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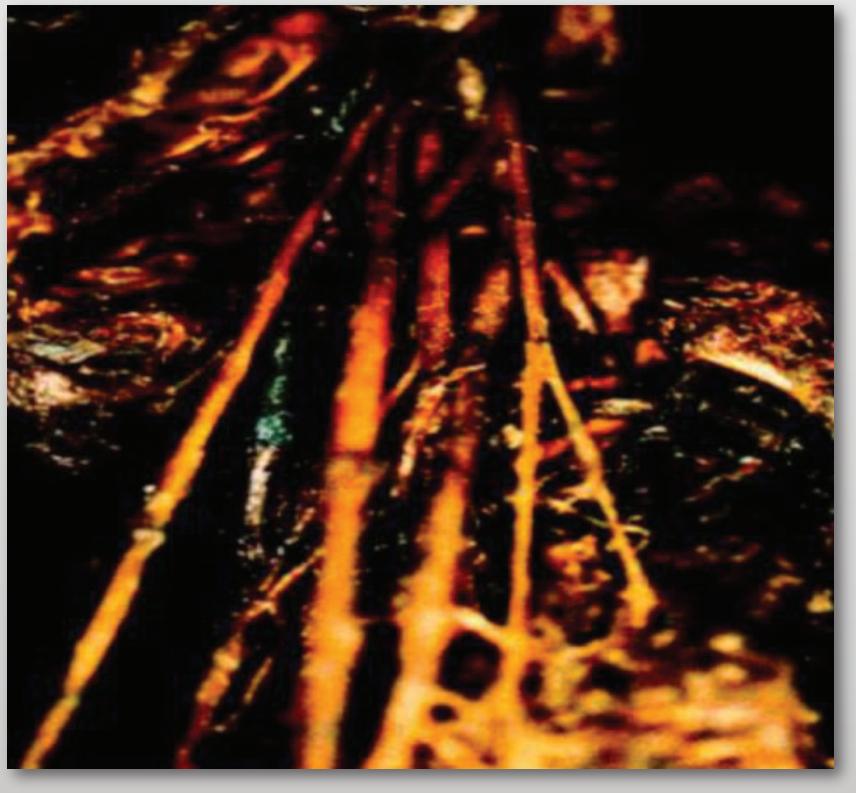

Anatomic variations of the brachial plexus.

(See paper by Mrvaljevic et al)

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2. Papantchev V, Hristov S, Todorova D, et al. Some variations of the circle of Willis, important for cerebral protection in aortic surgery — a study in Eastern Europeans. Eur J Cardiothorac Surg 2007; 31:982–998.
3. Jovanović S, Gajić I, Mandić B, Mandić J, Radivojević V. Oral lesions in patients with psychiatric disorders. Srp Arh Celok Lek 2010; 138:564–569. (Serbian)
4. Valença MM, Martins C, Andrade-Valença LPA. Trigeminal neuralgia associated with persistent primitive trigeminal artery. Migrâneas cefaléias (Brasil) 2008; 11:30–32.
5. Belenkaya RM. Structural variants of the brain base arteries. Vopr neirokhir 1974; 5:23–29. (Russian)

Abstract:

6. Tontisirin N, Muangman SL, Suz P, et al. Early childhood gender in anterior and posterior cerebral blood flow velocity and autoregulation. In Abstract of Pediatrics 2007. (doi:10.1542/peds. 2006-2110; published online February 5).

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7. Patten MB. Human embryology, 3rd edn. McGraw-Hill: New York, 1968.
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9. Lie TA. Congenital malformations of the carotid and vertebral arterial systems, including the persistent anastomoses. In: Vinken PJ, Bruyn GW (eds) Handbook of clinical neurology, vol. 12. North Holland: Amsterdam, 1972; pp 289–339.

Unpublished data:

10. Reed ML. *Si-SiO_2 interface trap anneal kinetics*, PhD thesis. Stanford University: Stanford, 1987.

Online document:

11. Apostolides PJ, Lawton MT, David CA, Spetzler RF. Clinical images: persistent primitive trigeminal artery with and without aneurysm. Barrow Quarterly 1997; 13(4). http://www.thebarrow.org/Education_And_Resources/Barrow_Quarterly/204843
12. Cerebrovascular embryology, in: power point; 2000. http://brainavm.oci.utoronto.ca/staff/Wallace/2000_curriculum/index.html

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Editorial

WHAT IS YOUR REAL NATURE: THE HEDGEHOG OR THE FOX

Greek poet Archilochus says: „The fox knows many things, but the hedgehog knows one big thing". The words may have a sense of universal difference between scholars, scientists and in general between human beings. And as you may presume the hedgehog always defeats fox. This simplified classification into only two big categories enable us to divide intellectual and artistic personality in: these with centripetal and those with centrifugal ideas.

Isaiah Berlin further expands this idea to divide writers and thinkers into two categories: hedgehogs, who view the world through the lens of a single defining idea (examples given include Plato, Dante, Pascal, Hegel, Dostoyevsky, Nietzsche, Proust…), and foxes, who are seeking a wide variety of experiences and for whom the world cannot be simplified to a single idea. Examples given include Herodotus, Aristotle, Erasmus, Shakespeare, Molière, Goethe, Pushkin, Balzac…

Sir Harold Himsworth was a distinguished clinical scientist at a time when modern clinical science was at an important stage of development. He made remarquable contributions to the clinical investigation and etiology of diabetes mellitus and of liver necrosis. When asked for reviewing the manuscript sent to the Lancet in 1943 about the discovery that alloxan could produce diabetes in animals, he considered as his duty to check the experiment. It didn't work, so he rejected the paper. When the authors protested, he realized that he had accidentally inactivated the alloxan by boiling, and the paper was finally accepted. I wanted to bring to your attention this anecdote about Himsworth which classes him as a hedgehog.

It is difficult to expect such degree of intellectual curiosity and devotion in our reviewers. I don't intend to force you to be so judgmental and to classify our authors in the categories mentioned above. Weather you estimate yourself as the hedgehog or the fox, enjoy reading new issue of Facta

Inspired by:

1. Gale EAM. Commentary: The Hedgehog and the fox: Sir Harold Himsworth (1905-93). Int J Epidemiol 2013; 42: 1602–1607.
2. Isaiah Berlin. The Hedgehog and the fox. Weidenfeld & Nicolson 1953.

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Original Article

ANALYSIS OF THE ANATOMIC VARIATIONS OF THE BRACHIAL PLEXUS AND ITS BRANCHES AT THE LEVEL OF FORMATION AND BRANCHING OF ITS TRUNCI

Milutin Mrvaljević[1], Srbislav Pajić[1], Pavle Popović[1], Jovan Grujić[2], Marko Petrović[3], Ljudmila Jablan[4], Sonja Giljaca[5], Petre Stavrevski[6], Nataša Rančić[7], Saša Knežević[2]

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Abstract. *Although the terminal branches of brachial plexus that originate from lateral and medial fasciculus are well protected by muscle mass and vascular-neuronal petal of axilla and upper arm, the number of traumatic damage and injuries increases, according to the published reports of neurosurgeons working on pathology of peripheral nerves, as well as traumatologists, orthopedics, microsurgeons and plastic surgeons. This is certainly contributed by urbanization, industrialization, migration and increased number of traffic accidents. Knowing the microstructure of the peripheral nerve truncus leads to the possibility of applying various techniques of nerve grafting, as well as possibility of re-implantation of detached spinal roots, seen in traction injuries of brachial plexus, in which the mechanism of injury needs to be considered. Considering frequent injuries of terminal branches of lateral and medial fasciculus and a substantial pathology of plexus brachialis, the aim of our research was to study surgical-anatomical relations between terminal branches of medial and lateral fasciculus and substantial morphology of terminal branches of both fasciculi, particularly regarding the place and way of formation, as well as the number of their anastomoses. The studies of the terminal branches of medial and lateral fasciculus on our preparation materials are based on the dissection of axilla and anterior part of the upper arm, on 50 cadavers, adults of both genders, at Institute of Anatomy and Institute of Forensic Medicine at School of Medicine in Belgrade. The way of formation of the terminal branches of lateral fasciculus on our preparation materials was always the same. These branches were usually formed after the bifurcation or diverging of lateral fasciculus to radix lateralis nervi mediani and musculocutaneous nerve. Exceptionally, after fusion of lateral fasciculus and medial root of nervus medianus, there is no bifurcation, and formed nervous truncus is a result of existence of the pre- or postfixational type of brachial plexus. Analyzing our preparation materials, we determined that high bifurcation of lateral fasciculus (LF) exists in 18% of cases and that it is projected in the line of anterior edge of clavicle. Medium high bifurcation of LF is projected in the line of the top of the acromion of scapula and is seen in 61% of all cases. Low bifurcation is usually placed in the line of inferior edge of pectoral minor muscle, in 8% of cases. Fasciculus without bifurcation is noticed in 13% of cases. Measuring the shortest distance between anterior edge of clavicle and the point of bifurcation of LF resulted in a wide range from 0.5 to 9.7 cm, with 4.2 cm average. In cases of transplantation, implantation and re-implantation of nervous trunci of plexus brachialis, it is very important to consider the shape and the thickness of nervous truncus, the number of fasciculi, the number of nerve fibers, as well as the quantity and schedule of peri- and intrafascicular connective tissue, providing the normal irrigation of the nerve. Finally, we can conclude that mentioned facts prompted us to undertake a systematic research of great terminal branches of plexus brachialis that originate from lateral and medial fasciculus, trying to ensure that our anatomical findings receive a comprehensive clinical confirmation.*

Key words: *peripheral nerves, brachial plexus, lateral fasciculus, medial fasciculus, truncus.*

Introduction

The first more comprehensive studies of plexus brachialis performed on the autopsy material date back to second half of the past century (*Walsch, 1877*), and yet the interest of morphologists and clinical researchers still remains current. The great variability of the way of forming the brachial plexus (pre- and postfixation of the

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plexus), its primary trunci, secondary trunci (fasciculi), as well as terminal branches [1–3], contributes to the higher interest for this topic. There is a great variability in view of the place of origin of the plexus, way of forming and its pathway, lateral branches, the great number of mutual anastomoses within the plexus, as well as with adjacent nerves. There is a possibility of potential variations, including those that have not been discovered and described. Therefore, before every surgical treatment, different morphological possibilities of brachial plexus must be considered, due to its great variability and confusing effect on even experienced surgeons [4–6].

During surgical interventions in axilla and upper arm, the damage of terminal branches [7–9] of plexus (median nerve, musculocutaneous and ulnar nerve) is common, due to replacement of the nerve with anastomosis and vice versa, or impossibility to differentiate some of the terminal branches of plexus or their variations (such as the absence of bifurcation of trunci and fasciculi, and variations non separation) [10–12]. Injuries may vary from insignificant superficial nervous truncus damage, to partial or complete interruption of the nervous truncus [13–15]. The discontinuity or injuries of the truncus and its nerves may cause the paralysis of muscles and loss of sensibility within the area of their innervation. Not every time does the discontinuity of the nerve lead to paralysis of corresponding muscle group, due to voluminous anastomosis, where nerve impulses through anastomosis enter to the dissected nervous truncus [16–20].

The Objectives

Concerning frequent injuries of terminal branches of the lateral and medial fasciculi, as well as substantial pathology of brachial plexus, the aim of our research was to eventually expand the previous scientific knowledge in this field.

Therefore, the aim of our research was to study:

- Surgical-anatomical relations between terminal branches of medial and lateral fasciculi,
- Syntrophic and skeletal relations of these elements, which are of great importance in surgery of the neck, shoulder, upper arm and thorax,
- Substantial morphology of terminal branches of both fasciculi, particularly concerning the site and way of their origin, and their anastomosis.

Complying with objectives, the following aims of the study are:

1. To determine morphological variations in the way of origin and the site of the onset of large terminal branches of the medial and lateral fasciculus, which are most commonly damaged: radix medialis nervi mediani, n. ulnaris, radix lateralis nervi mediani, n. medianus and n. musculocutaneus.

2. To determine the morphology of the aforementioned nerves in the region of the axilla and arm: the appearance, shape, length, thickness, etc.

3. To determine the existence of anastomosis of these nerves, both between themselves and with other adjacent and surrounding nerves.

Material and Methods

The study of the terminal branches of lateral fasciculus in our preparation material is based on the dissection of the axilla and the anterior part of the upper arm, on 50 cadavers, adults of both genders, at the Anatomical Institute and the Institute of Forensic Medicine of the School of Medicine in Belgrade.

We performed the dissection on 24 female cadavers and 26 male cadavers, which amounted to 48 and 52 dissected cases, respectively. Moreover, in 48 dissected cases in females, 24 were performed on the left and 24 on the right hand side, while in 52 male cadavers, 26 were done on the left and 26 on the right hand side in order to facilitate and have better comparison. Subsequently, the total number of cases in our study equals to 100.

During the dissection we recorded all possible differences, in relation to the right and left hand side as well as in relation to the eventual differences in gender, in order to determine the prevalence of some morphological variations on the left or right side, i.e. in women and men.

The dissection was performed by making medial incision along sulcus bicipitalis medialis, from the clavicular bone to the middle of the elbow. At the end of this incision, we made cross-cuts to increase the area of examined field. After the separation of the skin and the subcutaneous elements, we detached the tendons of m. pectoralis major and m. pectoralis minor, which were then removed. Next, we eliminated parts of deltoid muscle (pars acromialis et pars clavicularis musculi deltoidei). Subsequently, we obtained three prominent topographic points: acromion, processus coracoideus and margo anterior claviculae, from which we later performed different measurements. They included: the distance of the point or position of the bifurcation of the lateral fasciculus, the distance of the site or point of junction with n.medianus, and the distance of the bifurcation point of the lateral fasciculus from the bone topographic elements mentioned above.

The point of bifurcation of the lateral fasciculus is also the site of the onset of n.musculocutaneus, and the site of the occurrence of the lateral root of the median nerve (radix lateralis nervi mediani). Junction point for the both roots of the median nerve also represents a point of origin or the development of n.medianus itself. Such anatomical topography indicates the importance of knowing the variability of these distances. It should be noted that during all dissections and measurements, the upper extremity was maintained in a position of medium abduction and supination, which is a normal middle position of the arm.

The following elements were taken into account: the length, the thickness and the shape of the nervous truncus. Furthermore, we noted the existence of variations in the origin and the path of mentioned nerves, and the number and variations of their lateral branches. The great attention was given to the anastomosis of the examined nerves that were sometimes quite frequent and well expressed, and may cause confusion when it comes to differentiation of individual nervous truncus. The study is specifically

focused to the anastomosis of the median nerve, which has a central position and the greatest thickness in relation to the abovementioned nerves. The intention was to present its anastomosis with musculoskeletal nerve (n. musculocutaneus) and elbow nerve (n.ulnaris). We carried out the classification of all anastomosis and classified them into several types, for easier orientation and identification of morphological variations of these anastomoses.

The Results

Results of the research of terminal branches of lateral fasciculus

The way in which the lateral fasciculus was formed in our preparation materials was always the same. These branches were usually formed by bifurcation or diverging of lateral fasciculus on radix lateralis nervi mediani and nervus musculocutaneus. Exceptionally, in the fusion of the lateral fasciculus with the inner root of the medianus there is no bifurcation and the formed nerve truncus is the result of the existence of a pre or post-fixation type of brachial plexus.

The site of the formation of the terminal branches of the lateral fasciculus (LF) corresponds to the point of bifurcation of LF, which is variable and of whose height depends the length of musculocutaneous nerve (NMC) and the lateral root of the n. medianus (RLNM) (Table 1).

Analyzing our dissected material, we found that high bifurcation of LF exists in 18% of cases, and they are positioned at the height of the front edge of the clavicular bone. Medium high LF bifurcation is projected at the height of the top of the scapular bone (processus coracoideus scapulae) and is found in 61% of all cases. Low bifurcation, usually found at the height of the lower edge of the musculus pectoralis minor, is found in 8% of cases. The absence of bifurcation was registered in 13% of cases. Measuring the shortest distance from the front edge of the clavicula to the point of bifurcation of LF, we obtained the results that vary in wide range of 0.5 to 9.7 cm, average 4.2 cm.

1. Nervus musculocutaneus (NMC)

It is well known that nervus musculocutaneus (NMC) is a lateral branch of the lateral fasciculus (LF), which passing the point of bifurcation proceeds downwards, diagonally and laterally. Upon entering the upper arm, it usually perforates m.coracobrachialis diagonally, and then descends between m. biceps brachi and m.brachialis. Then, it appears in the bicipital groove, along the lateral edge of m. biceps, and descends downwards, ending at 1–3cm above epicondylus lateralis humeri, where it provides its final skin branch: nervus cutaneous antebrachii lateralis.

Reviewing our dissected material, we found nervus musculocutaneus (NMC) piercing m. coracobrachialis (MCB) in 86% of all cases. That way, the MCB justifies the name of the pierced muscle (m.perforatus), given by Casserius back in the 16th century. Within this percentage, we also included cases where NMC pierces another muscle of the anterior part of the arm, and not MCB.

In 14% of our preparation material, NMC does not break through the MCB, but following the medial edge of the MCB and while passing that way, provides the branches for the innervation of m. biceps brachii, m. coracobrachialis and m.brachialis. In the lower third of the upper arm, in these cases, the NMC turns laterally, between m. biceps and m. brachialis, appearing in sulcus bicipitalis lateralis, giving its final branch just above the lateral epicondylus of the humerus. As seen, there are significant deviations from the classic description of the route of delivery and the NMV path, which must be kept in mind in surgical interventions in the area of the axilla and upper arm. Variations in MCB perforation, as well as variations of the NMV path, according to our observations, are almost equally represented in both male and female, as well as on the right and left extremities of the examinees. This is somewhat confirmed by the literary data, obtained and published in professional literature in the last 10 years.

a) Types of perforation of the muscle coracobrachialis (MCB) by musculocutaneous nerve (NMC)

Analyzing the method of MCB perforation by NMV on our dissected material, we found that there are 2 basic forms of perforation: superficial and deep.

Table 1 Explored cadaveric material

Examined Material					Position of bifurcation of FL				Perforation of MCB from NMC	
Gender	Number	Material	Left	Right	High l bifurcation	Medium high bifurcation	Low bifurcation	Non Existant	Present	Not present
	50	100	50	50	18%	61%	8%	13%	86%	14%
Female Cadavers	24	48	24	24						
Male Cadavers	26	52	26	26						
Points of occurrence					Clavicular bone	Processus coracoideus	m. pectoralis minor			
Deep perforation									80%	
Superficial perforation									6%	
Total	50	100	50	50	100%				100%	

Table 2 Analysis of the results of the research of the terminal branches of the lateral fasciculus

Angle of perforation measurements				Types of perforations of MCB by NMC					Anastomosis of NM with NMC	
	Minimal value	Mean value	Maximum value	High perforation	Medium high perforation	Low perforation	Perforation of other muscles instead of MCB	Double perforation	When NMC derives from FL	When NMC derives from FNS
High perforation	10	16	18							
Medium high perforation	19	21	26							
Low perforation	33	39	45	51%	17%	7%	3%	2%	31%	6%
Superficial perforation	6	9	11							
One anastamosis									27%	
Two anastamosis									4%	
Variation A										3%
Variation B										2%
Variation C										1%
Total				100%						

Superficial perforations of the MCB are in those cases where the NMC, when perforating the MCB, superficially involves only a few muscle fibers, which are transferred as a bridge over the nerve. This can occur in any segment of the MCB, in m. brachialis or m. biceps brachi instead of MCB, or it can be observed as double perforation, when two muscles are penetrated repeatedly (both superficially, or one superficially and one deeply) (Table 2).

Deep perforation of MCB occurs when NMC passes through the MCB muscle body, forming both shorter and longer muscle tunnels in the MCB. In this situation, deep perforation of MCB can occur in its upper, middle or lower part, and therefore we distinguish high, medium and low perforation of the m. coracobrachialis (MCB). Deep perforation can also be found if another muscle is perforated instead of MCB (m. biceps brachii or m. brachialis), as well as in double perforation, when another muscle is perforated along with the MCB. According to our findings, perforation of MCB or some other muscle happens in 86% of cases (in 80% of these cases, we noted deep perforation, and in 6%, it was superficial).

b) Deep perforation forms of MCB

The high perforation of MCB by NMC occurs in 51% of cases in our material. In this case, NMC after separation from the LF perforates the MCB diagonally in its upper third, making a rather long muscular tunnel in the MCB muscle body. The point of entry of the nerve into the muscle is at the back of the muscle, while the point where the nerve exits the muscle is usually on its front. We noted that in case of the high perforation of MCB, the muscle tunnel is the longest, because the nerve passes through biggest part of the muscle mass of the MCB.

During this perforation, there is an incomplete but correct division of the muscle into two parts: the upper-outer part which is smaller and the lower-inner part is much larger, and the boundary between represents the NMC itself in its muscular tunnel (Figs 1–4).

Medium to high perforation of MCB was observed in our material in 17% of cases and is second in frequency. In this form of perforation, NMC perforates the MCB in the middle third of its muscular mass, making the muscular tunnel of medium length. It is often encountered in low or medium high bifurcation of the lateral fasciculus (LF). The muscular tunnel is located in the middle of the MCB, and in it the NMC divides the muscle into two almost identical parts: the upper-outer and lower-inner part. Since the MCB muscle body in this part is rounded, the point of entry and the point of NMC exit are in the front area of the muscle.

Low perforation MCB was found in 7% of cases. There may be a low LF bifurcation, although it is not mandatory because it is also seen in high bifurcation LF. Perforation occurs in the lower third of the muscular body, which is at this height of spindle-like appearance, gradually narrowing into the ultimate tendon with attachment on the medial side or edge of humerus (tuberositas coracobrachialis). The muscle tunnel formed by passing of NMC through the lower third of the MCB is about the same direction as in the previous perforations, but it is significantly shorter in comparison to the high and middle perforation, due to the fact that at this point the muscle mass is significantly reduced since the muscle exceeds its final tendon. The point of entry and the point where the nerve comes out of the muscle is located on the inner and outer sides of the lower body of the muscle, where the NMC divides the muscle into two uneven parts: the upper-outer part and the much smaller lower-inner part.

Fig. 1 Slim RLNM and RMNM, NMC is thick and separates the medial diagonal anastomosis for NM, which becomes thicker. NMC perforates the MCB and gives 2 branches before perforating the MCB, NU is behind NM, visible at the bottom of the image.

Fig. 2 FL is clearly seen, with NMC that perforates MCB, and short RLNM. We detect RMNM, which is longer than RLNM, part of FM and NU. Fine thin upper diagonal anastomosis between NMC and NM.

Fig. 3 FL is less visible and FM well detectable, classical appearance of NM. In the lower part, the presence of long thin anastomosis between NU and NCAM.

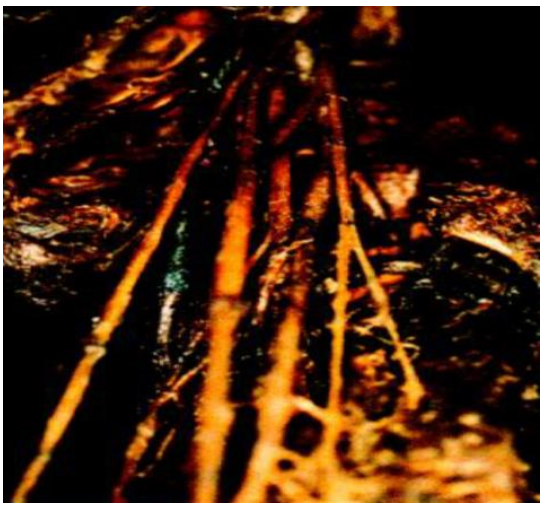

Fig. 4 High origin point of NM and well expressed anastomosis (NMC-NM) below. NMC does not perforate MCB and gives a branch for MCB and MBB.

Perforation of another muscle instead of MCB was found in 3% of cases, of which the 2 perforations were of the short head of the biceps (2%) and 1 case of m. brachialis perforation (1%). In two cases of caput breve musculi bicipitis brachii, we found the usual division of LF, and the perforation was performed in the upper third of the short head of muscle in the first case, and in the second case in the middle third of the short biceps head. After passing through short head of m. biceps, in both cases the NMC was superficial and subcutaneous, and after crossing the long head, it went along the sulcus bicipitalis lateralis and continued its usual path. The length of the muscular tunnel in the short head in the first case was 3.7cm and in the second case 2.8cm. In the case of perforation of m. brachialis, NMC, after its usual occurrence, went along the inner edge of the MCB, and in the lower third of this muscle, its direction goes diagonally and laterally, between m. biceps and m. brachialis, deeply involving the second muscle, creating a 3.2cm long muscle tunnel. It then goes into the outer bicipital groove from where it continues its usual path, to the epicondylus lateralis, where it gives the final branch - nervus cutaneus antebrachii lateralis.

Double perforation or perforation of two muscles with the same nerve, in our material, was documented in 2% of cases. In both cases, NMC had a usual origin, with high MCB perforation. Upon leaving the MCB, the NMC kept the deep side of the long biceps head in a length of 3.2cm, while in the second case, diagonally perforated both short and long head in length of 4.3 cm. After entering the sulcus bicipitalis lateralis, both nerves continued the usual pathway for the NMC, with the separation of the small lateral and well-defined terminal branches of this nerve.

c) Superficial perforation of MCB by NMC

This phenomenon is noticed in 6% of our material, although it is rarely mentioned in the professional literature. This relatively significant percentage observed in our preparation material is a consequence of careful preparation material, since the fibers of MCB that cover NMC are small and thin and easily ruptured by harsh and inadequate dissection technique.

Unlike other authors, we consider that the superficial perforation can be observed in the lower, as well as in the middle and upper thirds of the MCB. Moreover, we have found it 4 times in the lower third, 2 times in the middle and 1 time in the upper third of the MCB.

In this case, the muscular tunnels are very short, and we can call them muscle bridges over the NMC, and their length range goes from 0.4 to 0.9 cm.

In the literature, it is also described the double superficial perforations (MCB with MBB or MB) or perforation of any other muscle without MCB perforation. We have not observed such cases in our study.

d) Variations in the distribution of lateral branches of NMC

During the dissection, we observed and recorded the way of formation and morphological variations of lateral branches of the NMC.

We focused on the following lateral branches of NMC: ramus vascularis, ramus articularis, ramus osseus, nervus musculi coracobrachialis superior, nervus musculi coracobrachialis inferior, nervus musculi brachialis and nervus musculi bicipitis brachii.

Ramus vascularis, a non-permanent branch, was observed in 7% of cases. It is usually separated from the supramuscular segment of NMC, after division from the LF or before entering the MCB. It innervates the walls of the following blood vessels in the form of a network of fine thin branches, followed by: a. circumflexa humeri anterior, vv. circumflexae humeri anteriores, a. circumflexa humeri posterior, vv. circumflexae humeri posteriores.

Ramus articularis**,** a non-permanent branch, occurs in 9% of cases. It usually separates from NMB in 6% of cases, or from extramuscular part of NMC in 3% of cases. One or more branches lead to the articular capsule of the elbow (articulatio cubiti).

Ramus osseus, a non-permanent branch, is found in 17% of cases. It is separated from the intramuscular segment of NMC (10%) or from the extramuscular segment of NMC (7%). This nerve follows a. nutritia humeri and together they enter the foramen nutritium on humerus.

Nervus musculi coracobrachialis superior is constant branch but highly variable. It occurs from the supramuscular part of the NMC (81%), from the external root of n. medianus (RLNM) (3%), from the FL (11%) or from FNS (FL with RMNM) (5% of cases).

Nervus musculi coracobrachialis inferior is a constant branch that was observed in 90% of the cases as the branch of the lower part of the truncus of NMC, and in 10% of cases as the branch of the fused nerve truncus (LF plus RMNM).

Nervus musculi brachialis is a constant, voluminous branch, the second thickest branch, which separates usually in the intramuscular segment of NMC, below the biceps branch (80%) or in the upper part of the tunnel (20%).

Nervus musculi bicipitis brachii is a constant, thickest branch of the NMC. It separates in the center of the tunnel from NMC, by a unique truncus, in 75% of cases. This truncus is later divided into nervus capitis brevis musculi bicipitis brachii and nervus capitis longi musculi bicipitis brachii. In 5% of cases, both nerves start separately from the NMC, at the beginning of the tunnel, and in 10% of cases also separately, at the end of the muscle tunnel.

2. Radix lateralis nervi mediani (RLNM)

The lateral root of n.medianus, after separation from the FL, descends diagonally downward and inward, to connect at the front side of a. axillaris with the medial root of n. medianus, whereby forming the central nerve of the arm - n. medianus.

The shape of the nerve at the cross-section of the nervous truncus is regular and round in the upper part, while in the lower part it remains flat, due to the pressure of the nerve on the wall of a. axillaris. Concerning its thickness, it is sometimes very thin, and in these cases usually there is an anastomosis just below it, which enhances the lateral root of n. medianus.

Some anatomists tend to refer to RLNM and anastomosis beneath it as a double or separated lateral root of n. medianus. However, it was definitely established that this is a high upper-internal anastomosis between NMC and NM in 5% of cases.

In terms of the length of this root, we noticed that there is a great variability. According to our measurements, the minimum length of the RLNM is 9mm, the middle root length is 3.4cm and the maximum value is 13.5cm. In the last case, RMNM is even longer, due to a very low start position of n. medianus.

In 13% of cases, there is no RLNM in our material, as there was no division of FL, but the entire FL was merged with RMNM and formed a fused thick nervous truncus. It essentially contains NMC, RLNM and RMNM.

Regarding the distribution of lateral branches, RLNM is very poor. Thus, as already mentioned, it has been observed that in 3% of the cases, RLNM provides

the upper branch nerve to m.coracobrachialis (nervus musculi coracobrachialis superior).

In one preparation material only, we observed an extremely rare case in which RLNM provides the root or branch for n.ulnaris (1% of cases). The root is quite voluminous, and it significantly enhances the diameter of ulnar nerve. A similar case was not found in the professional literature published over the last 10 years, although we are familiar with the great morphological variability of the terminal branches of plexus brachialis, including its various anastomoses.

In our materials we also measured the angle of bifurcation of the LF, the angle of junction of roots of n.medianus, as well as the angle of bifurcation of the MF, since these angles are in mutual correlation.

Discussion

Analyzing the previously published research results, our findings can be compared with the results of other authors.

Terminal branches of LF in 87% of cases derive from bifurcation of LF to NMC and RLNM, while in 13% of cases they occur from the fused nervous truncus. High LF bifurcation is noted in 18% of cases, medium high in 61% and low bifurcation in 8% of cases. The results of some researches [19–20] show that in 89% terminal branches of LF appear from bifurcation to NMC and RLNM, while in 11% of cases they appear from the fused nervous truncus. The distance from the anterior edge of the clavicular bone to the point of bifurcation of LF, amounts to an average 4.2cm, and the extreme values are 0,5cm and 0.7cm, which correlates with intraoperative findings [21].

Nervus musculocutaneus (NMC**)** in 86% of cases perforates MCB, and therefore, this muscle deserves the name of musculus perforates, given by Casserius back in the 16th century. In 14% of cases, NMC does not perforate MCB, but follows the internal edge of the MCB, after which it continues its usual path. In 13% of cases, in reports, NMC does not perforate the MCB, but follows the anterior edge of the MCB [12,20,21,22]. Out of 86% of the cases when NMC perforates MCB, in 51% of cases there is high MCB perforation by NMC and in 17% of cases - a medium high perforation, and in 7% of cases – a low perforation. In 3% of cases, there is perforation of another muscle instead of MCB (MBB, MB), while in 2% of cases, there is perforation of 2 muscles with the same nerve (double perforation). The described cases of perforation (89%) belong to the deep perforation type, while in 6% of cases, a type of superficial perforation is noticed (when the muscle was affected superficially), which is 86% in total. This research is in correlation to other authors' research [12,18,23–26].

In the case of MCB perforations, the NMC with the humerus axis forms the angle of perforation. The average value of this angle at high bifurcations is 16^0 (min.10^0, max. 18^0), at a medium high 21^0 (min. 19^0, max. 26^0) and at low bifurcations 39^0 (min. 33^0, max. 45^0). In superficial perforations, the angle becomes sharp again and amounts to an average 9^0 (min. 6^0, max. 11^0). In available literature, we have not found the related data to compare with our results.

Due to the perforation of MCB by NMC, a muscle tunnel is formed, in which the intramuscular segment of the NMC is located and wrapped with connective tissue. The average length of the tunnel is 3.4cm, minimum 4mm for superficial perforations, and maximum 11cm. In 83% of cases, the tunnel is simple and in the form of tubes, while in 3% of cases, it also contains one or two accessory anastomosis muscle tunnels.

On the histological material of the muscular tunnel, the NMC is seen transversally cut, centrally positioned, with clear fascicular structures and sheaths, with the presence of a large number of epi- and peri-neural blood vessels. The layer of loose connective tissue comes next, protects the nerve from injury and allows easier sliding movement through the tunnel, in different movements in the shoulder and elbow joint. Behind it is a layer of transverse muscle fibers, which form the tunnel walls.

In terms of the distribution of lateral branches of NMC, we noted the following: ramus vascularis (7%), ramus osseus (17%) and rami articularis (9% of cases), with different variation of genesis. We also distinguished four constant branches: n. MCB superior, n. MCB inferior, n. musculi brachialis and n. musculi bicipitis brachii, with great variability of their origin. The same conclusions were made in other researches [6,9,11,13,27–31].

Radix lateralis nervi mediani (RLNM) does not show many morphological variations. The average root length is 3.4cm, maximum 13.5cm and minimum 9mm.

In 13% of cases, RLNM does not exist because FL has merged with RMNM and formed a fused nerve truncus, while in 5% of cases there is a double RLNM, which is in fact a high upper anastomosis between NMC and NM. In 3% of the RLNM dissected material, there is a upper branch for MCB (n. MCB superior), and in an extremely rare case (1%) it gives the anastomotic branch for the elbow nerve (n.ulnaris). In some researches, the results have showed that in 14% of cases RLNM does not exist, due to the fusion and formed fused truncus [13,16–18,32].

Conclusion

The origin of terminal branches of lateral fasciculus in our prepared material was always the same. These branches were usually formed by bifurcation or diverging of lateral fasciculus to radix lateralis nervi mediani and n. musculocutaneus. Exceptionally, fusing the lateral fasciculus with medial root of n. medianus, there is no bifurcation, and the formed nervous truncus is a result of existence of the pre- or postfixational type of brachial plexus.

During the surgical interventions in axillar and upper arm area, or postoperative, the transitory paralysis of some terminal branches of brachial plexus are described, including transitory paralysis of n. medianus, n.

ulnaris and n. musculocutaneus. They occur due to the damage of wall and the rupture of arteries of these nerves (arteria nervi mediani, vasa nervi musculocutanei, vasa nervi ulnaris). Therefore, postoperative ischemia of nervous truncus automatically continues after paralysis. This paralysis is transitory, so as soon as the irrigation of the nerve is normalized, the paralysis vanishes.

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Original Article

PEER VIOLENCE AS PREDICTOR OF CYBERBULLYING AMONG ADOLESCENTS

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Abstract. *The aim of this cross-sectional study was to examine individual, familial and peer variables as predictors of cyberbullying in early adolescence. The research included (N = 226) male students from Valjevo, aged 15.56 (SD = 0.68). The following measuring instruments were used: Socio-demographic Questionnaire, Violence Among School Children Questionnaire, Parent Behavior Questionnaire. The internal consistency of the questionnaire was examined using Cronbach's alpha coefficient. The results of correlation analysis have shown minute and statistically significant correlation between the scores of applied variables. Hierarchical regression model has explained 36% of the variance of traditional peer violence and 10% of cyberbullying. All the examined variables have proven to be statistically significant predictors of traditional peer violence, but not cyberbullying. Seeing that the predictor variables of traditional peer violence partly explain cyberbullying, it is necessary to examine other potential determinants such as frequency of use of electronic media, electronic victimization and others, which would contribute to the prediction of the examined criterion. The applied questionnaires are of optimal use in everyday practice in Serbia and can provide relevant information in evaluating traditional peer violence and cyberbullying among preadolescents.*

Key words: *violence, individual variables, parent behavior, peer variables*.

Introduction

Traditional peer violence most often occurs in real world (in school or school environment). It includes various forms of violent behavior which an enforcer inflicts on a victim. Even with the fact that this phenomenon is often explored [1–3], its content and scope are still insufficiently explored. Depending on the method of introducing violence among peers, the students discern three categories: a) bullies – students who enforce violence exclusively on peers, b) victims – students who only experience violent behavior, and c) provocative victims – students who both enforce and experience violent behavior. Direct violence – teasing, hitting or intimidating, and indirect violence – exclusion, gossiping or scheming, represent the basic forms of traditional peer violence [4,5]. Besides, there is a distinction between physical and verbal violence, relational or emotional/mental, or sexual and economic violence [6].

In the last decade of the XXI century there has been a rise in *cyberbullying*, which is realized in the unreal world: the Internet, mobile phones [7,8,9]. It is enforced via electronic communication, for example e-mail, SMS and social networks (Facebook, Twitter, internet forums and such), where the bully can remain anonymous and hide behind temporary internet addresses, nicks or unknown mobile phone number [10,11]. Unlike traditional peer violence which is usually enforced within one class or school, cyber-bullying among peers can involve significant number of children: from other towns and countries [12–14]. In addition, it includes written, visual message which remains permanently on the Internet and can harass victim over and over again on the daily basis, whereas traditional peer violence (verbal abuse and teasing) comes and goes, often without eyewitnesses [15].

Therefore, cyberbullying is filled with fear since the characteristic personality traits of the bully are hidden, and violence can be enforced any time and any place [16]. Also, statistically significant correlation between enforcing traditional violence and cyberbullying has been found, and large number of traditional bullies enforce cyberbullying as well, that is to say the same student bully in various circumstances.

Peer violence is conditioned by the methods and conception of measuring violence among children [17–19]. The studies [20] have shown that the prevalence of traditional violence among school population is minimal for bullies and victims if it is required of a preadolescent to name a peer, while it is identical in self-determining the frequency of violent behavior among peers. Foreign studies on traditional peer violence among children between ages 10 to 15 indicate 10-30% of victimization, and 3-26% of violence [21]. The research on traditional violence and cyberbullying among peers include one latent dimension (peer violence), which in its basis has the same individual,

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familial and peer predictors. The study on *individual factors* – gender and age [22], points to the fact that boys, more so than girls, are physically and verbally more violent. On the other hand, in exploring cyber-bullying [23] there were no statistically significant gender differences to be found, while the research has revealed that in all forms of traditional violence and cyber-bullying the bullies were usually older students. The research has shown that, apart from gender and age, modest school success is a risk determinant of traditional violent and aggressive behavior among preadolescents, where bullies follow school's house rules, have bad communication with teachers, bad grades, and a large number of unexcused absences [24].

Familial factors have dominant function in developing traditional violence, where the respectful parenting style has proven to be a dominant determinant of traditional peer violence [25]. The deficiency of parental love, especially during childhood, probably generates future violent behavior [26]. Violent children are most often the ones who live with parents who are emotionally cold, distant and depressed [27]. Preadolescents – traditional bullies live in families where parents often punish them, threaten and use force in order to discipline [28]. It these types of families, children learn that violence is an appropriate method of conflict resolution with peers. Statistically significant predictors of aggressive and violent behavior among children are: authoritarian parenting style, lack of parental control, strict discipline, unprincipled methods of upbringing, parental differences and parents' insufficient involvement in child's life. Exposing oneself to danger is manifested when parents are not competent enough to define the implicit scope of violent behavior towards peers, siblings and adults, meaning when they are too complaisant towards aggressive behavior [29]. Cyberbullies grow up in families with no parental control and love, where strict discipline and punishment is enforced, which proves that authoritarian parental style is a significant predictor of cyberbullying.

Peer factors (number of friends and peer acceptance) represent consequential predictors of traditional peer violence [30]. The children who use force are not socially isolated, they have friends of the same number and behavior which they imitate. Peer unacceptance is the quality determinant of traditional peer violence [31], where students who feel rejected draw attention to themselves in order to acquire certain position within the peer group. The same tendency is found in cyberbullying, where peer rejection represents a reliable factor of cyberbullying [32].

Current studies precisely define the traditional victimization as the quality predictor of traditional peer violence [28] and cyberbullying [33]. When it comes to traditional violence in the older age groups, victims of violence find themselves in the position where they are no longer the weakest and where they have an opportunity to demonstrate their superiority over younger students and thus relieve themselves of stress over the experienced violence. For preadolescents who cannot demonstrate their superiority in school, electronic – unreal world, where they can be shielded from danger, becomes a parallel world where they can be superior and use violence.

The main *aim of this research* was to examine the perceived contribution of individual (age, gender and school success), familial (parental punishment, parental love, parental control and parental tolerance) and peer predictors (number of friends, peer acceptance, earlier traditional victimization) in explaining cyberbullying among adolescents. Keeping in mind that cyberbullying is a form of peer violence, the *presupposition* is that the examined individual, familial and peer variable will statistically significantly predict traditional violence and cyberbullying in early adolescence.

The Method

Participants and procedure

This transversal research was conducted in September 2017 on the participant sample (N = 226) of VIII grade elementary school students of "Vladika Nikolaj Velimirović", "Desanka Maksimović" and "Milovan Glišić" in Valjevo. The average age of participants was 15.56 (SD = 0.68).

The research was conducted in accordance with the Declaration of Helsinki, where the school principals and parents gave formal consent to students' participation in the research. The empirical data was obtained anonymously and voluntarily during regular classes. The size of the group varied from 20 to 30 participants. At the start of the examination, the students were told that the results would be used exclusively for research purposes. Using pen and paper, they were shown the example of the solved task, after which they were asked to cooperate and answer truthfully. They could have quit the testing any time they wished, without any consequences. It took them approximately 40 minutes to complete the task.

Predictor of socio-demographic variables

Before beginning the testing on the questionnaire specially designed for the needs of this research, demographic data on participants' age, gender and school success were collected and it formed the basis for answer distribution of arithmetic mean of all six scores (grade point average, mother tongue grade and mathematics grade at the end of the first semester and at the end of the previous school year). The reliability of internal consistency (*Cronbach's alpha*) of school success in this research is high and it was (α = 0.86). Besides, data on peer acceptance (two items on a three-point Likert scale (1 – never, 2 – sometimes, 3 – often)) were collected using special form, where a participant self-evaluated personal feelings about peer acceptance or rejection, as well as the number of his/her best friends.

Violence Among School Children Questionnaire [34]. It examines the frequency of committed violent acts in school and victimization, and it consists of two scales, Violence among children scale and Victimization scale, with 19 items each:

- *Violence among children scale* – it measures the frequency of violent acts committed against peers (it includes two subscales: physical violence and verbal violence, which represents traditional peer violence and cyber-bullying),
- *Victimization scale* – it measures the frequency of violence experienced in school, and it includes two subscales: physical victimization and verbal victimization, which link traditional and cyber-victimization. The participant is tasked with making an "X" next to the frequency of each individual perceived form of violence on a 5-point Likert scale (1 = never, 2 = rarely-few times a year, 3 = sometimes-once a month, 4 = often-few times a month and 5 = always-almost daily).

The results for every subscale are represented as mean value of answers on the measured subscales, where the higher score means more frequent act or experience of violence. Based on self-evaluation, the participants are classified in four categories: traditional bullies, cyberbullies, victims of violence and provocative victims.

Traditional bully is a participant who, at least on the one item of verbal or physical violence (traditional violence) subscale, circled that he/she displayed the described behavior "always (almost daily)" or "often (few times a month)". The category *cyberbully* consists of participants who at least once circled, on the items of cyberbullying subscale, that they experience the described behavior "always (almost daily)" or "often (few times a month)". The category *victims of violence* consists of participants who at least on the one item of the given scale marked that they experience the described behavior "always" or "often". The category *provocative victims* consists of participants who at least on the one item of the given violence and victimization subscales, marked that they experience the described behavior "always (almost daily)" or "often (few times a month)". The reliability of internal consistency is high [35]: for Violence among children scale and its subscales it is from .75 to .88, and for Victimization scale and its subscales it is from 0.73 to 0.90.

Parent Behavior Questionnaire (URP-29 [36]). It examines behavior of parents towards their child and it consists of seven scales (29 items). Four scales (16 items) were used in this research: parental warmth (4 items), control (4 items), leniency (3 items) and punishment (5 items). The participant had the task to evaluate the two identical questionnaires (one pertains to mother, the other to father) on a 4-point Likert scale, to which extent the described behaviors relate to characteristic behavior of their mother and father (1 = completely untrue, 2 = not exactly true, 3 = quite true, 4 = completely true). The result for each subscale is shown as mean value of the answers to all items of subscale (subscale refers which pertains mother and subscale that pertains father, or subscale of the results from both subscales combined). The reliability of internal consistency (Cronbach alpha) is from 0.84 to 0.90.

Data processing

Statistical data analysis contained many methods of descriptive statistics (sample minimum, sample maximum, arithmetic mean, measures of variability – standard deviation, asymmetric distribution coefficient – skewness and skewness coefficient – heavy-tailed or light-tailed data – kurtosis), Pearson correlation coefficient and hierarchical regression analysis. The level of statistical significance was $p < .05$. Statistical data processing was conducted using SPSS software (*Statistical Package for the Social Science*), version 17.0.

Results

Table 1 shows the presence of two forms of violence: traditional violence and cyberbullying. It is clear that in this sample of adolescents there are significantly more students who self-evaluated that they belong more in the group of problems with traditional violence than cyberbullying.

Table 2 shows descriptive indicators of participants for individual item variables of scales and subscale, Violence among school children questionnaire and subscale, Parent behavior questionnaire, as well as the indicators of normal distribution of skewness and kurtosis. The obtained measures of distribution of asymmetric coefficient range from ±3, distribution of homogeneity ±10, which is proven by Gaussian law of normal distribution, or justified by use of parametric process of statistical data processing [37].

Table 3 shows the value of parametric Pearson correlation coefficient of the examined variables, which examines the level of linear correlation between traditional violence and cyber-bullying.

The results of correlation analysis point to minor to statistically significant correlations between the examined variables from r=.01 to .52, which, from the statistical viewpoint, enables the conducting of hierarchical linear regression analysis [38].

Table 1 Representation of various forms of violence

Function in violence	Traditional violence		Cyberbullying	
	f	%	*f*	%
Bystanders	113	50.00	203	89.82
Victims	75	33.18	11	4.86
Provocative victims	26	11.50	2	.88
Bullies	12	5.30	10	4.42

Table 2 Score distribution of the variables traditional violence and cyberbullying

Variable	Min	Max	AM	SD	Sk	Ku
Traditional violence	1.00	3.90	1.38	.43	.52	.19
Cyber-bullying	1	3.45	.99	.17	.71	1.06
School success	1.22	4.94	3.81	.95	.55	-98
Parental punishment	1	4	2.06	.58	.91	.27
Parental warmth	1	4	3.62	.47	.33	.45
Parental control	1	4	3.23	.59	.26	1.05
Parental leniency	1	4	2.37	.70	.44	.83
Number of friends	0	19	4.26	3.46	.61	.54
Peer acceptance	.95	2.96	2.55	.52	.88	.37
Peer victimization	1	4.42	1.77	.60	.57	.69

Annotation: AM = arithmetic mean, SD = standard deviation, Min = sample minimum, Max = sample maximum, Sk = skewness, Ku = kurtosis, the value of standard error of Sk is .09,and of Ku is .15.

With the aim of examining individual contribution of nine predictor variables in predicting the criterion – traditional peer violence and cyber-bullying, two hierarchical regression analyses were applied through two steps (Table 4 and Table 5).

Three predictors (age, gender and school success) introduced in the first regression model reveal individual characteristics of adolescents and directly influence their actions. In the second model, there are four predictors (parental punishment, parental warmth, parental control and parental leniency) which show direct familial environment of participants. The third regression model three predictor variables (number of friends, peer acceptance and traditional peer violence) were introduced, and they imply peer correlation.

The intensity of all three input predictors on the criterion traditional peer violence is the following: male *gender* (β=.19; $p<.05$), *age* (β=.17; $p<.05$), modest *school success* (β=-.13; $p=.05$), while these three individual predictor variables have no statistically relevant predictive contribution.

The prediction of cyberbullying based on the group of predictors of four familial variables is most intensely represented by *parental punishment* (β=.18; $p<.05$) and *parental leniency* (β=.14; $p<.05$), while all familial variables statistically significantly predict traditional peer violence (from β=.13 to β=.32). It is interesting that the values of standardized beta coefficient of both variables

Table 4 The results of hierarchical regression analysis for predicting traditional peer violence

Predictors	1. step (model)	β	2. step (model)	β	3. step (model)	β
Age	.17*		.15*		.14*	
Gender	.19*		.17*		.15	
School success	.05		-.14*		-.13*	
Parental punishment			.24**		.19*	
Parental warmth			-.08		.13*	
Parental control			.29**		.32**	
Parental leniency			.14*		.16*	
Number of friends					.13*	
Peer acceptance					-.23*	
Early traditional peer victimization					.53*	
R	.22		.41		.60	
R^2	.03		.20		.36	
ΔF	10.20**		21.45**		40.62**	

Legend. β =The value of standardized regression coefficient; *R*=multiple correlation coefficient; R^2=coefficient of determination (total contribution of predictors to explained variance); Δ*F*=the change of F relations after certain groups of predictors have been introduced. *$p<.05$, **$p<.01$.

Table 5 The results of hierarchical regression analyses of predicting cyberbullying

Predictors	1. step (model)	β	2. step (model)	β	3. step (model)	β
Age	.03		.01		.08	
Gender	-01		.04			
School success	-.05		-.02		-.07	
Parental punishment			.14*		.18*	
Parental warmth			-.03		-.06	
Parental control			-.08		-.04	
Parental leniency			.09		.14*	
Number of friends					.13*	
Peer acceptance					.15*	
Early traditional peer victimization					.30**	
R	.10		.19		.28	
R^2	.03		.05		.10	
ΔF	3.12		10.84**		12.66**	

Legend. *β*=The value of standardized regression coefficient; *R*=multiple correlation coefficient; R^2= coefficient of determination (total contribution of predictors to explained variance); Δ*F*=the change of F relations after certain groups of predictors have been introduced; *$p<.05$, **$p<.01$.

Table 3 Intercorrelations between traditional violence and cyberbullying

Variables	$_v1$	$_v2$	$_v3$	$_v4$	$_v5$	$_v6$	$_v7$	$_v8$	$_v9$	$_v10$
Traditional peer violence ($_v1$)	-	.52	-.09	.20	.15	.27**	.14*	-.03	-.05	.53**
Cyber-bullying ($_v2$)		-	-.02	-.19*	-.08	.17*	.14*	.16*	-.01	.30**
School success ($_v3$)			-	-.17*	.20*	.19*	-.15*	.14*	.20**	.17*
Parental punishment ($_v4$)				-	.16*	.09	.04	-.01	.18*	-.24**
Parental warmth ($_v5$)					-	.48**	.16*	-.01	.20**	-.24**
Parental control ($_v6$)						-	-.01	-.07	.03	.20**
Parental leniency ($_v7$)							-	*.14**	*.02*	*.06*
Number of friends ($_v8$)								-	*.09*	*.01*
Peer acceptance ($_v9$)									-	*-.50*
Peer victimization ($_v10$)										-

*$p < .05$; **$p < .01$

of peer relations have shown statistical significance in explaining traditional peer violence and cyberbullying, where lower peer acceptance and number of friends more clearly determine both forms of violence. The best determinant of both forms of peer violence is earlier traditional victimization of adolescents.

Lastly, the final regression equation shows the entire model, all three analyzed groups of predictor variables, which accounted for 36% of the total criterion variance of traditional peer violence, and 10% of total variance on the scale of cyber-bullying. With that, the obtained significant beta coefficients of individual characteristics of students, their family environment and peer relations possess relatively good predictive validity, but clearly there are other unexplored factors which could be useful in acquiring more exact predictions of criterion variables.

Discussion and Conclusion

This study examines the partial contribution of individual, family and peer predictive variables in explaining traditional violence and cyberbullying during adolescence. Research results [19,39–42] have revealed statistical significance of individual variables in predicting traditional peer violence, while research results [39,43] have indicated that older male adolescents with modest school success are more prone to traditional peer violence, whereas individual characteristics of students were found to be statistically insignificant in predicting cyberbullying. Despite the fact that current research [44] has determined that unlike female adolescents, male adolescents are more often cyberbullies, the study has not proven these gender differences. This is likely because some items which were used to examine cyberbullying are more identical to verbal violence which is the part of traditional violence [45], and for which gender differentiation has not been determined in previous researches [46]. At the same time, the study [14,17,47] has revealed that older adolescents are more often prone to cyber-bullying, where that form of violence culminates at the end of elementary and start of high school. It is assumed that the aforementioned study did not include the highest domain of cyberbullying, since the participants were elementary school students. Even though the findings of the current study [48] revealed that preadolescents who are cyberbullying have moderate school success and more unexcused absences, it was not exactly determined whether that includes only the students, provocative victims or only victims. Bullies most often have many school absences [49–51]. The authors state that, based on their personality dimensions, cyberbullies are similar to relational bullies who possess sophisticated manipulation skills and therefore are not less intelligent or bad at school.

The anticipated family variables (more punishment, less parental warmth, less parental control and more parental leniency) revealed statistically significant predictability of traditional peer violence [48]. Also, it has been proven that only the variables (parental punishment and leniency) are statistically significant determinants of cyberbullying. The authors [52] have determined that strict discipline and punishment correlate with the frequency of cyberbullying. If the child cannot manifest its frustration in the objective environment because it fears parents' or teachers' punishment, and because of its bad status within a peer group where it doesn't have the option of being violent, that child will transfer its dissatisfaction to the unreal world, where it can get power and sense of security due to the anonymity of electronic means and thus be safe from punishment. Also, parental freedom proved to be a significant predictor of cyberbullying. In the research [53], it has been found that students who regularly cyberbully often have parents who do not know how to set the comprehensive rules of conduct. In both real and unreal world, such parents do not know how to set precise limits and rules, so their children do not perceive the consequences of bullying in the real world. That is why they do not have set rules on bullying in unreal world. Besides, parental control and warmth were not considered relevant for predicting cyberbullying [19]. It is possible that the variable of parental control, which includes precise information about how and where the child spends time, does not represent quality control which is fundamental for online activities which are directly related to the Internet or some social network. When it comes to cyberbullying, parental control should be directed towards child's time spent in front of the screen, meaning mobile phone and the Internet, as well as the content and activities which children partake in the unreal world, which this variable did not examine. Despite the fact that the study [30] determined that the deficiency of warmth and correlation with parents generates cyberbullying, this study did not confirm that. Perhaps, that could be explained by the minimum number of students who cyberbully in this research, as well as by the minimum variance which made this variable statistically insignificant. Seeing how this research did not include the highest level of cyberbullying (age and the most violent group of adolescents were not statistically significant determinants in the research), there is a possibility that this group of participants lacks parental warmth, which is very important in predicting cyberbullying.

The study [54] has pointed out that peer variables are significant for predicting traditional violence and cyberbullying, ant that significant determinants for both forms of violence were greater number of friends and the lack of peer acceptance. It is interesting that in the research [55] significant correlation between variables number of friends and cyberbullying has not been determined, which has been determined in this research. Greater number of friends a child spends time with and partakes in activities contribute its behavior. Violent students have friends who are also violent and who support violent behavior, so it is expected that they support cyberbullying as well [56]. Students feel the need to be part of a peer group and experience a sense of belonging, especially during the period of preadolescence. However, when that feeling is disrupted, there is a possibility that during preadolescence

a student will try in a violent manner to gain a satisfactory position within the peer group in order to be accepted [13]. If the student is unable to gain such position in the real world, for example in class, there is a possibility to transfer into the unreal world, and using cyberbullying create the desired unreal position, which then could be easily transferred into the real world – the classroom. Early recognition of the victim of traditional violence, victimized on purpose or not, represents a dominant predictor of traditional peer violence and cyberbullying, where in the unreal world adolescents have the opportunity to relieve the accumulated stress over bullying in school [11,44]. In the real world, for example in school, preadolescents who experience violence are more likely to become provocative victims, meaning the victims who act violently in order to banish the feeling of helplessness and accumulated dissatisfaction [1,57].

This research has shown that traditional violence can be interpreted better with individual, familial and peer predictor variables, while cyberbullying has smaller number of statistically significant predictors and relatively small percentage of the explained variability. The obtained findings suggest that cyberbullying should not be analyzed simply as another form of peer violence, but that it is necessary to examine the forms of cyberbullying and additional presupposed predictor variables which are most likely characteristic of this form of violence (for example the frequency of using mass media, electronic victimization, number of online friends, parental control over the use of internet and so on). It is most interesting to compare the number of friends a student has in the real world (for example in the classroom or sports club) and in the unreal world (active online friends), as well as the differentiated support adolescents get from friends in the real world and those with whom they communicate online, and their contribution in explaining peer violence.

While analyzing the obtained results of this research, it is important to keep in mind some of its methodological shortcomings. The participants of this research were elementary school seniors (VIII grade) who are the group of preadolescents who are expected to be on the highest level of bullying and being bullied, which limits generalization of other age groups. Also, the data was collected only using the method of self-evaluation. Besides, only the predictors of the two most present forms of traditional peer violence (verbal and physical) were used, and not other forms such as relational, economic and sexual violence, where some of them are statistically significant for predicting electronic violence. However, despite the aforementioned limitations, the obtained research data are a quality basis for new empirical research of traditional violence and cyberbullying during early adolescence.

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Original Article

CONTROL OF GLYCEMIA AND CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH TYPE 2 DIABETES IN PRIMARY CARE IN MONTENEGRO

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Abstract. *Some observational studies have shown that only a small number of diabetic patients achieve optimum control of glycaemia and cardiovascular risk factors. The aim of this study was to analyze whether patients with type 2 diabetes mellitus treated in primary care achieve adequate control of glycemic levels and cardiovascular risk factors. This was a retrospective, record-based, cross-sectional study that included eligible patients from 35 to 90 years old with type 2 diabetes mellitus treated in Primary Health Care Center in Podgorica. We investigated electronic records of 531 diabetic patients. The observed prevalence of type 2 diabetes mellitus among individuals between ages 35 and 90 years, was 11,84 %. Half of the patients were female. The mean age was 65,88±9,86 years. The mean value of HbA1c was 7,56±1,71. Fifty-nine percents of patients achieved optimal levels of HbA1c ≤ 7 %. Also, more than half of patients achieved target levels of blood pressure while 27.9% achieved LDL ≤ 2.6 mmol/L. Fifty percent of patients were non-smokers and 45.1 % were obese. Among patients on primary prevention only 5.7 % had met all target levels while on secondary prevention that number was even smaller 3.7 %. Our study showed that control of HbA1c and blood pressure was similar to other studies but reaching target levels of LDL was challenging for our patients. Further analysis are needed in order to discover the reasons for poor control of certain CVRF and to develop strategies for its optimal management.*

Key words: *diabetes mellitus type 2, management, risk factors, targets*.

Introduction

Diabetes mellitus is a serious, chronic disease with an overall estimated prevalence of 8.5 % in Europe [1]. More than 85% of diabetic patients suffer from type 2 diabetes mellitus (T2DM) which usually occurs later in life [2]. In 50 % of cases T2DM remains undiagnosed and untreated for some period of time leading to serious chronic complications at the time of diagnosis [3].

Cardiovascular disease (CVD) is one of the most important complications in diabetic patients that reduces the quality of life and causes premature death. Several studies have shown that the risk of developing CVD in diabetic patients is 2 to 3 times higher than in patients with normal blood glucose levels [4]. CVD is also the most prevalent cause of death in diabetic patients mostly due to an increased risk of stroke and myocardial infarction [5]. This represents a major public health burden, so prevention and the adequate treatment of this disease is a priority for health systems.

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The existence of national and international guidelines for the management of the patients with diabetes has eased the care for these patients and set the standards for their treatment. In 2017 American diabetes association (ADA) has issued the guidelines in which special emphasis is placed on the field of work of family physicians. They should have one of the most important roles in adequate caring for diabetic patients because adequate metabolic control and control of cardiovascular risk factors (CVRF) can prevent or slow down CVD in these patients [6]. Unfortunately, some observational studies have shown that there has been a discrepancy between official recommendations and everyday practice, and that only 7-14% of patients with diabetes achieve optimum control of CVRF [7,8].

The aim of this study was to analyze whether patients with T2DM treated in Primary Health Care Center in Podgorica achieve adequate control of glycemic levels and CVRF.

Subjects and Methods

This was a record-based cross-sectional study that included eligible patients with T2DM treated in Primary Health Care Center in Podgorica which is the main primary health care provider in Montenegro. According to the data that researchers got from National Health Insurance Fund, this

Primary Health Care Center operates with 119 444 insurance covered citizens aged 35 to 90 years and 14 144 of them have T2DM. They are all registered with a general practitioner/family doctor. We analyzed 531 electronic records of randomly selected patients who have been diagnosed with T2DM (International Classification of Diseases 10 [ICD-10] codes E11 and E14) before January 1 2016. For every patient we collected following data that have been recorded until the end of March 2017: age; sex; time since diagnosis; the presence of: retinopathy (ICD-10 codes E11.3 and H36.0); neuropathy (ICD-10 code G63.2); nephropathy (ICD code E11.21 or estimated glomerular filtration rate [GFR] with the MDRD [modification of diet in renal disease] formula [9] based on the most recent serum creatinine level recorded over the previous 15 months); coronary artery disease (ICD-10 codes I20, I21, I22, I23 and I24); stroke (ICD-10 codes I63, I64, G45 and G46), peripheral arterial vessel diseases (ICD-10 code I73.9) and chronic heart failure (ICD-10 code I50). We also collected data about glycemic control (the most recently recorded values of glycosylated hemoglobin [HbA1c] over the previous 15 months) and control of the CVRF - the most recently reported body mass index (BMI) over the previous 36 months; mean values of systolic (SBP) and diastolic blood pressure (DBP) over the previous 12 months; smoking status; the most recently recorded levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) over the previous 12 months.

In order to asses whether they have achieved control of glycemic levels and CVRF we used current ADA guidelines and European guidelines on cardiovascular disease prevention [6,10]. Target levels for glycemic control was HbA1c $\leq$ 7 % and for CVRF: BP $\leq$ 140/85, TC $\leq$ 5,0 mmol/L, TG $\leq$ 1,7, HDL $\geq$ 1,0 mmol/L for men and $\geq$ 1,2 mmol/L for women, LDL $\leq$ 2,6 mmol/L for primary prevention and $\leq$ 1,8 mmol/L for secondary prevention.

The approval of the local Ethics Committee was obtained.

Statistical analysis

Statistical version R 2.15.3 Software (R Foundation for Statistical Computing, Vienna, Austria) was used to perform the statistical analysis [11]. All data are presented as the arithmetic mean ± standard deviation or as absolute and relative numbers. We used Chi square test for comparison of categorical data according to sex. Continuous variables were compared with t test and Mann-Whitney test. The zero hypothesis was tested with a significance threshold $p<0.05$.

Results

The prevalence of T2DM among individuals between ages 35 and 90 years, was 11,84 %. Out of 531 patients whose records we investigated 50.5 % were female. The mean age of the patients was 65,88±9,86 years. The majority of them were between 60 and 69 years old. Table 1 shows clinical and laboratory characteristics of the study population. The mean value of HbA1c was 7,56±1,71 and there was no significant difference between men and women (p=0,445).

Women had higher levels of SBP compared to men (p=0.003). Smoking categories differed by gender (p<0.001), in the female population non-smokers were dominant. Women also had significantly higher levels of TC (p<0,001) as well as levels of HDL and LDL (p=0.010; p=0.013).

Table 1 Clinical and laboratory characteristic of the study population

Characteristics (n, %)	Total (n=531)	Men (n=263)	Women (n=268)	p
Age (years) †	65.88±9.86	64.79±10.27	66.95±9.41	0.012[1]
Age group				
35-39	5 (0.9)	3(1.1)	2(0.7)	0.662[2]
40-49	25(4.7)	16(6.1)	9(3.4)	
50-59	93(17.6)	53 (20.2)	40(15.0)	
60-69	222(42.0)	100(42.0)	112(41.9)	
70-79	139(26.3)	57(21.8)	82(30.7)	
80-89	45(8.5)	23(8.8)	22(8.2)	
Diabetes duration (≥8 years)	272(52.0)	127(49.0)	145(54.9)	0.421[2]
HbA1c (%)*	7.56±1.71	7.53±1.70	7.59±1,72	0.445[1]
Hypertension	456(85.9)	219(83.3)	237(88.4)	0.088[1]
Systolic blood pressure (mmHg)†	142.03±18.77	139.25±16.96	144.87±20.11	0.003[1]
Diastolic blood pressure (mmHg)†	84.23±9.51	83.88±9.26	84.59±9.78	0.457[1]
Smokers	87(32.8)	48(36.6)	39(29.1)	0.250[2]
Ex-smokers	45(17.0)	34(26.0)	11(8.2)	<0.001[2]
Body mass index (kg/m2) †	29.67±5.57	29.11±5.17	30.22±5.90	0.163[3]
Total cholesterol (μmol/L) †	5.60±1.46	5.29±1.21	5.89±1.62	<0.001[3]
Triglycerides (mmol/L) †	2.28±1.36	2.36±1.37	2.21±1.34	0.230[3]
HDL-cholesterol (mmol/L) †	1.20±0.46	1.14±0.44	1.27±0.47	0.010[3]
LDL-cholesterol (mmol/L) †	3.29±1.26	3.09±1.08	3.48±1.38	0.013[3]

[1]t test, [2] Chi-squared test, [3] Mann-Whitney test, † Mean± standard deviation, *Glycated haemoglobin.

Prevalence of micro and macroangiopathic complications is shown in Table 2. There were no significant differences in the prevalence of neuropathy, retinopathy and nephropathy between men and women (p=1.000; p=0,948; p=0.842) assessed by ICD code records. Taking into account levels of serum creatinine, number of patients with GFR between 30 and 89 mL/min is 60.8 %. Almost one third of patients had coronary artery disease and 18.1 % had heart attack or stroke. Heart attack was more frequently observed in male patients while there was no difference between men and women regarding stroke (p=0.046, p=0.455). Researchers got data also from National Health Insurance Fund about number of patients with history of acute myocardial infraction. Out of 14 144 patients 1629 had heart attack which is 11.52 % prevalence rate and in concordance with prevalence rate from our study sample (11.4 %).

Table 3 shows results of achieved treatment goals regarding glucoregulation and control of CVRF. Fifty-nine percent of patients achieved optimal levels of HbA1c (≤ 7 %). Target levels of SBP≤140 mmHg were more frequently attained by men (p=0.038), while there was not significant difference in attaining target DBP≤85 mmHg between men and women (p=0.646). Obesity was more frequent among women (p=0.025). Significant difference between men and women in achieving target lipid levels was seen only in achieving LDL≤1.8 mmol/L which was more frequently observed in male population (p=0.039). In patients on primary prevention only 5.7 % had met target levels of HbA1c≤7 %, BP≤140/85 mmHg and LDL≤2.6 mmol/L while on secondary prevention (HbA1c≤7 %, BP≤140/85 mmHg, LDL≤1.8 mmol/L) that number was even smaller 3.7 %.

Table 2 Prevalence of diabetes-related micro- and macroangiopathic complications, as assessed by ICD code records and laboratory data

Characteristics (n,%)	Total (n=531)	Men (n=263)	Women (n=268)	p[1]
Retinopathy	103 (19.6)	52 (19.9)	51 (19.3)	0.948
Neuropathy	171 (32.4)	85 (32.4)	86 (32.5)	1.000
Nephropathy	31 (5.8)	15 (5.7)	16 (5.8)	0.842
Creatinine μmol/L†	83.61±35.94	88.63±33.66	78.09±37.63	<0.001[2]
GFR[3] (mL/min/1.73m^2)†	76.91±21.21	79.17±19.93	74.43±22.34	0.137[2]
GFR < 30	10 (3.2)	3 (1.8)	7 (4.6)	0.213
30<GFR<60	64 (20.4)	27 (16.6)	37 (24.7)	0.263
GFR > 90	124 (39.2)	69 (41.6)	55 (36.7)	0.120
Coronary artery disease	158 (30.3)	79 (30.5)	79 (30.0)	0.887
Heart attack	59 (11.4)	37 (14.4)	22 (8.4)	0.046
Heart attack with revascularisation	34 (6.4)	22 (8.4)	12 (4.8)	0.098
Revascularisation without heart attack	25 (4.7)	9 (3.4)	16 (6.0)	0.237
Stroke	35 (6.7)	20 (7.7)	15 (5.7)	0.455
Peripheral artery disease	67 (12.8)	37 (14.3)	30 (11.4)	0.394
Chronic heart failure	50 (9.6)	26 (10.0)	24 (9.2)	0.848
At least one complication	322 (60.6)	163 (62.0)	159 (59.3)	0.592

[1] Chi-squared test, [2] Mann-Whitney test, † Mean ± standard deviation, [3] Glomerular filtration rate.

Table 3 Results of achieved treatment goals regarding glucoregulation and control of CVRF.

Characteristics†	Total	Men	Women	p[1]
HbA1c≤7% *	314 (59.1)	159(60.5)	155(57.8)	0.599
Systolic blood pressure ≤ 140 mmHg	172(57.6)	129 (62.9)	105(52.5)	0.038
Diastolic blood pressure ≤ 85 mmHg	258 (62.2)	133(64.9)	125(62.2)	0.646
Body mass index ≤ 30 kg/m^2	124 (54,9)	67 (63,2)	57 (47,5)	0.025
Non-smokers (%)	133 (50.2)	49 (37.4)	84 (62.7)	<0.001
Total cholesterol ≤ 5.0 μmol/L	154 (29.0)	86 (32.7)	68 (25.4)	0.078
Triglycerides ≤ 1.7 mmol/L	162 (30.5)	77(29.3)	85(31.7)	0.606
HDL-cholesterol ≥ 1 ≥1,2 mmol/L	121 (38.0)	58 (37.7)	63 (38.2)*	0.903
LDL-cholesterol < 1.8 mmol/L (n=330)	24(7.3)	17(10.6)	7(4.1)	0.039
LDL-cholesterol < 2.6 mmol/L	92(27.9)	49(53.3)	43(46.7)	0.402
Primary prevention: HbA1c≤7 %, blood pressure ≤ 140/85 mmHg, LDL-cholesterol ≤ 2.6 mmol/L	16 (5.7)	9 (6.5)	7 (4.8)	0.719
Secondary prevention: HbA1c≤7 %, Blood pressure ≤ 140/85 mmHg, LDL-cholesterol ≤ 1.8 mmol/L	5 (3.7)	3 (4.3)	2 (3.1)	0.699

† count (%), [1] Chi-squared test, * Glycated haemoglobin.

Discussion

According to the report of the International Diabetes Federation (IDF) prevalence of diabetes in Montenegro for the age group from 20 to 79 years for 2017 is 12.8 %. Majority of them suffer from T2DM [12]. These data place Montenegro among countries with the highest prevalence rates in Europe. Our estimated prevalence for Podgorica, which is the capital of Montenegro, is similar. IDF also reports that diabetes prevalence is slightly higher in men than women and that age group 65-79 years has the highest prevalence of diabetes [12]. We also got similar data for gender and age distribution. For half of the patients, disease duration could not be estimated precisely because electronic records have been introduced since 2009. So, we couldn't conclude whether these patients had diabetes before 2009 and for how long.

Electronic records were also a good tool to evaluate the percent of diabetic patients with hypertension which is the common comorbid condition. Many observational studies in Europe have reported similar hypertension rates in patients with T2DM (above 75 %) [13]. Hypertension in patients with T2DM quadruple CV risk and BP measured in office is good predictor of CV morbidity and mortality [14,15]. Therefore, ADA recommends that BP should be measured in diabetic patients routinely at every visit [6]. Mean values of SBP and DBP were slightly higher than in a methodologically similar study conducted in Spain [7]. Data about BMI and smoking habit were also similar like in Spanish study where women had significantly higher values of BMI (30.5±5.6 kg/m^2 women vs 28.8±4.3 kg/m^2 men, $p<0.005$) and percent of smokers was higher among men (24% of men vs 6.0 % of women, $p<0.005$). Mean values of serum lipid levels in our study pointed to already known characteristic features of diabetic dyslipidemia. This includes high levels of plasma TG, low levels of HDL and increased concentration of LDL [16]. Elevated LDL levels represent independent risk factor for CVD and major target for its prevention. According to meta-analysis that included data from 18 686 diabetic patients reduction of LDL per 1 mmol/L resulted in 9 % reduction of all cause mortality [17]. Framingham Study showed that there was no significant difference in the prevalence of elevated LDL levels among diabetic and non-diabetic individuals, but other studies showed that there was gender difference in diabetic patients regarding lipid levels. Russo et al. conducted a large Italian study in which diabetic female patients had significantly higher levels of TC, HDL and LDL than male patients ($p<0.000$) [18]. Our study showed the same results regarding gender-related differences.

Mean level of HbA1c from our study was also comparable to that from other study whose objective was to asses prescribing trends and glycemic control in patients with T2DM in Catalonia (Spain) during 2007-2013. In this study, the level of HbA1c was around 7.2 % with no significant difference across years suggesting that suboptimal glycemic control is a common problem [19]. We found that more than a half of our patients achieved target levels of HbA1c ≤ 7 % (59.1 %) which is a good result compared to other countries where the percentage of patients who were not at target varied from 26 % in the Netherlands up to 52 % in Turkey [20]. Maintaining good glycemic control is very important because it reduces the risk of developing microvascular and macrovascular complications [21].

In current study, diabetic neuropathy was the most commonly reported among microvascular complications, while other studies suggest that diabetic retinopathy may be the most common microvascular complication with prevalence rates ranging from 25-40 % [22,23]. This may be explained by an inadequate diagnosis being entered into the medical records due to a lack of time, poor doctor-patient communication, etc. For the same reason, the number of patients with reported nephropathy is only 5.8% while the number of patients with impaired renal function and GFR≤60 ml/min/1.73m^2 is 23.7% which is similar to the Spanish study (20 %) [7]. Data about macrovascular complications were more accurately entered in the medical records because the only way for patient to get certain medicines was to have adequate diagnosis on the recipe. Coronary heart disease was seen in almost one third of patients which is higher percentage compared to other European studies whose results varied from 11.3 % to 16.2% [7,24]. One of these studies was big Italian multicenter cohort study which enrolled 19 468 patients with the aim to estimate the prevalence of coronary heart disease. The percentage of patients with heart attack (4.5 % of males vs 2.0 % of females, $p<0.0001$) was lower from that observed in our study (14.4 % of males vs 8.4 % of females, $p=0.046$).

The reason for higher percentage of coronary heart disease in our study could be poor control of cardiovascular risk factors. We found that glycemic control, as well as control of blood pressure did not differ much from other studies whereas lipid control was harder to achieve. In other studies the number of patients who achieved target LDL ≤ 1.8 mmol/L varied from 37.9 % to 56.2 %, while more than two thirds (72.4 %) achieved LDL ≤ 2.6 mmol/L [7,25]. According to National Health and Nutrition Examination Survey data from 2007–2010, 18.8 % of diabetic patients achieved all three goals, while in the Spanish study that number was 25 % [7,26]. Disappointingly, a small proportion of patients in our study met all three goals in primary (5.7 %) and in secondary prevention (3.7 %). Some of the reasons for inadequate treatment of dyslipidemia could lie with reluctance among physicians to intensify treatment and with patients not complying with the regimen because they have to pay for some of the drugs (statins). Concerning the fact that LDL plays a central role in the pathogenesis of CVD, more aggressive control of this modifiable risk factor is needed alone, as well as in combination with glycemic and blood pressure control.

Our study has several strengths and limitations. To the best of authors' knowledge this is the first study

that investigates control of glycaemia and CVRF in patients with T2DM in Montenegro. Another important strength derives from inclusion of data from primary care database that are closer to the real-life than data from randomized clinical trials which have strictly controlled conditions. Retrospective design and incomplete medical records represent main limitations. That is why some of the diabetes-related complications (microvascular complications) were underreported and its real prevalence could not be estimated.

Conclusion

Our study showed high prevalence of T2DM in Montenegro. This represents significant burden for our health care system especially due to the large number of complications that diabetes carries with itself. Good control of the disease can prevent many of these complications but according to a large number of studies this still remains a challenge. In the current study the number of diabetic patients with coronary heart disease was higher compared to other European studies. Also, control of HbA1c and blood pressure was similar to other studies but reaching target levels of LDL was challenging for our patients. Further analyses are needed in order to discover the reasons for poor control of certain CVRF and to develop strategies for its optimal management.

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Case Report

GIANT COLONIC POLYPS IN PEDIATRIC PATIENT WITH FAMILIAL ADENOMATOUS POLYPOSIS

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Abstract. *This article describes a 16-year-old girl with signs of malnutrition, rectal bleeding, hypoalbuminemia and anemia. At the age of 6 months she was operated on for hepatoblastoma. Last two years she has been followed by endocrinologist because of amenorrhea. Her family history was unremarkable. Esophagogastroduodenoscopy revealed multiple small gastric polyps. Colonoscopy showed a few polyps in rectum and hundreds of them (3-25 mm in diameter) in sigmoid and descending colon. Giant colonic polyps at splenic flexure region prevented further passage of the scope. The diagnosis of FAP was established based on the endoscopy and pathology of colonic polyps removed by snare polypectomy. Extraintestinal manifestations of FAP have not been detected. The patient underwent prophylactic surgery (restorative proctocolectomy). The post-operative course was uneventful. In our knowledge, this is the first report of giant colonic polyps in a pediatric patient suffering from FAP. This clinical syndrome can be presented not only with different genetic backgrounds and diverse clinical pictures but also with intriguing endoscopic findings.*

Key words: *polyps, familial, polyposis, pediatric, patient.*

Introduction

Familial adenomatous polyposis (FAP) is the most frequent inherited polyposis syndrome caused by mutation in the adenomatous polyposis gene (APC) on chromosome 5q21 [1] The estimated prevalence of FAP is between 1:5000 and 1:17000 [2]. This syndrome is inherited in an autosomal dominant manner, although around 20–30% patients have *de novo* mutations [1]. It is characterized by the early onset (second or third decade of life) of hundreds to thousands colorectal adenomas. Without prophylactic colectomy, all affected patients develop colorectal cancer (CRC) by the age of 40-50 years. In the remainder of gastrointestinal tract adenomas can be found in stomach and small bowel. The most common extraintestinal manifestations of FAP are: congenital hypertrophy of the retinal pigment epithelium (CHRPE), desmoid tumors, epidermoid cysts and osteomas [3]. In addition, FAP is associated with an increased risk of malignant tumors at other sites including: thyroid (in 2-7% cases), liver (< 2% cases) and brain (< 1% cases) [4]. Patients with milder forms of this syndrome - attenuated FAP and MYTUH associated polyposis rarely have intestinal manifestations in childhood.

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A 16-year-old girl presented with rectal bleeding and signs of malnutrition (body height 155 cm (P12), body weight 29 kg, BMI 12,1 kg/m^2). At the age of 6 months she was operated on for hepatoblastoma. At the age of 11 months 3 cysts in her left kidney were revealed by ultrasound. Last two years she has been followed by endocrinologist because of amenorrhea. Her family history was unremarkable. The initial work up showed anemia (Hb 9.8X10, Er 4.68X10, Hct 32.9%) and hypoalbuminemia (S-Alb 24.7 g/L). Stool was negative on ova and parasites, bacteria and Clostridium difficile toxins A/B. Esophagogastroduodenoscopy revealed multiple small gastric polyps. Colonoscopy showed a few polyps in rectum and hundreds of them (3-25 mm in diameter) in sigmoid and descending colon. Giant colonic polyps (Fig.1) at splenic flexure region prevented further passage of the scope. Pathology of polyps removed by snare polypectomy showed tubulovillous adenomas with low grade dysplasia (Fig. 2). On fundoscopic exam signs of CHRPE have not been seen. Abdominal ultrasound and magnetic resonance imaging excluded presence of desmoid tumors, but revealed three small cysts in the left kidney.

The patient underwent restorative proctocolectomy at another hospital. Post-operative pathology has not proved CRC.

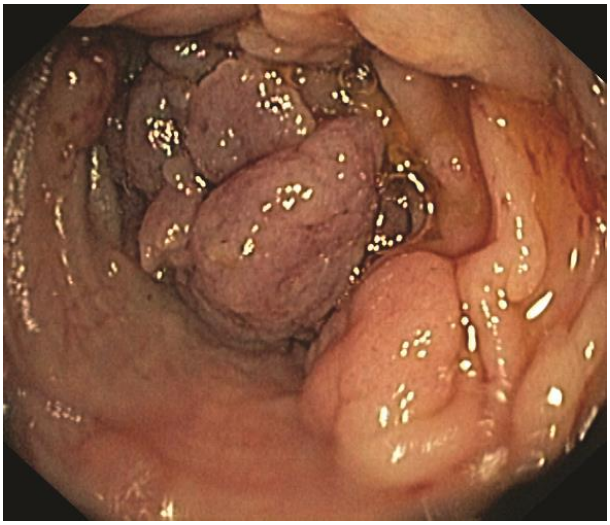

Fig. 1 Large colonic polyps at splenic flexure region

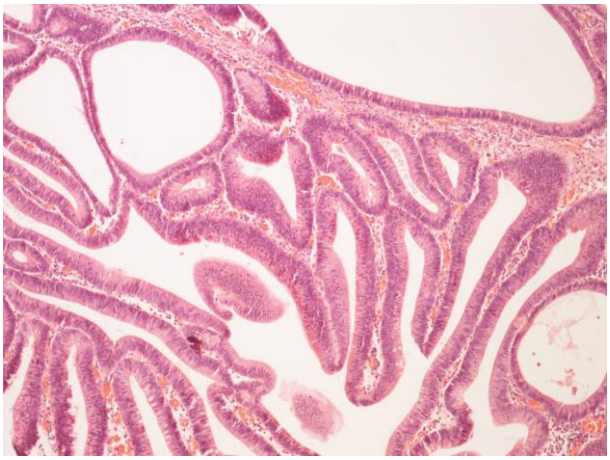

Fig. 2 Tubulovillous adenoma with low grade dysplasia

Discussion

Herein we describe a case of an adolescent female, with a unique endoscopic finding - giant colonic polyps at the splenic flexure region. The diagnosis of FAP was established based on the endoscopy and pathology of colonic polyps, removed by snare polypectomy. Unfortunately, the genetic test for FAP was not available in our institution. Therefore, we were not able to determine the type of mutation associated with this unusual endoscopic finding and the severe course of the disease.

Up until now more than 800 mutations of APC gene have been discovered in patients with classic and attenuated forms of FAP. Genotype-phenotype correlation studies indicated that mutation between codons 1250 and 1464 of APC gene and especially mutation at codon 1309 were associated with a severe clinical phenotype in FAP patients [5]. The genetic screening should be performed in all first degree relatives of FAP patients and should be started at the age of 10 years [4]. Families need to be informed that mutation can be found in only 70-90% cases.

Biannual flexible colonoscopy of at-risk children generally should begin at the age 10 years [4].

If the FAP symptoms become apparent at an earlier age or there is positive family history of: aggressive disease or mutation associated with a severe clinical phenotype, earlier colonoscopy is reasonable. Upper endoscopic surveillance (with end- and side-viewing scopes) should begin at the time when colonic adenomas are identified, or at the age of 20–25 years.

Rectal bleeding is the most common clinical sign described in patients with FAP. All clinical signs and laboratory findings in our patient, including rectal bleeding, severe malnutrition, amenorrhea, anemia, and hypoalbuminemia, were caused by the severe course of the disease. Our patient' history indicated that she was operated on in early infancy for hepatoblastoma. The risk of hepatoblastoma is 850 times greater in patients with FAP than in the general population; in most cases, it occurs within the first three years of life [6]. There is still no consensus regarding hepatoblastoma screening in patients with FAP. Some clinicians recommend that liver palpation, abdominal ultrasound, and alpha-fetoprotein level in serum should be done every 3–6 months during the first 5 years of life [7].

The patient underwent restorative proctocolectomy due to the presence of significant symptoms which is one of absolute indications for prophylactic surgery in patients with FAP according to recently published American College of Gastroenterology clinical guideline [8].

Restorative proctocolectomy is the surgical procedure of choice in the vast majority of FAP patients [9]. Alternatively, ileorectal anastomosis can be done in patients with a small number of adenomas in rectum. Regardless of the type of surgical procedure, regular endoscopic surveillance is a must for all operated patients in order to detect polyp recurrence.

Conclusion

In our knowledge, this is the first report of giant colonic polyps in a pediatric patient suffering from FAP. This is the most common inherited polyposis syndrome in childhood that can be presented not only with different genetic backgrounds and diverse clinical pictures, but also with intriguing endoscopic findings.

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Case Reports

THE APPLICATION OF STIMULATOR IN THE TREATMENT OF CLEFT LIP AND PALATE IN GOLDENHAR SYNDROME, TRISOMY 13 AND LOBAR HOLOPROSENCEPHALY WITH A MEDIAN CLEFT LIP

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Abstract. *The clinical picture of a newborn with a syndromic cleft lip and palate is severe. The orthodontic and surgical treatment of the cleft is complex and long-term. It is further complicated by various birth defects which can be life-threatening for a newborn or can make the therapy itself more difficult. The induction of a newborn into total anesthesia with a view to performing the surgery of a cleft is often made difficult or time-limited. This paper presents pre-surgical orthodontic therapy in newborns with three severe types of cleft, UCLP, BCLP and premaxillary agenesis with median cleft lip which occurred within three rare syndromes - Goldenhar syndome, lobar holoprosencephaly with a median cleft lip and trisomy 13 (47XX+13). Pre-surgical orthodontic therapy was conducted by means of RBJ stimulators without extra oral fixation, whose construction was conditioned by the type of cleft. With active treatment of RBJ stimulators, the cleft area in all three types of cleft was significantly reduced, as well as the protrusion of the premaxilla in BCLP. By directing the growth of cleft segments of newborn's upper jaw, the most approximate shape to a healthy newborn's jaw shape is achieved. All three types of described stimulators used in the therapy of syndromic cleft lip and palate enabled primarily the feeding of newborns, and thus their survival. With their orthopedic treatment they created optimal conditions for successful performing of surgical care of syndromic cleft lip and palate.*

Key words: *Prenatal development, craniofacial growth, infant orthopedics, feeding.*

Introduction

The early orthodontic therapy by means of stimulators in different types of cleft lip and palate is a useful therapeutic procedure in the earliest period of life. Its two advantages are enabling the function of feeding in newborns and pre-surgical therapy. There are numerous assertions which confirm the efficiency of its application in nonsyndromic cleft lip and palate [1–4].

Clefts which occur within various types of syndromes further enlarge the severity and seriousness of the clinical picture of these syndromes. Over 400 syndromes within which clefts occur were described in the literature [5]. Thirty percent of all orofacial clefts fall into the category of syndromic clefts. They were described for the first time as early as 1940s when anatomic classification of clefts was attempted and it was noticed that in many individuals affected by clefts there were adjoined defects which, to a great extent, affect the survival of newborns or affect the therapy. Cleft lip and palate most commonly occur within following syndromes: Van der Woude syndrome (CLP and CP), Microdeletio n22q11.2 syndrome (CP), Stickler syndrome (CP), Treacher Collins syndrome (CP), Opiz syndrome (CLP), Kabuki syndrome, Smith Lemli Opiz syndrome (CP), etc.

Many of these are quite rare, having been reported in a handful of families or individuals.

The surgery of cleft lip and palate in newborns is made difficult due to broad communication between nasal and oral cavity, the lack of available tissue for closing communication, protruded premaxilla, in BCLP, the lack of bony foundation in median cleft lip, dislocation of cleft segments, etc. Pre-surgical orthodontic therapy has a goal of directing a cleft segment of the upper jaw in the direction of closing the cleft and forming one regular shape of the upper jaw from the cleft segments.

The treatment of syndromic cleft lip and palate is further complicated by numerous birth defects; heart, nephrological, metabolic, etc. The induction of a newborn into total anesthesia for the surgical therapy of cleft lip and palate in severe cases is sometimes unmanageable or time-limited. For these reasons, a proper pre-surgical orthopedic preparation of newborns is of essential importance. It not only facilitates performing of surgery and achieving the best possible results, but it also reduces the time duration of anesthesia in newborns.

The paper describes the application of RBJ stimulators in three different entities: Goldenhar syndrome, lobar holoprosencephaly with a median cleft lip and trisomy 13 (47XX+13).

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Patients and Methods

Patients

Goldenhar syndrome/oculo-auriculo-vertebral spectrum, hemifacial microsomia, facio-auriculo-vertebral syndrome, and first and second branchial arch syndrome represent similar errors in morphogenesis with gradation of severity [6]. The syndrome is characterized by varying degrees of prevalently unilateral underdevelopment of the craniofacial structures (orbit, ear, and mandible) in association with vertebral, cardiac, renal, and central nervous system defects (Fig. 1). The frequency of occurrence is estimated to be 1 per 3000 to 1 per 7000 with a slight male predominance [6]. The syndrome is a sporadic condition. Cleft lip and palate has been reported in 16% of affected individuals, and 36% have mental retardation.

Trisomy 13 or syndroma Patau (47 XX +13) (Fig. 2) is the third most common autosomal trisomy occurring with an incidence of 1:5000 live births. The most characteristic malformations include varying degrees of holoprosencephaly, microphthalmia, scalp defects (Fig. 2D), cardiac defects and polydactyly (Fig. 2C). CL/P occurs in 60-80% of cases and is midline when associated with HPC. Newborns most commonly live up to 7 days. Growth deficiency and severe cognitive impairment are typical. Most cases of trisomy 13 are a result of nondisjunction often associated with advanced maternal age. Families are typically counseled that there is less than 1% recurrence risk. Types of clefts which are described within this syndrome are: midline cleft lip and palate, bilateral cleft lip and palate and unilateral cleft lip and palate [7].

Lobar holoprosencephaly with a median cleft lip is a complex malformation of the brain associated with the median facial defects (Fig. 3). Variability of the clinical picture is the characteristic of this anomaly. In most cases, the degree of severity of the facial anomaly correlates with degree of damage to the brain [8] Facial anomalies are divided into five groups: cyclopia, ethmocephaly, cebocephaly, premaxillary agenesis with median cleft lip, and other less severe manifestations [9]. Premaxillary agenesis with median cleft lip is a complete median lip cleft, and when associated with hypotelorism, it is the fourth type of facial anomaly within HPC. A face with this anomaly is characterized by the absence of crista galli, the nasal bone, the complete premaxilla, and nasal septum. Its occurrence is 1:16 000 of live-born infants [9].

These three anomalies are followed by different types of clefts, which, according to severity belong to severe forms of clefts. A newborn with Goldenhar syndrome, according to the severity of the clinical picture has a milder form of this syndrome, but unilateral complete cleft of primary and secondary palatum influences that it obtains the shape of a middle-degree anomaly (Fig. 1C). There is a great dislocation of a bigger segment of palatal extension along with a nose septum to one side due to the existence of complete cleft of primary and secondary cleft. A nose wing and unformed nostril are also broadly long-drawn on the side of cleft. Lateralization, which is a characteristic of this syndrome, is reflected in this type of cleft.

The severe form of complete bilateral cleft of primary and secondary palate even further emphasizes the severity of the clinical picture of a newborn with trisomy 13. The premaxilla carried by the nose septum is clearly distinguished from the rest of the face. There is a big cleft at the level of palatal extensions which achieves complete communication between oral and nasal cavity with the protruded premaxilla (Fig. 2B).

The most severe type of cleft, which is at the same time very rare, is median cleft lip (which occurs together with congenital, complete lack of the premaxilla) (Fig. 3B). Due to the non-existence of frontonasal process which participates in the forming of the middle part of the face, a newborn does not have nasal bones, premaxilla, so that there is almost no boundary between the two cavities.

Fig. 1 The face appearance of a newborn with Goldenhar syndrome. Note auricular tag, epibulbar dermoid non-typical UCLP.

Fig. 2 The face appearance of a newborn with trisomy 13. In addition to BCLP, features that are apparent include the bulbous nose, up-sweep to the scalp hair pattern and postaxial polydactyly.

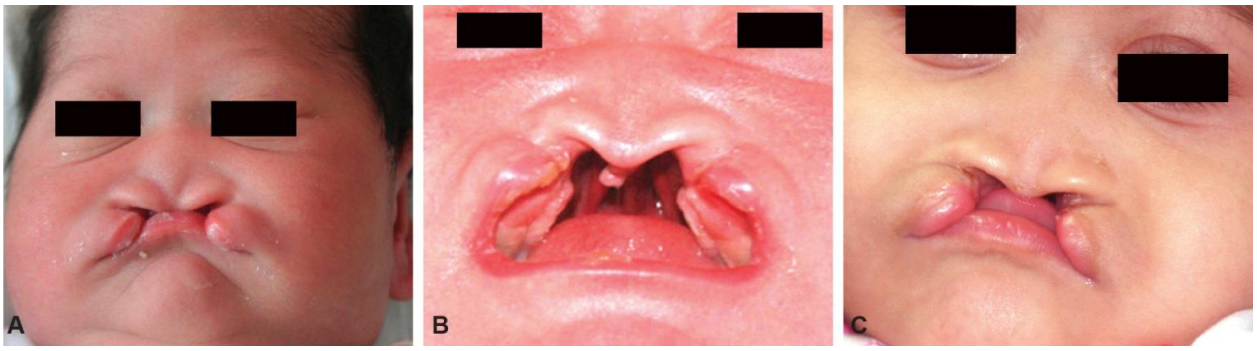

Fig. 3 The face appearance of a newborn with Lobar holoprosencephaly with a median cleft lip. Note the lack of crista galli, the nasal bone, the complete premaxilla, and nasal septum [8].

Methods

All three types of clefts are very difficult for surgical care. In unilateral cleft, the most difficult thing is to achieve the symmetry due to lateralization of structures that are involved in the formation of a nose and lips. It is difficult to surgically care for bilateral cleft due to the protruded maxilla, since it often comes to dehiscence due to tissue tension, but in comparison with surgical repair of the palate, it is by far easier than the median cleft with premaxillary agenesis in which it is almost impossible to repair the palate due to the lack of bony tissue.

The role of RBJ stimulators has a great significance in all three types of clefts within pre-surgical therapy. The active effect of stimulators is mostly expressed by activating an orthodontic screw which is implemented in the construction of stimulators in all three types of clefts, as well as the specific cutting of an acrylic plate. Some of the basic principles which are common regardless of the type of cleft are: the screw is always placed at the right angle in relation to the line that joins two sides of acrylic plate, the big segment serves as the strongpoint for the movement of a smaller segment, the acrylic plate covers palatal segments to the boundary between mobile and immobile mucous membranes, as well as the fact that the basic condition for efficient and the only action of stimulators is a perfectly taken impression between the upper jaw of a newborn. The difference between stimulators used in orthopedic and surgical therapy of these three clefts is in the line of plate cutting. In unilateral cleft of primary and secondary palate the line of acrylic plate cutting is in the shape

Fig. 4 Taking impressions, impression, cast model and stimulator in Goldenhar syndrome (A, D, G, J), trisomy 13 (B, E, H, K) and lobar holoprosencephaly with a median cleft Lip (C, F, I, L).

of Z. In such a way, a smaller palatal segment moves in the medio-mesial direction after activating the screw, thus reducing the cleft area between palatal segments as well as the cleft at the level of alveolar edges and at the same time it achieves the closest possible regular shape of the upper jaw (Fig. 4J). Since the problem with BCLP lies in the protruded premaxilla, the cap with the premaxilla is most often pulled backwards between cleft palatal segments by means of the open screw (Fig. 4K). After that, different types of stimulators are possible. Median cleft lip with premaxillary agenesis only has transversally separated palatal segments, so that by means of activating the open screw in a straight line, we direct segments towards each other (Fig. 4L).

The basic requirement for efficient action of stimulators is a perfectly taken impression of a morphologically altered upper jaw in all three syndromes. On a proper impression, after the pouring of a cast model, a complete mucosa of a hard palate and alveolar edges should be outlined. Each crease, plica, lateral sulcus on a hard palate, frenulum on the alveolar edge can act as an excellent retainer, but also quite the opposite, as destabilizers of a stimulator (Fig. 4G–I). This is why it is necessary to release these anatomic details from the acrylic plate of stimulators, to bypass every plica and frenulum.

Taking impressions has its specificities Fig. 4A–C. The impression is always taken when a newborn is awake, it is even desirable that the infant is crying. This is important, on one hand because we can then see the face color of a newborn, and on the other hand, in such a way, anatomic details are better marked. It is especially important that it then comes to the lowering of the soft palate, by which the boundary between hard and soft palate is clearly outlined, and at the same time it represents the distal boundary of a future stimulator. Even a slightly elongated distal stimulator can cause an urge to vomit, which is completely undesirable. The impression consists of two phases. The first anatomic impression is always taken with alginates, and the other corrective impression with addition silicones. The anatomic impression gives only basic outlines. The addition impression (corrective) taken with addition silicones represents a key step towards the application of stimulators (Fig. 4D–F). It shows the most minute details, sine it is taken with the help of hydrophilic and hydrophobic material that is in a liquid state. Taking impressions is based on doctor's expertise and good knowledge of the characteristics of impression masses.

The role of stimulators is twofold. Besides its role in pre-surgical therapy in all three syndromes, its invaluable importance is to enable the function of feeding immediately after the birth. Namely, due to the existence of broad communication between a nasal and oral cavity, there is no possibility of creating negative pressure in the mouths of newborns which is necessary for sucking milk. At the attempt of feeding it comes to chocking, coughing, aspiration of milk, often cyanosis or developing pneumonia. In such situation parents succumb to panic and they are in constant fear of their newborn's survival. After the application of a stimulator that closes communication between an oral and nasal cavity, it serves as an artificial palate. In such a way, conditions are made for a tongue to resist from the hard side of the acrylic plate and to perform its function that it has during breastfeeding. Apart from that, in this way, the tongue is disabled to stay inserted high towards a nasal cavity into the empty space between cleft palatal segments ever broadening it. The tongue position becomes physiological and has the power to participate in the regular development of occlusion and other orofacial functions. Orthopedic pre-surgical therapy by means of stimulators is based on biological foundations and the aspect of individuality. Numerous studies have shown that the growth of bony segments of the upper jaw affected by cleft is not disturbed [10–13]. Only the directions of the growth of bony segments are disturbed. The role of stimulators is in directing growth. The growth is led in the direction of closing the cleft area and achieving the shape of the upper jaw as regular as possible. In this way, an excellent pre-surgical preparation is performed that creates conditions not only for facilitated performing of surgery, but making the aesthetic and functional results of surgery as good as possible.

The aspect of individuality in pre-surgical orthodontic therapy by means of stimulators is also very important. Our observations are in compliance with many authors who confirmed that regardless of the classification of clefts, there are great individual differences within the same group. They relate not only to the differences in the morphology of the cleft-affected upper jaw, but to the type of growth as well. This is why this should be taken into account when constructing stimulators. A good orthodontist must recognize the type of growth at the very beginning of newborn's life, to 'listen to' it later and to design stimulators in accordance with that, changing them every month until the first surgical intervention.

Stimulators presented in this paper have one more characteristic that distinguishes them in relation to other appliances described in orthodontic therapy of newborns with clefts, and that is the lack of extra oral fixation which helps in the retention of appliances. Different means of retention are described. From caps on the heads of newborns, various elastic bands or even pins directly placed in palatal segments which prevented appliances from falling out [14]. The retention of stimulators is achieved with construction that was made after a perfectly taken impression of a cleft upper jaw. In such a way, with a strong strongpoint on the segments of the upper jaw, a stimulator gives excellent orthodontic results. The effects of its action were confirmed with a 3D computer analysis [4].

Conclusion

The role of RBJ stimulators in pre-surgical orthodontic therapy is multiple. By enabling the function of feeding at the very beginning of life, it solves the essential problem of newborn's survival. With its active effect it

directs the growth of cleft segments, reduces the size of cleft and creates the conditions for successful achievement of the best possible aesthetic and functional results of surgical interventions to come. With proper pre-surgical therapy, they reduce the duration of surgical therapy, and thus the duration of total anesthesia which is often impossible in syndromes due to the existence of multiple birth defects. The therapy is comfortable since it does not damage the sensitive mucosa of newborns. The lack of extra oral fixation positively affects parents' psychic state and their environment. Positive effects of therapy with stimulators are confirmed with a 3D computer analysis, and their use is therefore recommended in the therapy of syndromic clefts.

Research ethics and patient consent. This research involving human subjects is conducted according to the World Medical Association Declaration of Helsinki and with approval of the institution.

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Case Report

ADVANCED LYPOSARCOMA MYXOIDES OF THE EXTREMITY

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Abstract. *Sarcomas are soft tissue tumors arising from primitive mesenchyme. Small incidence (4-5/100 000 in Europe) is the reason their pathogenesis is relatively unknown. Patient (38) complained of a growth on the upper part of right thigh, the size of a child's head. A magnetic resonance imaging (MRI) scan was done and tumefaction was described: oval shape, 13.5 x 7.5 x 11cm in diameter, without infiltration of surrounding tissue. The tumor was surgically removed and was pathohistologically verified as low grade liposarcoma myxoides. After initial presentation the patient presented a series of recurrences and metastases in the abdominal wall, extremities and liver. Soft tissue metastasis from the lower extremities to the liver occur in 0.5% of cases and they are usually small and multiple, as in the presented patient. The European Sarcoma Medical Oncologist's guide recommends that every extremity tumor larger than 5cm and suspicious of malignancy should be evaluated using biopsy and imaging methods. A biopsy should be done before excision under ultrasound or computerized tomography (CT) guidance with the goal of planning the best therapy protocol and prevention of a generalized disease with metastases. The recommended imaging method is an MRI scan, although sarcomas can have a benign presentation. Standard therapy includes surgical resection with local radiotherapy. Liposarcoma myxoides, a rare soft tissue tumor, demands biopsy and complete surgical removal with detailed and continuous postoperative imaging follow-up and oncological therapy. The therapeutic goal is to increase survival and preserve extremity function.*

Key words: *Sarcoma, Liposarcoma.*

Introduction

Adult soft tissue sarcomas are malignant tumors which develop from primitive mesenchyme. Their incidence is small (around 4-5/100000 cases per year in Europe) [1] which is the main reason their pathogenesis and metastasizing pattern is relatively unknown, and that is also the reason why we have few large randomized prospective studies on this topic. Therefore, scientific papers in the form of case presentations are a valuable source of information in the ongoing research of this disease.

Case Presentation

The patient (38 years old) complained to his general practice doctor in July 2013 of a large growth the size of a child's head on the inner side of his right thigh. After a physical exam and laboratory analysis of blood and urine, a magnetic resonance imaging (MRI) scan of the lower extremities was done, which described a tumefaction beneath the pubic bone and between the obturator muscles: clear margins, oval shape, and 13.5 x 7.5 x 11cm, without infiltration of surrounding tissue, benign in appearance. After one month the tumor was surgically removed. The tumor was pathohistologically verified as a primary mesenchyme tumor type low grade myxoid liposarcoma. Tumor immunophenotipisation: CD34-, p53-, Cyclin D1+, rear individual cells <1%, Ki-67+ diffuse heterogeneous weak to intensive immunopositivity in around 15% of tumor cells. He was referred to a multidisciplinary team in September 2013 which indicated a follow up every two months with regular MRI scans. After ten months, a recurrence was diagnosed, when a reoperation was done as well as regional lymph node dissection. After that, the multidisciplinary team indicated postoperative local radiotherapy (RT) which was not conducted due to technical reasons. In the meantime, the patient was diagnosed with a tumor in the abdominal wall. He was operated on for the third time in July 2014 where the abdominal wall tumor was removed and the pathohistological finding was the same as before (low grade liposarcoma myxoides). The multidisciplinary team requested a postoperative computerized tomography (CT) scan of the thorax and abdomen. A suspicious lesion was then noticed in the liver as well as a group of enlarged lymph nodes in the mediastinum. MRI of the right thigh did not show any sign of recurrence. A positron emission tomography (PET) scan was

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done which showed a nodular tumefaction in the neck on the left posterior side in the subcutaneous tissue 12mm in diameter as well as a circular defect in the medial part of hind knee area in the subcutaneous tissue. The multidisciplinary team indicated systemic chemotherapy in three cycles using monotherapy with Doxorubicin. Because of a new tumefaction in the left elbow and a recurrence in the primary surgical site, the chemotherapy was continued for three more cycles, but was aborted due to cardiotoxity. The above-mentioned recurrence was surgically removed in September 2015. RT was again not applied. This was followed by recurrence in January 2016. CT scan of the thorax, abdomen and pelvis was done confirming lesion in the second segment of liver (5.7cm) (Fig. 1) as well as in the right inguinal area.

Five months after that, ultrasound of the abdomen showed enlargement of the solitary soft tissue lesion in the left lobe of the liver (9.8 x 9.2 cm). The patient was referred to our clinic for further treatment of the liver lesion in July 2016. After adequate preoperative preparation, „J" laparotomy was performed (with continuous ischemia using the Pringle maneuver), finding a large solid tumefaction in the left lobe of the liver 10x8 cm in size. The tumor was verified as a myxoid liposarcoma metastasis. In the follow up course the patient was diagnosed with multiple liver and lung metastases which were verified with CT scans. Table 1 is showing all the therapeutic and diagnostic procedures performed in the patient in chronological order.

Discussion

Liposarcoma is the second most common soft tissue sarcoma. The exact cause of their occurence is unknown. Patients usualy first notice a growth on the extremity after an injury. However it is certain that liposarcomas do not occur because of trauma. They most often occur between 30 and 50 years of age with a mild male predominance. They can occur anywhere in the body where fat tissue is present, most commonly in the deep fat tissue of the extremity (59%), abdomen and thorax (19%), retroperitoneum (15%), head and neck (9%) [2]. The greatest survival rate is with liposarcoma of the extremities and the least with retroperitoneal sarcomas. The local recurrence rate is arround 78% [3].

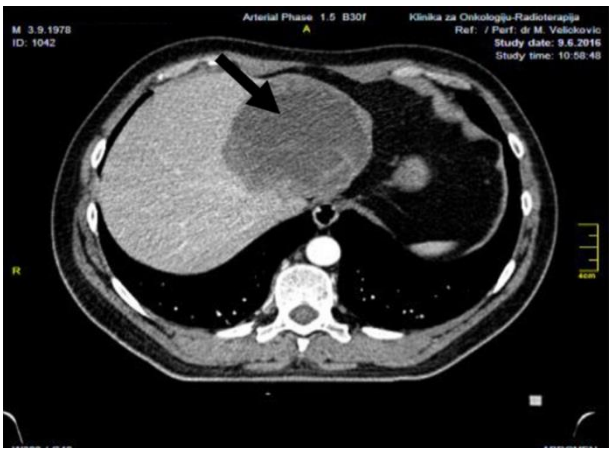

Fig. 1 Transverse abdominal CT scan. Large metastasis is visible in second segment (black arrow)

Table 1 Overview of the diagnostic and therapy procedures.

Disease events	Time period
Operation- excision of the growth in the right thigh (PH: low grade myxoid liposarcoma)	August 2013
Operation- excision of the recurrent growth on the right thigh with dissection of the regional lymph nodes (PH: low grade myxoid liposarcoma)	May 2014
Radiotherapy indicated- not executed	
Operation- excision of the growth in the abdominal wall (PH: liposarcoma myxoides)	July 2014
CT of the thorax and abdomen confirms presence of enlarged lymph nodes in the mediastinum and a focal lesion on the liver	August 2014
PET/CT reveals tumor lesions in the neck hind knee area	September 2014
Local recurrence in the right thigh and left elbow	September 2014
Chemotherapy is conducted but cancelled after five cycles because of cardio toxicity	October 2014
Operation- excision of the local recurrence on the right thigh	September 2015
Radiotherapy indicated- not executed	September 2015
Operation- excision of the local recurrence on the right thigh	December 2015
Local recurrence on the right thigh	January 2016
Enlargement of the liver focal lesion	May 2016
Operation- excision of the liver metastasis	July 2016
Multiple metastasis in the lung and liver	February 2017

According to the histology type, liposarcomas can be classified as: dedifferentiated, myxoid and pleomorphic [4]. Myxoid liposarcoma is the most common subtype and it is more frequent in younger people. It is different from other liposarcomas in its unusual pattern of metastasis in tissues such as: bones (most common), retro-peritoneum, extremities and the axillary region, while other localities are affected only in advanced stages of the disease [5,6].

All other liposarcomas usually present with metastases primarily in the lungs. Soft tissue sarcoma metastases of the lower extremities occur in the liver in around 0.5% of cases [7] and usually present as small multiple metastases and rarely as big solitary tumors such as the one in the patient described in this presentation.

According to the European society of medical oncologists (ESMO), every patient with a tumor suspicious for soft tissue sarcoma of the extremity should be referred to a specialized diagnostic center for a three-way evaluation: biopsy, physical exam and imaging [8]. The recommended imaging method for evaluation is MRI, which was used for diagnosing the presented patient as well. However, initially the tumefaction was described as a benign tumor lesion with clear margins and no infiltration of surrounding tissue. As shown by Francois et al. myxoid liposarcomas, although malignant tumors, can deceive with their benign appearance [9]. For this reason, any growth which is larger than 5cm and deeply seated in the tissue should be suspicious for malignancy. An important diagnostic tool which is also used for planning further therapy is a tumor biopsy which should be done before tumor excision. The first biopsy is performed under ultrasound or CT guidance and in case of failure, a surgical biopsy is needed. The histological classification should be made according to the World Health Organization classification from 2013. The grade of the malignancy should always be determined if possible, because it has prognostic value. The grade is determined based on degree of necrosis, differentiation of the tumor and mitosis count [10].

As far as other diagnostic modalities are concerned, the ESMO guide recommends CT of the thorax, for patients who were diagnosed with soft tissue sarcoma by biopsy, in order to rule out pulmonary metastases before definitive treatment. CT of the abdomen and pelvis do not have to be done routinely, but they are recommended in certain histological types, including myxoid liposarcomas. Early diagnostics could lead to earlier discovery of metastatic disease, and an earlier introduction of systemic chemotherapy.

Wide excision with negative margins in combination with postoperative radiotherapy is the standard in treating tumors of the trunk and extremity because that provides a high degree of local control with preservation of extremity function. The margin of surgical excision depends on multiple factors: histological subtype of the tumor, application of preoperative chemo or/and radiotherapy and presence of anatomical barriers (fascia, periost etc.). In some cases amputation of the extremity should be considered. Although radiation therapy is reserved mostly for patients with high grade tumors, it can be justified in low grade tumors which are deeply seated in the tissue and larger than 5cm. This decision should be made by a multidisciplinary team taking in consideration the anatomical localization of the tumor, as well as the risk/benefit ratio in radiating patients with a low grade tumor. Local radiation therapy reduces the incidence of local recurrence which is often related to metastatic disease. The presented patient did not receive any local radiation therapy due to technical reasons, which may have led to multiple recurrences and the generalized metastatic disease. However, since this is a case presentation and this is only one case, it is difficult to draw conclusions and determine correlation between the absence of radiotherapy and advancement of the disease.

Neoadjuvant radiotherapy is not recommended as a routine method, but it can be used in radiosensitive subtypes such as myxoid liposarcomas in order to shrink the tumor preoperatively. The main drawbacks of this method are postoperative surgical complications which occur at the site of tumor excision.

The role of adjuvant chemotherapy has not been confirmed, therefore it is also not recommended as a routine method. It can however be used in patients whose tumor is near an anatomical structure which could be damaged using radiotherapy or in certain chemo-sensitive tumors.

Advanced disease with extrapulmonary metastases is best treated with systemic chemotherapy. In certain patients, metastases can be treated surgically, depending on the localization of the tumor and progression of the disease. Standard chemotherapy used today is Doxorubicin as a monotherapy, since it has not been formally proven that polytherapy is superior to monotherapy. On the other hand, some studies are in favor of polytherapy in certain chemo-sensitive types of tumors [11]. The most dangerous side effect of Doxorubicin is cardio toxicity, which was observed in the presented patient.

As far as follow up is concerned, the ESMO guide recommends that all patients with low grade tumors should be controlled every four to six months in the first three to five years and then once a year. Standard control should encompass a physical exam (and MRI scan if needed), as well as a chest X ray to rule out pulmonary metastases.

Regarding prognosis in these patients, negative prognostic factors are: age (>45 years) [12], size of the tumor (>10 cm) [13], percentage of differentiation of cells (>5%)[14] and tumor necrosis [12]. All of these factors were present in the presented patient except his age.

Conclusion

Liposarcomas rarely metastasize from the extremity to the liver. When they do, it is usually in the form of multiple metastases, and rarely as large solitary tumefactions, which is a sign of an advanced stage of the disease. According to the ESMO guide, if there is suspicion of a soft tissue sarcoma, it is necessary to do an ultrasound or CT guided biopsy before excision in order to plan a therapeutic protocol based on the pathohistological diagnosis. In order to prevent recurrence, it is necessary to consider local radiotherapy after surgical excision in tumors that are primary, deeply seated and larger than 5cm even though they are low grade. Also, it is recommended to do a CT or a chest X-ray of the thorax and in subtypes such as liposarcoma myxoides a CT of the abdomen and pelvis as well, in order to rule out the presence of metastases. Systemic chemotherapy is the method of choice in treating advanced disease with extra-pulmonary metastases and in certain cases, surgical therapy can be performed. Follow up in low grade tumors should be done every six months in the first two to three years with a thorough physical exam and a chest X-ray.

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