАТСТВО ЗА ПРИЈАВА НА ТРУД ОД СОРАБОТНИЦИТЕ НА ММП

"Македонски медицински преглед" (ММП) е стручно списание на Македонското лекарско друштво, првенствено наменето на лекарите од општа практика, специјалистите од одделните медицински дисциплини и истражувачите во областа на базичните медицински и други сродни науки.

Списанието ги има следниве рубрики и категории на трудови:

1. **Изворни трудови**
2. **Соопштувања за клинички и лабораториски искуства**
3. **Прикази на случаи**
4. **Од практика за практика**
5. **Едукативни статии**
6. **Вариае (**писма од редакцијата, општествена хроника**,** прикази на книги, извештаи од конгреси, симпозиуми и други стручни собири, рубриката ,,Во сеќавање,, и др).

Изворните трудови имаат белези на научни трудови, додека трудовите категоризирани во рубриките 2-5 имаат белези на стручни трудови.
Во ММП се објавуваат трудови на членовите на МЛД или на членови на други стручни здруженија. Авторите се одговорни за почитувањето на етичките начела при медицинските истражувања, а изнесените ставови, изведени од анализата на сопствените резултати, не се нужно и ставови на Редакцијата на ММП.
Редакцијата ги испраќа ракописите на стручна рецензија; рецензентот (ите) и Редакцијата ја определуваат дефинитивната категоризација на ракописот кој е прифатен за печатење. Редакцијата го задржува правото ракописите да ги печати според рецензираниот приоритет.
Упатството за соработниците на ММП е во согласност со Ванкуверските правила за изедначени барања за ракописите кои се праќаат до биомедицинските списанија.

1. ТЕКСТ НА РАКОПИСОТ

Сите ракописи се испраќаат во електронска форма на електронската адреса (е-маил) на МЛД-ММП, со двоен проред и најмногу 28 редови на страница. Трудот се поднесува на англиски јазик латиничен фонт Times New Roman големина 12 и апстракт на македонски јазик. Лево, горе и долу треба да се остави слободна маргина од најмалку 3 см, а десно од 2,5 см.. Редниот број на страниците се пишува во десниот горен агол.
Ракописот на трудот треба да е придружен со писмо на првиот автор, со изјава дека истиот текст не е веќе објавен или поднесен/прифатен за печатење во друго списание или стручна публикација и со потврда дека ракописот е прегледан и одобрен од сите коавтори, односно со придружна декларација за евентуален конфликт на интереси со некој од авторите.

Насловната страна треба да има: наслов на македонски и англиски, имиња и презимиња на авторите, како и институциите на кои им припаѓаат, имињата на авторите и насловот на установата се поврзуваат со арапски бројки; автор за кореспондеција со сите детали (тел. е-маил); категорија на трудот; краток наслов (до 65 карактери заедно со празниот простор); како и информација за придонесот за трудот на секој коавтор (идеја, дизајн, собирање на податоци, статистистичка обработка, пишување на трудот).

Насловот треба концизно да ја изрази содржината на трудот. Се препорачува да се избегнува употреба на кратенки во насловот.

Изворните трудови и **соопштувањата** го имаат следниов формален редослед: насловна страна, извадок на македонски јазик (вовед, методи, резултати, заклучок) со клучни зборови, извадок на македонски јазик со клучни зборови, вовед, материјал и методи, резултати, дискусија и

заклучоци, литература и прилози (табели, графици и слики) и легенди за прилозите во еден фајл.

Приказите на случаи треба да содржат вовед, детален приказ на случајот, дискусија со заклучок и литература со прилози.

Извадокот на македонски јазик треба да содржи најмногу 250 зборови и да биде структуриран со сите битни чинители изнесени во трудот: вовед со целта на трудот, методот, резултати (со нумерички податоци) и заклучоци. Заедно со извадокот, треба да се достават и до 5 клучни, индексни зборови.

Извадокот на англиски јазик мора да е со содржина идентична со содржината на извадокот на македонски јазик. Клучните зборови треба да се во согласност со MeSH (Medical Sibject Headings) листата на Index Medicus.

Воведот треба да претставува краток и јасен приказ на испитуваниот проблем и целите на истражувањето, со наведување на етичкиот комитет односно институцијата која го одобрила испитувањето (клиничка студија која се работи според принципите на Хелсиншката декларација за пациентите и нивните права).

Методите треба да бидат точно назначени, за да се овозможи повторување на прикажаното истражување. Особено е важно да се прецизираат критериумите за селекција на опсервираните случаи, воведените модификации на веќе познатите методи, како и идентификација на употребените лекови според генеричното име, дозите и начинот на администрација.

Резултатите треба да се прикажат јасно, по логичен редослед. Резултатите се изнесуваат во стандардните СИ единици. Во текстот треба да се назначи оптималното место каде ќе се вметнат табелите и илустрациите, за да се избегне непотребното повторување на изнесените податоци. Значајноста на резултатите треба да се обработи статистички, со детален опис на употребените статистички методи на крајот на делот *методи*.

Дискусијата треба да ги истакне импликациите од добиените резултати, споредени со постојните сознанија за испитуваниот проблем.

Заклучоците треба да не бидат подолги од 150 зборови.

2. ПРИЛОЗИ

Како прилог-документација на трудовите предложени за печатење, може да се достават до 5 прилога (табели, фигури,/слики - илустрации).

Табелите се доставуваат на крајот на трудот во истиот фајл. Секоја табела треба да има свој наслов и реден број кој ја поврзува со текстот. Хоризонтални и вертикални линии на табелата не се дозволени; ознаките на колоните во табелата се пишуваат скратено или со симбол, а нивното објаснување се пишува на дното на табелата, во вид на легенда.

Илустрациите се доставуваат со реден број како слика во црно-бела техника, а секоја слика треба да е придружена со легенда (опис).

Микрофотографиите може да содржат посебни ознаки во вид на стрелки или симболи. Покрај описот на сликата, мора да се наведе и зголемувањето и видот на боењето на препаратот (ако тоа веќе не е направено во секцијата *материјал и методи*).

Сите ознаки на фотографиите мора да бидат доволно големи, за да може јасно да се распознаат и по смалувањето во печатницата, при нивното вклучување во печатената страница на списанието.

3. ЛИТЕРАТУРА

Цитираната литература се пишува на крајот на трудот по заклучоците, со редни броеви според редоследот на појавувањето на цитатот на текстот на трудот ставени во средни загради и без простор меѓу нив (ако се последователни треба да се поврзани со цртичка, на пр. [3-6]).
Литературата се цитира на следниов начин (кратенките за насловите на списанијата треба да се според листата прифатени vo Index Medicus):

а) ***статија во списание*** (се наведуваат сите автори, ако ги има до 4 или помалку; ако ги има повеќе од 4 се наведуваат првите 3 автори и се додава: *и сор.*) Neglia JP Meadows AT, Robison LL *et al*. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 325:1330-6.

б) заеднички автор

GIVIO (Interdisciplinary group for cancer care evaluation). Reducing diagnostic delay in breast cancer. Possible therapeutic implications. *Cancer* 1986; 58: 1756-61.

в) ***без автор*** **-** анонимно. Breast screening: new evidence. (*Editoriall Lancet* 1984; i :1217-8).

г) ***поглавје во книга или монографија***

Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. Vo: Sodeman WA Jr, Sodeman WA, Ed. Pathogenic physiology: mechanisms of disease. Philadelphia; W B Saunders, 1974: 457-72.

Првите отпечатоци на трудовите им се праќаат на авторите за корекција: авторите се должни коригираниот отпечаток да и го вратат на Редакцијата на ММП во рок од 2 дена.

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Известување за членовите на МЛД

Сите што сакаат и натаму да го добиваат списанието треба да ја имаат уплатено членаринатa за 2019 година во висина од 600 денари и за тоа да ја информираат стручната служба на Македонско лекарско друштво, писмено или преку телефон.

Детални информации можете да добиете на телефонот на Друштвото 02 3 162 557.

Известување за рецензентите за ММП

Во склад со правилникот на УКИМ рецензентите што навремено и одговорно ќе ја одработат рецензијата ќе добијат 0.4 бода кои се собираат за унапредување во академските звања. Бодовите можат да се добијат и ретроградно преку побарување во МЛД - 3162 557.