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ММР

Original article

MENOPAUSAL TRANSITION AS A CAUSE OF EMOTIONAL DISTURBANCE, INSOMNIA AND SEXUAL DYSFUNCTION

МЕНОПАУЗАЛНА ТРАНЗИЦИЈА КАКО ПРИЧИНА ЗА ПОЈАВА НА ЕМОЦИОНАЛНА НЕСТАБИЛНОСТ, НЕСОНИЦА И СЕКСУАЛНА ДИСФУНКЦИЈА

Aneta Sima[1], Anita Arsovska[2], Jadranka Georgievska[1], Valentina Velkoska- Nakova[3] and Slagana Simeonova-Krstevska[1]

University Clinic of Obstetrics and Gynecology - Skopje[1], University Clinic of Neurology Skopje,[2] University of Science "GoceDelcev" – Stip[3], Republic od North Macedonia

Abstract

Aim. This study is aimed toexplain and prove the changes in psychosocial functioning of women in the period of perimenopause.
Methods. This was a prospective cohort study which included 71 patients aged 45-50 years, with irregular cycles, who came to the University Clinic of Gynecology and Obstetrics in Skopje due to a gynecological problem in a period of one year(from 2017 to 2018). In addition to gynecological examination and history, all patients with a doctor's help filled out an anonymous questionnaire (modified following the example of the SWAN Study-Study of Women's Health Across the Nation). Data analyzed: place of residence, degree of education, ethnicity, emotional instability, insomnia, sexual dysfunction.
Results. Most of the patients lived in the city, had completed secondary education and were Macedonians; more than half of them had emotional changes, insomnia and sexual dysfunction. Chi-square test showed a statistically significant difference in the incidence of depression and insomnia among women living in the countryside (p=0.0067 and p=0.029, respectively), as well as more frequent depression in women with primary and secondary education. In Macedonian women, insomnia wasstatistically significantly more common.
Spearman's correlation analysis showed a statistically significant positive correlation between depression and sexual dysfunction (p <0.01).
Discussion. Perimenopause as a period is characterized by many changes in the body, but also by changes in the psychosocialfunctioning of the woman. All changes in the body (hot flushes, slow metabolism, hypertension, genital dryness, initial osteoporosis), undoubtedly affect the psychological health of the woman, which is rarely paid attention and even less properly treated. Half of the patients feel changes in the emotional sphere (irritability, neurosis, depression), problems with insomnia (difficulty sleeping, frequent waking, short sleep), as well as sexual dysfunction (decreased libido, dryness of the genitals, dyspareunia).
Conclusion. All of the difficulties encountered in the period of perimenopause in a woman are combined, somatic and psychic, and stemming from one another. This has significantly impaired quality of life in these patients and simultaneous diagnosis and treatment of all these conditions is necessary.

Keywords: perimenopause, emotional disturbance, insomnia, sexual dysfunction

Correspondence to: Aneta Sima, University Clinic of Obstetrics and Gynecology - Skopje, Republic of North Macedonia; E-mail: aneta_sima@yahoo.com

Абстракт

Цел. Оваа студија треба да ги објасни и докаже промените во психо-социјалната сфера кај жената во периодот на перименопауза.
Методи. Студијата е проспективна кохортна, беа вклучени 71 пациентка на возраст од 45-50 години, со нередовни циклуси, кои се јавиле на преглед на УГАК заради гинеколошки проблем, во период од една година (2018-2019). Покрај гинеколошки преглед и анамнеза сите пациентки со помош од лекар пополнија анонимен прашалник (модифициран по примерот на SWAN студија-Study of Womens Health Across the Nation). Податоци кои беа анализирани: место на живеење, степен на образование, етничка припадност, емоционална нестабилност, несоница, сексуална дисфункција.
Резултати. Најголем дел од пациентките живееле во град, имале средно образование и биле македонки, кај повеќе од половината биле присутни емоционални промени, несоница и сексуална дисфункција. Chi square тестот покажа статистички значајна разлика во појавата на депресија и несоница кај жени кои живеат во село (p=0,0067 и p=0,029 соодветно), како и почеста депресија кај жените со основно и сред-

но образование. Кај македонките несоницата е статистички значајно почеста.
Сперма новата корелација прикажа статистички значајна позитивна корелација помеѓу депресијата и сексуалнатадисфункција (p<0,01).
Дискусија. Перименопаузата како период се карактеризира со многу промени во телесната, но и во психичката сфера кај жената. Сите промени во организмот (топлибранови, успорен метаболизам, хипертензија, сувост на гениталии, почетна остеопороза), не сомнено влијаат на психичкото здравје на жената, на што ретко се обрнува внимание а уште помалку правилно се третира. Половина од пациентките чувствуваат промени во емоционална сфера (раздразливост, неуроза, депресија), проблеми со несоница (тешко заспивање, често будење, краток сон), како и сексуална дисфункција (намалено либидо, сувост на гениталии, диспареунија).
Заклучок. Сите наведени потешкотии во периодот на перименопауза кај жената се комбинирани- соматски и психички и произлегуваат една од друга. Со тоа е значително нарушен квалитетот на живот кај овие пациентки и неопходна е симултана дијагноза и третман на сите овие состојби заедно.

Клучни зборови: перименопауза, емоционална нестабилност, несоница, сексуална дисфункција

Introduction

Menopause indicates a permanent cessation of the menstrual cycle, which occurs at an average age of 50 years. The age of menopause depends on many factors: most commonly genetic, age of menarche, socioeconomic status, race, smoking, etc [1]. This period passes through several stages that in factmean a transition from a reproductive life to a postmenopausal period. The menopausal transition begins with the variability of the length of the menstrual cycle accompanied by an increase in FSH levels and ends with the last menstrual cycle. This period, the so-called perimenopause, may occur 5-8 years before menopause, lasts for 4-5 years on average and is characterized by cycle irregularities, hormonal variability, and also reflectson other organic systems [2]. Menopause is defined retrospectively, after 12 months of amenorrhea. The main consequences of menopause are associated with estrogen deficiency, which explains all pathophysiological changes. The most common symptoms are: genital atrophy, osteoporosis, vasomotor symptoms, cardiovascular disease, cognitive decline, and sexualdysfunction [3]. According to the North American Menopause Society (NAMS), about 23% of women in this period are affected by mood swings. The emotional aspects of menopausal transition are increasingly being explored. The most frequent changes in the psychic sphere are: irritability (70% of women emphasize irritability as their main emotional problem in the early stages of transition, describe themselves as less tolerant and sensitive), depression (a common and serious emotional state that occurs in 1 of 5 women), anxiety (women experience tension, nervousness, caring and panic attacks), episodes of crying (alternating with periods of laughter), insomnia (lack of sleep further emphasizes mood swings and interferes with daily normal functioning, and occurs in 40-50% of women) [4]. The question arises as to how menopause causes these symptoms. During transition to menopause the level of estrogen in the body decreases and thisdeficiency leads to disturbance of the homeostasis of serotonin and norepinephrine (these are two substances that are associated with the onset of depression) [5]. Also, low levels of estrogen lead to irritability, tremor, stress, forgetfulness, concentration difficulties, etc. The researchers have proven high levels of brain protein monoamine oxidase A, which is responsible for the onset of depression. Night sweats and hot flushesare physical manifestations that exacerbate additional psychic experiences and severely impair the quality of life of these patients [6]. Risk factors for this condition include: a history of previous PMSs, previous episodes of depression or other mental health problems, as well as dissatisfaction with relationships, stress, a difficult life situation, etc. [7].
Sleep disorders are a common problem in perimenopause; studies show that this is the main reason women seek professional help; sleep disorders also disturb women's quality of life. Difficult sleep, frequent waking, insomnia are the most common forms of disorder. The consequences are chronic fatigue, inability to carry out everyday tasks, which significantly reduces the quality of life [8]. Problems in the sphere of sexual life are increasing and more pronounced inmenopause. Patients complain of vaginal dryness, pain during intercourse, reduced to absent libido, etc. All these symptoms in combination have a synergistic effect and can completely disrupt the normal life course [9].

Material and methods

This was a prospective cohort study which included 71 patients aged 45-50 years, with irregular cycles, who came to the University Clinic of Gynecology and Obstetrics in Skopj due to a gynecological problem in a period of one year (from 2017-2018). In addition to the gynecological examination and history, all patients with the help of a doctor filled out an anonymous questionnaire (modified following the example of the SWAN Study -Study of Women's Health Across the Nation) [4]. Data analyzed: place of residence, degree of education, ethnicity, emotional instability, insomnia, sexual dysfunction. Patients were first informed about their participation in the study and they signed a con-

sent, after which filled out the questionnaire in a special room without a third person. The obtained data were statistically analyzed using the SPSS version 20, and the tests used were: Chi square test, Spearman' correlation, ANOVA.

Results

As illustrated in Table 1, majority of the analyzed patients live in the city, have completed secondary education and are Macedonians. More than a half are depressed, have insomnia and sexual dysfunction.The Chi-square test showed a statistically significant difference in the onset of depression and insomnia among women living in the countryside as opposed to urban living (p=0.0067 and p=0.029, respectively). There was no statistically significant difference in sexual dysfunction in relation to the place of residence.
The Chi-square test showed a statistically significant difference in the incidence of depression in women according to the level of education (p=0.03). Women with primary and secondary education were more depressed than women with higher education. The frequency of insomnia and sexual dysfunction did not differ statistically regarding the level of education. In terms of ethnicity, the difference in the occurrence of depression, insomnia and sexual dysfunction in women of Macedonian and other nationalities was compared.

Table 1. Sociodemographic analysis and occurrence of symptoms

Country side	24(33.8%)
City	47(66.2%)
Education level	
primary	20(28.2%)
secondary	40(56.3%)
college	11(15.5%)
Ethnicity	
Macedonian	53(74.6%)
Albanian	13(18.3%)
Roma	4(5.6%)
Bosniaks	1(1.4%)
Depression	46(64.8%)
Insomnia	48(67.6%)
Sexual dysfunction	42(59.1%)
Symptoms triad	18(26 %)

The occurrence of insomnia was statistically signifycant in women of Macedonian nationality (p=0.03). Spearman's correlation showed a statistically signifycant positive correlation between depression and sexual dysfunction (r=0.347, p<0.01). It means that women who are depressed have sexual dysfunction, too.

Table 2. ANOVA analysis of variables

Characteristics	**0 (n=4)**	**1 (n=19)**	**2 (n=27)**	**3 (n=21)**	**ANOVA P вредност**
Age	47	46.6	51.18	49.71	0.167
City	4	17	18	9	**0.017**
Education					
≤ secondary	4	12	25	19	0.701
>secondary	-	7	2	2	
Ethnicity					
Macedonian	4	17	19	14	
Albanian	-	2	5	5	0.465
Roma	-	1	2	2	
Bosniaks	-	-	1	-	

Table 2 shows a comparison between age, urban living, level of education and ethnicity in relation to depression, insomnia and sexual dysfunction. The analysis between the groups showed a statistically significant difference only in relation to the place of residence. Women living in the city have less trouble.

Discussion

Menopause as a period in the life of a woman has been investigated from all aspects many times. Numerous studies provide data on somatic and psychological changes. Menopausal transition becomes an interesting field of research and attracts great interest among world scientists [10]. This was exactly the motive for performing this study, with particular emphasis on the emotional aspect of perimenopause [11]. Hormonal fluctuations in this period are the cause of numerous somatic disorders (hot flushes, sweating, increased body weight, fatigue, risk of cardiovascular disease, osteoporosis, etc.), which mostly occur in women between 45-60 years (according to Greenblum *et al* [3]. However, besides somatic changes, psychosocial changes are also associated with anxiety, irritability, insomnia, changes in sexual life [12]. In the SWAN study, these symptoms are grouped into the so-called triad of symptoms (depressed mood, insomniaand sexual problems) and the results show that only 5% of the total number of patients surveyed have these symptoms, while in other studies the percentage is up to 20% (our results are 26%) [4]. This percentage refers to the presence of all three symptoms at the same time. In our study isolated symptoms such as depression had 64.8% of patients, insomnia had 67.6%, and sexual dysfunction reported 59.1%. This large difference in the appearance of symptoms is explained by the pre-

sence of stress factors of life, socioeconomic impacts, and all factors of living that affect social and health well-being. The quality of life in modern and economically developed countries in Europe and America is the key factor for this difference in the frequency of the occurrence of the mentioned symptoms [13]. In our country, unfortunately women are not yet encouraged to talk about these changes and to seek professional help, but believe that these are normal occurrences thatgo with menopause. Most studies on this topic have been conducted in the United States, where there is a high prevalence of somatic and psychological symptoms (anxiety, nervousness, stress, depression). All these symptoms are related to each other and occur either intermittently or at the same time, which further emphasizes their effect [14].

Conclusion

Perimenopause with its pathophysiological mechanisms is a trigger period for the appearance of serious disorders in women, on both, somatic and psychosocial grounds. The intensity of somatic disorders has a cumulative effect and reflects on the psychic sphere in the woman and prevents normal daily functioning. More than half of women in this period suffer from this type of disorder, and this fact is not to be underestimated. These results indicate that a serious approach should be taken first in the diagnosis of these disorders; each doctor should pay attention to patients in perimenopause. Moreover, patients are to be advised on changing their lifestyle (diet, physical activity, stress management, medication and psychotherapy). The goal is to alleviate somatic symptoms, to ease the psychological tension, and ultimately, to improve the quality of life of perimenopausal women.

Conflict of interest statement. None declared.

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ММР

Original article

ЛАПАРОСКОПСКА АПЕНДЕКТОМИЈАВО КЛИНИЧКА БОЛНИЦА-ШТИП ОД 2014-2019

LAPAROSCOPIC APPENDECTOMY IN CLINICAL HOSPITAL -SHTIP (2014-2019)

Aleksandar Mitevski[1], Petar Markov[1], Ilija Milev[2] and Nikola Jankulovski[3]

[1]Re-Medika-Skopje, [2]Clinical Hospital-Shtip, [3]University Clinic for Digestive Surgery-Skopje, Republic of North Macedonia

Abstract

Introduction. Appendectomy is the most common emergency surgeryperformed and appendicitis is a trouble some disease for the surgeon despite numerous advances since its discovery. The first laparoscopic appendectomy was made in 1983 by Samm.Thirty years after the first laparoscopic appendectomy, appendectomy is still performed mostly by laparotomy in our country.
Methods. A retrospective study from 01.01.2014 till 01.01.2019 was conducted. Acute appendicitis cases from the registry of the Surgical Department in the Clinical Hospital-Shtip were analyzed. We used a standard three-port laparoscopic appendectomytechnique, and for open approach Mc Burnyor Rocky-Davis incision.
Results. In the 5-year-period, 309 patients with appendectomies were included in the study, 179 males and 130 females, 58% against42%.
The incidence of acute appendicitis was highest in the age group 16-30 years and in the group 6-15 years.
The smallest number of laparoscopic appendectomies were performed in 2014, 5(8%) ofa total of 59, and the largest number in 2017, 33(46%) of 72. Of the total number of 309 appendectomies in the analyzed period 86 (28%) were laparoscopic.
Conclusion. Laparoscopic appendectomy is the preferred choice in treatment of acute appendicitis. Introduced more than 30 years ago and recommended by endoscopic associations, only in the last decade laparoscopic appendectomy has emerged as afirst choice. In Macedonia and in the city of Shtip the percentage of laparoscopic appendectomies is lower than 50%. The best way to increase this percentage limit of 50% is to encourage surgeons to start with laparoscopic exploration and to include this technique in training the residents.

Keywords: acute appendicitis, open appendectomy, laparoscopic appendectomy.

Correspondence to: Aleksandar Mitevski, Re-Medika hospital, 16ta Makedonska brigda No. 18. 1000 Skopje; Phone: +389 71 21 78 71; E-mail: aleksandar.mitevski@ugd.edu.mk

Апстракт

Вовед. Апендектомијата е најчесто изведувана итна интервенција, сепак апендицитот не е едноставна болест за хирургот и покрај напредокот од нејзиното откривање. Првата лапароскопска апендектомија е опишана во 1983 од Samm. Триесет години по првата лапароскопска апендектомија во нашата држава апендектомијата најчесто се изведува со отворен пристап.
Методи. Направивме ретроспективна студија за периодот 01.01.2014-01.01.2019. Беа анализирани пациенти со акутен апендицит од датотеката на Хируршкото оделение во Клиничка болница-Штип. Пациентите беа оперирани со лапароскопска техника со три порта и отворена апендектомија со инцизија по McBurny или Rocky-Davis.
Резултати. Во период од 5 години 309 пациенти беа вклучени во студијата, 179 машки, а 130 женски, 58% наспроти 42%.
Инциденцата на акутен апендицит беше највисока во возрасните групи од 16-30 и од 6-15 години.
Најнизок број на лапароскопски апендектомии биле изведени во 2014, 7 од 59 или 8%, а највисок број во 2017, 33 од 72 или 46%. Од 309 апендектомии во анализираниот период 86 биле лапароскопски или 28%.
Заклучок. Лапароскопската апендектомија е лекување од избор за акутен апендицит. Иако опишана пред 30 години и препорачана од ендоскопските здруженија, во последната деценија стана прв избор при третман на акутен апендицит. Во Македонија и во Штип сеуште процентот на лапароскопски апендектомии е под 50%. Охрабрувањето на хирурзите да почнат со лапароскопска експлорација и да стане дел од тренингот на специјализантите е начин да се пробие таа граница од 50%.

Клучни зборови: акутен апендицит, отворена апендектомија, лапароскопска апендектомија

Introduction

Appendectomy is the most common surgery performed

in the emergency setting and yet appendicitis is a trouble some disease for the surgeon despite numerous advances since its discovery [1].
The first descriptions of appendix date from the 16th century [2]; Leonardo da Vinci depicted it in his anatomical notebooks and was later formally described by Capri and Vesalius [3]. The term "appendicitis" and the natural history of the inflamed appendix were first described by Fitz [4]. Mc Burney is the father of the current open approach for appendectomy; in 1889 he described the landmark that bears his name and more than 120 years ago, in 1894, the incision over it [5,6]. The first laparoscopic appendectomy was performed by Samm in 1983 [7], but the laparoscopic approach became widespread much later.
Thirty years after the first laparoscopic appendectomy, appendectomy is still performed by laparotomy in most of the cases in our country.

Materials and methods

We performed a retrospective study in a 5-year-period, from 01.01.2014 till 01.01.2019. Acute appendicitis cases from the registry of the Surgical Department in the Clinical Hospital-Shtip were analyzed. Also, we included the operative protocol in the survey. All patients that had open or laparoscopic appendectomy were included. Exclusion criteria: patients who had conversion from laparoscopic to open intervention regardless of the reason, patients with negative appendectomy in the presence of obvious other reason.
The appendectomies were performed in general anaesthesia; in patients operated on with laparoscopic approach oro-or nasogastric tube and urinary catheter were placed. In the group of patients with open approach nasogastric tube and urinary catheter were not routinely used.
Patients that were operated on with open approach had Mc Burny or Rocky-Davis skin incision and a muscle-splitting technique [8].
Laparoscopic appendectomy was made by using a standard three-port technique, umbilical port 5-10mm, suprapubic port 5mm and left lower quadrant port 5-10mm; patients were in supine position, in slight Trendelenburg position with tilt to the left. Mesentery was dissected and controlled with energy device;in several patients clips were used and the base of the appendix was secured using Endoloop; in few cases end corporeal suture ligation was performed [9,10].

Results

In the 5-year-period, 01.01.2014-01.01.2019, a total of 309 patients with open and laparoscopic appendectomies met the inclusion criteria for the study.
Of the total number of309 patients, 179 were males and 130 females, 58% against42% (Figure 1).

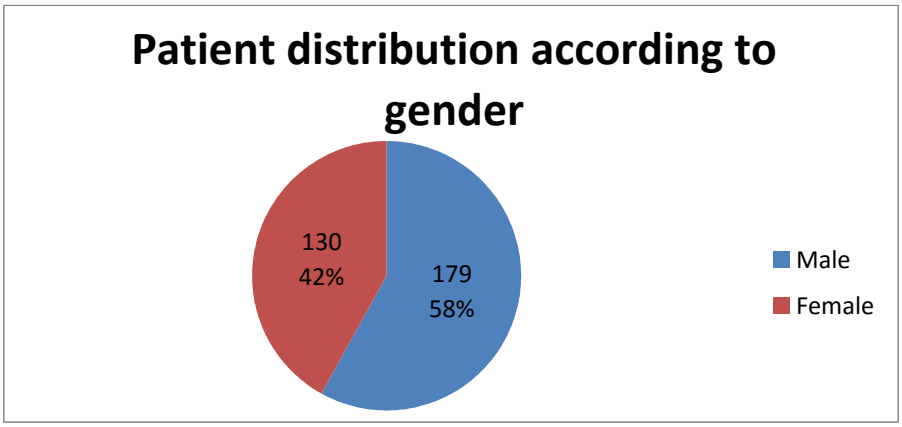

Fig. 1. Distribution of patients according to gender

Table1. Incidence of acute appendicitis according to age groups

	2014	2015	2016	2017	2018	Total
0 - 2	1					1
3 - 5	4	1	1	1		7
6 - 15	19	12	17	21	23	92
16 - 30	20	16	21	20	23	100
31 - 50	9	15	3	14	14	55
51 - 75	2	1	9	12	11	35
Over 75	1				2	3
Age data not available	3	7	2	4		16
Total	59	52	53	72	73	309

The incidence of patients with acute appendicitis was different in the age groups. The highest incidence was in the age group 16-30 years and in the age group 6-15 years (Table 1).
We compared the number of laparoscopic *versus* open appendectomies during the 5-year-period. The smallest number of laparoscopic appendectomies was performed in 2014, 5(8%) of a total of 59, and the highest number of laparoscopic appendectomies was performed in 2017, 33(46%) of 72. A total of 86 laparoscopic and 223 open interventions of the 309 appendectomies were performed in 5 years, or 28% *versus* 72% (Table 2, Figures 3 and 4).

Table 2. Percentage of laparoscopic and open appendectomies

	2014	2015	2016	2017	2018	Total	%
Open appendectomy	92%(54)	87%(45)	68%(36)	54%(39)	67%(49)	223	72%
Laparoscopic appendectomy	8%(5)	13%(7)	32%(17)	46%(33)	33%(24)	86	28%
Total	59	52	53	72	73	309	

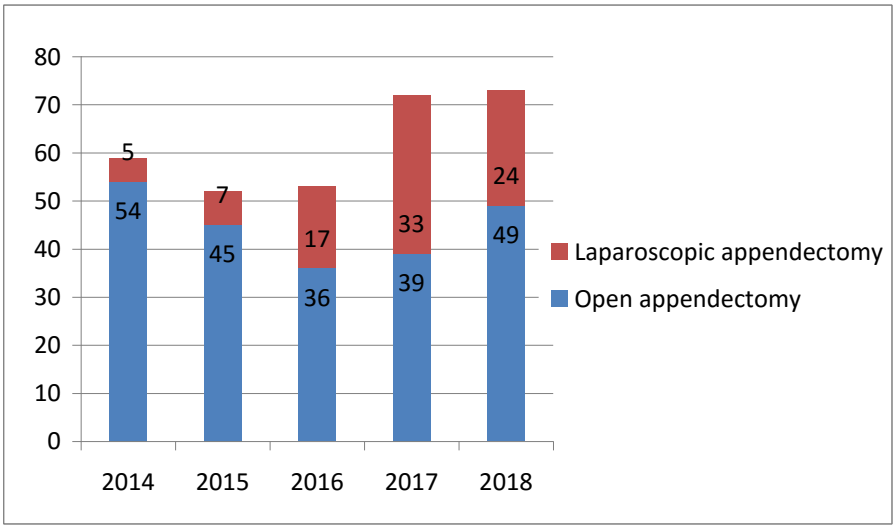

Fig. 3. Laparoscopic versus open appendectomy per year

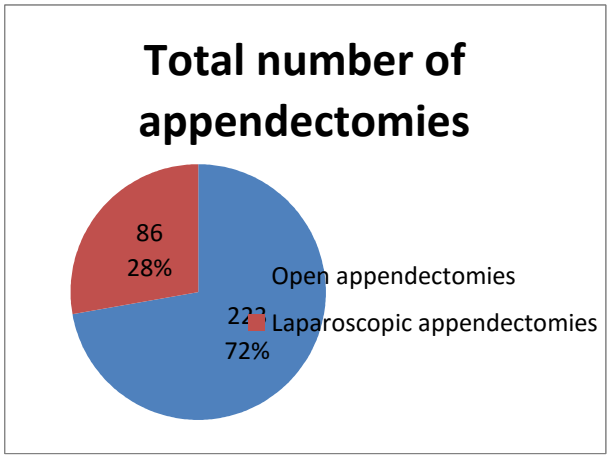

Fig. 4. Total number of laparoscopic versus open appendectomies

Discussion

The incidence of acute appendicitis during lifetime is 8% [11]. Acute appendicitis is more common in males thanin females, with ratio 1.4:1. In a lifetime 8.6% of males and 6.7% of females can developacute appendicitis [12].

In our study, of the total number of 309 patients 179 were males and 130 were females, or 58% *versus* 42%, which is close to the expected ratio.
The study of Addis *et al*. [12,8] found that young age was arisk factor and that 70% of patients presenting with acute appendicitis were less than 30 years old. The incidence in maleswashighest in the age group 10-14 years and in females 15-19 years. Similarly in our study, the incidence was highest in the two age groups 6-15 and 16-30; both age groups consisted of 192 patients or 62% of all analyzed patients.
More than 30 years have passed since the first performed laparoscopic appendectomy (LA) and surgery slowly turned away from open appendectomy (OA).Studies in Germanyshowed that in 2006, 46% of all appendectomies were open [13]. Also, studies from USA from 2000-2005 revealed that 53.7% of appendectomies were done with open approach and 46.3% with laparoscopic approach, with gradual increase of laparoscopic approach during that period from 32% to 58% [14].
Recent studies have shown the advantage of LA over OA [1,15-17]. Also, Cochrane Database of Systematic Reviews [18], recent guidelines by the Society of American Gastroenterology and Endoscopic Surgeons-SAGES

[19] and the World Society of Emergency Surgery-WSES [20] recommend over OA.

The first LA in the Clinical Hospital-Shtip was performed in 2012. Gradually the number of laparoscopic appendectomies has raised, in 2014 out of 59 appendectomies 5 (8%) were laparoscopic; in 2015 out of52, 7(13%) were laparoscopic; in 2016 the percentage of LA was 32%; in 2017-46% and in 2018-33%. During the analyzed 5-year-period, 86 LA were performed or 28% of all appendectomies, with the highest increase of LA from 8% to 46% between 2014 and 2017.

Conclusion

Laparoscopic appendectomy is the preferred choice in the treatment of acute appendicitis. It has been practiced/used for more than 30 years and the recommenddations are in favour of laparoscopic approach. Only in the last decade laparoscopic appendectomy has emerged as a first choice among surgeons. Still, in Macedonia and in the city of Shtip the percentage of laparoscopic appendectomies is lower than 50%. The best way to increase this percentage limit of 50% is to encourage surgeons to start with laparoscopic exploration and to include this technique in training the residents

Conflict of interest statement. None declared.

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ММР

Original article

ONE-LEVEL LUMBAR SPONDYLOLYSIS

ЛУМБАЛНА СПОНДИЛОЛИЗА НА ЕДНО НИВО

Hristijan Kostov, Tode Vraniskoski and Jasmin Ciriviri

Department for Orthopaedics and Traumatology, City General Hospital "8 Septemvri" Skopje, Republic of North Macedonia

Abstact

Introduction. Spondylolysis is a unilateral or bilateral defect or stress fracture of the isthmic portion of the *pars interarticularis* of the vertebra, without forward displacement of that vertebra on the adjacent vertebra [1-3]. It is a stress or fatigue fracture seen most often in children and adolescents [2-4]. It is the most common overuse sporting injury of the lower back, which has been reported to range from 13% to 47% among adolescent athletes [5-7]. The L5 and occasionally the L4 vertebrae are usually involved. [3-8]. Although spondylolysis has been reported to be more common in male than female patients, progression is more likely in female patients.
Aim. The aim of this paper is to present the advantages and disadvantages of conservative (as the most used or conventional metod) and operative treatment.
Methods. We report a case of one-level asymmetric lumbar spondylolysis in a 15-year-old girl. The patient had severe low back pain of increasing intensity with lumbar instability, which was evident on the dynamic radiographs. MRI demonstrated the presence of abnormalities and the three dimensional CT scan revealed complete asymmetric lumbar spondylolysis at the left L5 level. This case was treated surgically with using auto iliac bone graft and without intersegmental fixation using pedicle screws.
Results. The patient was relieved of her low back pain after the surgery.
Conclusion. Many patients with spondylolysis are asymptomatic and therefore require no treatment, but athletes whose sports involve repetitive hyperextension often present initially with pain during certain performance activities. This pain is either unilateral or bilateral, but it may become a more chronic, dull, midline lumbosacral pain in time. The treatment goals should include pain relief, healing of the spondylolysis, and prevention of further lumbar segment injury.
Discusion. Lumbar spondylolysis is common at the fourth and fifth lumbar vertebrae. Two factors play a determinant role in the pathogenesis of spondylolysis: the genetic factor and the mechanical factor of the lumbar spine. We consider that the mechanical factor of the lumbar spine affects the development of spondylolysis in people who are vulnerable due to a genetic factor.

Keywords: lower back pain, lumbar spondylolysis, fusion

Correspondence to: Tode Vraniskoski, Department for Orthopaedics and Traumatology, CGH "8 Septemvri", 1000 Skopje, Republic of North Macedonia; E-mail : todemk@hotmail.com

Абстракт

Вовед. Спондилолизатапретставува унилатерален или билатерален дефект или стрес фрактура на истмичниот дел од меѓу зглобниот сегмент на прешленот, без поместување кон напред на тој прешлен во однос на соседните прешлени [1-3]. Тоа естрес фрактура или фрактура од "замор" на прешленското тело која се сретнува најчесто кај децата и адолесцентите [2-4]. Се јавува како најчеста спортска повреда на долниот дел на грбот и се движи од 13% до 47% кај адолесцентните спортисти [5-7]. Најчесто се појавуваат на ниво L5 и повремено на L4 [3-8]. Инаку, спондилолизата се јавува почесто кај мажите отколку кај жените, а прогресијата е поверојатна кај женските пациенти.
Цел. Презентацијата е да ги прикаже предностите и недостатоците на конзервативниот метод (како најчесто користен или конвенционален метод) и оперативниот третман.
Методи. Ќе прикажеме случај на асиметрична (унилатерална) лумбална спондилолиза на едно нивокај 15-годишно девојче. Пациентката ималајака болка во долниот дел од рбетот со зголемување на интензитетот и лумбална нестабилност, што беше евидентно на динамичните радиографски снимки. Снимките од МР покажале присуство на абнормалности и скенирање со КТ и тридимензионална реконструкција откри асиметрична лумбална спондилолиза на L5 ниво од лево. Овој случај се третираше хируршки со задна фузија во ниво на L5-S1 со користење на коскен графт од илијачната коска, без интерсегментална фиксација и користење на педикуларни штрафови.

Резултати. По операцијата пациентката беше ослободена од долногрбната болка.
Заклучок. Кај многу пациенти спондилолизата е асимптоматска и затоа нема потреба од третман, но кај спортисти чија активност вклучува повторувачка хиперекстензија често се јавува болка за време на одредени активности и перформанси. Оваа болка е унилатерална или билатерална, но таа може да стане хронична, досадна и повремено да се појави по средната линија од лумбосакралниот рбет. Целта на третманот треба да вклучува обезболување, лекување на спондилолизата и превенција од понатамошни повреди лумбалниот сегмент.
Дискусија. Лумбална спондилолиза е честа појава во ниво на четвртиот и петтиот лумбален пршлен. Два фактори играат решавачка улога во патогенезата на спондилолизата: генетскиот фактор и механички фактор на лумбалниот 'рбет. Сметаме дека механичкиот фактор на лумбалниот 'рбет влијае на развојот на спондилолизата кај пациентите кои се изложени поради генетскиот фактор.

Клучни зборови: долногрбна болка, лумбална спондилолиза, фузија

Introduction

Spondylolysis is defined as a defect or stress fracture in the *pars interarticularis* of the vertebral arch [1]. The vast majority of cases occur in the lower lumbar vertebrae, commonly seen at the fourth and fifth lumbar vertebrae, in more than 95% of the total cases of spondylolysis [1]. However, multiple lumbar spondylolysis is an unusual and relatively rare finding. The incidence of multiple lumbar spondylolysis appears to vary between 1.2% [2,3] to 5.6% [4].

Anatomy and Pathophysiology

The lumbar vertebra consists of a body, pedicle, lamina, *pars interarticularis*, transverse process, spinous process and superior and inferior articular facets, which form joints that link the vertebrae together. When examining the vertebra, the *pars interarticularis* is the bony segment between the superior and inferior articular facet joints located anterior to the lamina and posterior to the pedicle. Separation of the *pars interarticularis* occurs when spondylolysis is present in the spinal column [3].
Spondylolysis is typically caused by a stress fracture of the bone, and is especially common in adolescents who over-train in activities. The *pars interarticularis* is vulnerable to fracture during spinal hyperextension, especially when combined with rotation, or when experiencing a force during a landing. This stress fracture most commonly occurs where the concave lumbar spine transitions to the convex sacrum (L5-S1). A significant amount of individuals with spondylolysis will develop spondylolisthesis, which is true for 50-81% of this population.

Epidemiology / Etiology

The cause of spondylolysis remains unknown, however many factors are thought to contribute to its development. The condition is present in up to 6% of the population, majority of which usually present asymptomatically [6]**.** Research supports that there are hereditary and acquired risk factors that can make one more susceptible to the defect. The disorder is generally more prevalent in males compared to females, and tends to occur earlier in males due to their involvement in more strenuous activities at a younger age [7]. In a young athlete, the spine is still growing which means there are many ossification centers, leaving points of weakness in the spine. This leaves young athletes at increased risk, particularly when involved in repetitive hyperextension and rotation across the lumbar spine [8]. Spondylolysis is a common cause of low back pain in preadolescents and adolescent athletes, as it accounts for about 50% of all low back pain [6]. It is believed that both repetitive trauma and an inherent genetic weakness can make an individual more susceptible to spondylolysis [9].

Signs / Symptoms

In majority of cases, spondylolysis presents asymptomatically which can make diagnosis both difficult and incidental [5]. When a patient does present with symptoms, there are general signs and symptoms a clinician will look for:

Clinical signs: [9,10]
- Pain on completion of the stork test (placed in hyperextension and rotation)
- Excessive lordotic posture
- Unilateral tenderness on palpation
- Visible on diagnostic imaging

The **scottie dog** (Scottish Terrier, Aberdeen Terrier) **sign** (Figure 1) refers to the normal appearance of the lumbar spine when seen on oblique radiographic projection. On oblique views, the posterior elements of vertebra form the figure of a Scottie dog with:
- the transverse process being the nose
- the pedicle forming the eye
- the inferior articular facet being the front leg
- the superior articular facet representing the ear
- the *pars interarticularis* (the portion of the lamina that lies between the facets) equivalent to the neck of the dog.

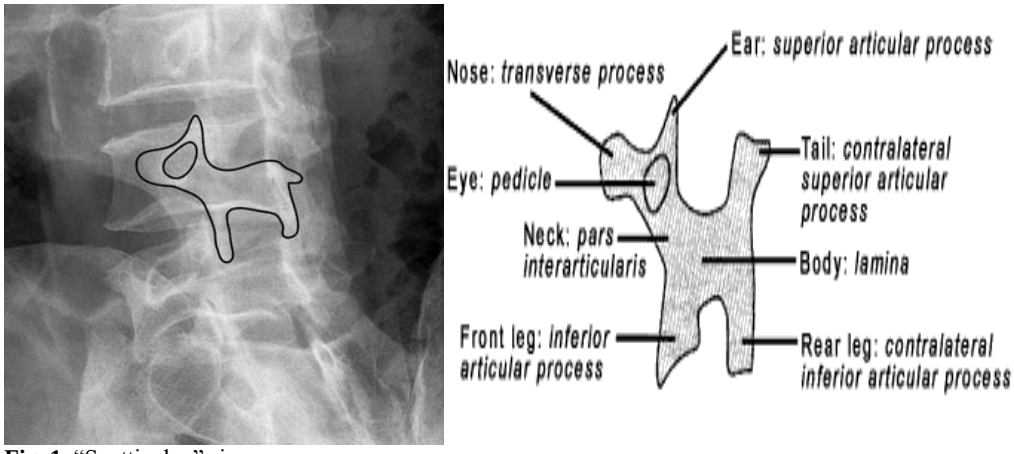

Fig. 1. "Scottie dog" sign

Scottie dog sign-refers to the normal appearance of the lumbar spine posterior elements when seen on oblique views.

If spondylolysis is present, the *pars interarticularis*, or the neck of the dog, will have a defect or break. It often looks as if the Scottish dog has a collar around the neck or doggy decapitation for those with a bloodier imagination (Figure 2).

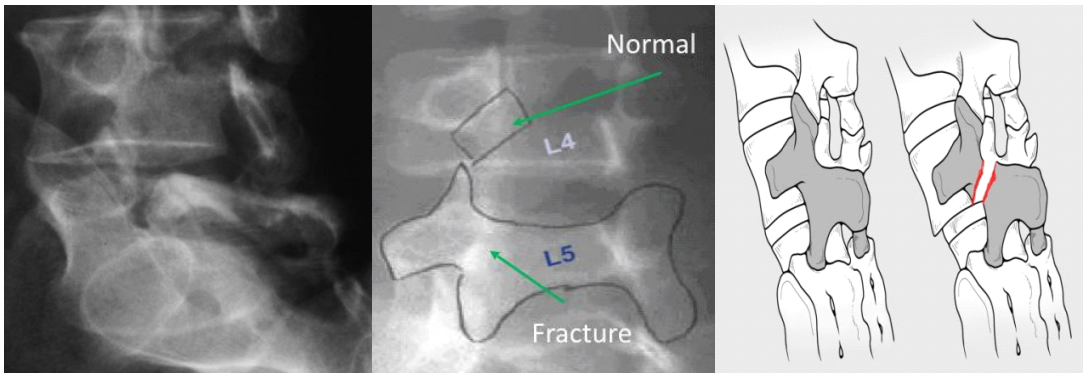

Fig. 2. "Scottie dog" sign

Symptoms: [9,10]

- Unilateral low back pain
- Pain that radiates into the buttocks or legs
- Onset of pain can be acute or gradual
- Pain that can restricts daily activities and it that worsens after strenuous activity
- Pain aggravated with lumbar hyperextension
- No tenderness to palpation is noted
- Range of motion is full
- Forward flexion does not increase symptoms
- Hyperextension mimicking the sporting movement generally elicits pain [11].
- If a unilateral defect is present, the one leg hyperextension test elicits pain on the involved side. This test is performed by the patient bearing weight on one leg, with both the hip and knee of the other extremity flexed while hyperextending the lumbar spine [11]. The maneuver is performed on both sides, and asymmetric low back pain indicates unilateral disease. Bilateral disease may show symmetric or asymmetric pain with this maneuver [18].

Risk Factors / Causes

The repetitive actions of flexion, extension, rotation, and torsion, either alone or in combination, that are often associated with resistance are the biomechanical movements that show the highest prevalence of lumbosacral spondylolysis (lumbar spondylolysis). The stress fracture of the *pars interarticularis* occurs on the side opposite to activity. For instance, for a right-handed player, the fracture occurs on the left side of the vertebrae [15].

Differential diagnoses

Lumbosacral disc injuries, lumbosacral discogenic pain syndrome, lumbosacral facet syndrome, lumbosacral spine acute bony injuries, lumbosacral spine sprain/strain injuries, lumbosacral spondylolisthesis, lumbosacral spondylolysis, myofascial pain in athletes, sacroiliac joint injury.

Treatment
Conservative Management

Treatment for spondylosis ranges from bracing, activity restriction, extension exercises, flexion exercises and deep abdominal strengthening, that were administered through physical therapy. The duration of physical therapy a patient receives varies upon the severity of spondylolysis, however typically ranges from three to six months [16].

- Deep abdominal co-contraction exercises [17]
- Activity restriction [19]
- Bracing, anti-lordotic brace (Boston brace) for 6-12 weeks [18,20].

Operative Management
Case study

The aim of this paper is to present the advantages and disadvantages of conservative (as the most used or conventional metod) and operative treatment.

Materials and methods

We report a case of one-level asymmetric lumbar spondylolysis in a 15-year-old girl. A 15-year-old girl visited our out-patient clinic for severe back pain that had developed spontaneously. The patient was a student at the secondary school. The initial assessment showed that lumbar extension reproduced the low back pain, without evidence of hamstring tightness and radicular symptoms.

Clinical evaluation

The initial assessment showed that lumbar extension reproduced the low back pain, without evidence of hamstring tightness and radicular symptoms. The patient had severe low back pain of increasing intensity with lumbar instability, which was evident on the dynamic radiographs. MRI demonstrated the presence of abnormalities and the three-dimensional CT scan (Figure 3) revealed complete asymmetric lumbar spondylolysis at the left L5 level.

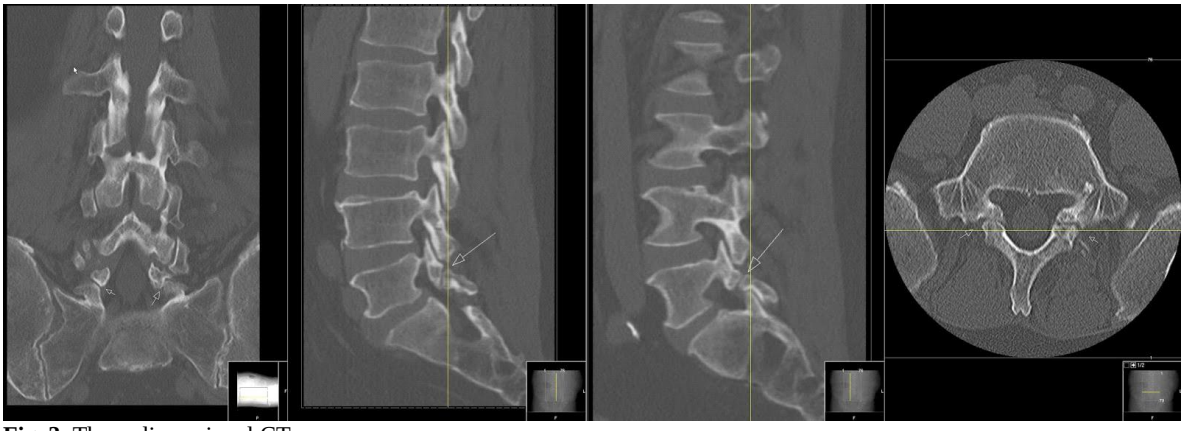

Fig. 3. Three-dimensional CT scan

Treatment

The treatment started in the middle of January 2016, with activity restriction, extension exercises, flexion exercises and deep abdominal strengthening that were administered through physical therapy. The duration of physical therapy was about four months. The goal of physical therapy was to minimize movement at the unstable defect of the *pars interarticularis*. Once the patient had completed physical therapy, and displayed no symptoms or inflammation in the lower back, she could continue with daily or athletic activities. However, after a few weeks the patient had the same back pain as in the previous 6 months.

When she came to us, we placed thoracolumbar sacral orthosis (TLSO), an anti-lordotic brace, to control and limit the spinal movement, and reduce the stress on the injured spinal segment [18,20]. Bracing immobilizes the spine in a flexed position for a short period to allow healing of the bony defect in *pars interarticularis* [20]. Our patient utilized the brace for 8 weeks and after that she wore thoracolumbar sacral orthosis (TLSO) for 4 weeks during daily activities.

The patient initially noticed a kyphosis in the lumbar area around one year ago. However, since it was not associated with any significant disability or pain, she was treated conservatively at that time. Yet, after a routine exercise program at the secondary school, she developed a low back pain for which she was prescribed oral medication. However, the back pain did not improve with the oral analgesics and it started to increase in intensity.

At the time of presentation at our outpatient clinic, a lumbar kyphosis was noticed in the standing position. In general, the kyhosis and instability of the lower back were moderate to severe. The kyphosis was found to be flexible because the kyphosis could be corrected when the low back area was pushed anteriorly by the

surgeon's hands. She had severe lower back pain. The visual analogue score (VAS) was 8 points. The patient also showed generalized ligamentous laxity. There were no neurological signs or symptoms. The initial radiographs showed a hypoplastic change in the spinous processes and lamina of the lumbar vertebrae, one-level spondylolysis and lumbar instability (Figure 4).

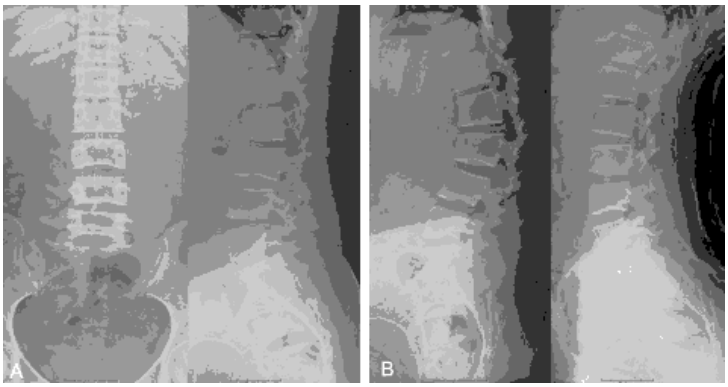

Fig. 4. Initial radiographs

Obvious instability of the L5/S1 segment was not noted intraoperatively. The *pars interarticularis* of L5-S1 were dystrophic, so we had to repair the defect.
Posterior lumbar interbody fusion was chosen. Because the patient had no neurologic symptoms, we did not need to open the neural canal, and laminectomy was not done. We took out the fractured pars of *pars interarticularis* of L5 and we performed spongioplasty with using auto iliac bone graft (alograft) (Figure 5, 6, 7, 8).

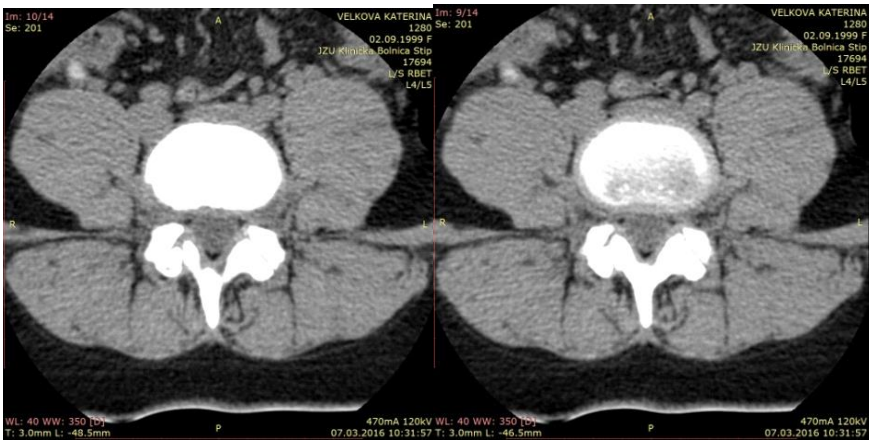

Fig. 5. **Fig. 6.**

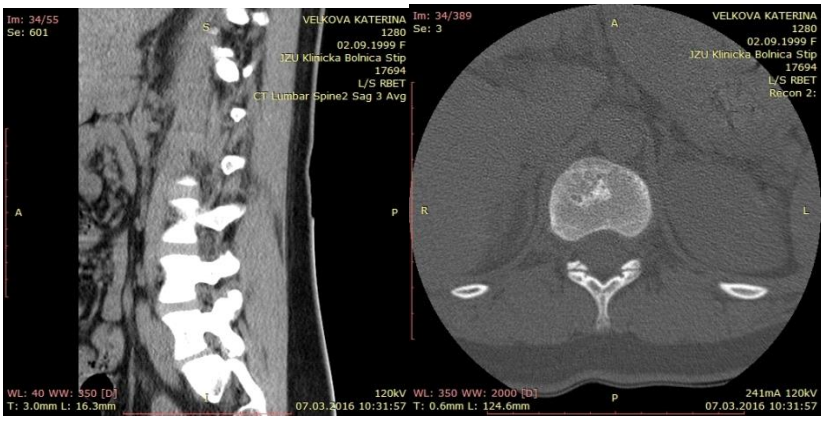

Fig 7. **Fig 8.**

Fig. 5-8. Postoperative radiographs

Results

After operation, the patient's lower back pain was much relieved and the VAS was 4 points. The postoperative 5 months follow-up of the patient showed no neurological deficit, no lumbar instability and no failure. There was a very good improvement of her symptoms and she was satisfied with the cosmetic result. The patient was completely relieved of lower back pain after the surgery, and the VAS was 2 points.

Discusion

Lumbar spondylolysis is common at the fourth and fifth lumbar vertebrae. The frequency of spondylolysis in the upper lumbar vertebrae has been estimated by various authors to be between 0.2% and 1.5% [6]. Two factors play a determinant role in the pathogenesis of spondylolysis: the genetic factor and the mechanical factor of the lumbar spine. Familial occurrence of spondylolysis has been demonstrated by Friberg [7], Willis [8] and Wiltse [9], and it supports the fact that a genetic factor can be involved with this malady, but the specific gene that affects spondylolysis is unknown. In the report by Wiltse [9], the youngest patient with spondylolysis was eight and a half month old. It is thought that spondylolysis is associated with the upright position. There may be a relation between repetitive trauma and spondylolysis. People employed in heavy industry and people who participate in contact sports seem to be particularly vulnerable to this condition [11,12]. So, multiple spondylolysis is more commonly seen among men for assessing the vertebral stability.
We consider that three dimensional CT is a very good and useful tool for the diagnosis of multiple spondylolysis and for making the decision on what level to fuse. In our case, because the patient had constant severe lower back pain for a long time and a spinal deformity and severe instability had developed, she underwent a single-stage posterolateral bone fusion without instrumentation. After the operation, the patient was free of her pain and spinal instability.
We report a well-treated case of one-level spondylolysis.

Conclusion

Many patients with spondylolysis are asymptomatic and therefore require no treatment, but athletes whose sports involve repetitive hyperextension often present initially with pain during certain performance activities. This pain is either unilateral or bilateral, but it may become a more chronic, dull, midline lumbosacral pain in time. The treatment goals should include pain relief, healing of the spondylolysis, and prevention of further lumbar segment injury.

Conflict of interest statement. None declared.

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ММР

Original article

HYPERTENSIVE DISORDERS IN PREGNANCY-PHYSICIANS'AWARENESS FOR EARLY DETECTION

ХИПЕРТЕНЗИВНИ НАРУШУВАЊА ВО БРЕМЕНОСТА-СВЕСНОСТ НА ДОКТОРИТЕ ЗА РАНА ДЕТЕКЦИЈА

Kristina Skeparovska[1] and Nikola Jankulovski[2]

[1]Special Hospital for Obstetrics and Gynecology "Mother Teresa"- Skopje, [2]University Clinic for Digestive Surgery, Medical Faculty, Skopje, Republic of North Macedonia

Abstract

Introduction. Hypertensive disorders in pregnancy are a major cause of perinatal morbidity and mortality. Early diagnosis, term delivery, and/or patient's transfer to a tertiary institution have a huge impact on favorable outcome.
Aim. To estimate ob-gyn physician's awareness for early detection of pregnancy hypertension i.e. for establishing diagnosis before the onset of symptoms.
Methods. Study population was consisted of all pregnant women in ≥37 week of gestation admitted to Special Hospital for Obstetrics and Gynecology "Mother Teresa" during the period 15.02-28.02.2018. The study was designed as a retrospective one, and the data were collected by a questionnaire.
Additionally, histories of all patients admitted to SHOG "Mother Teresa" between 01.01.2017 and 31.12.2017 under diagnosis of PIH/PE (pregnancy-induced hypertension/pre-eclampsia), were analyzed retrospectively whether the diagnosis was established during the hospital admission or before.
Results. Twenty-two percent of pregnant women that underwent regular antenatal check-ups did not have blood pressure measurement taken by their ob-gyn physician at all. Only in 16.7% of cases, the diagnosis was established early, i.e. before the onset of symptoms.
Conclusion. The awareness of ob-gyn physicians for early (pre-symptomatic) detection of hypertensive disorders in pregnancy is low.

Keywords: pregnancy-hypertension, preeclampsia, early detection, blood pressure

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Апстракт

Вовед. Хипертензивните нарушувања во бременоста се една од водечките причини за перинатален морбидитет и морталитет.
Навремената дијагноза, правовременото породување и/или транспортот на пациентката кон терциерен центар имаат големо влијание врз обезбедување на поволен исход при оваа патологија.
Цел. Да се испита свесноста (сензибилизираноста) на гинеколозите за детекција на истите пред пријавувањето на симптоми од страна на бремената жена т.е. за рана дијагноза.
Методи. Како материјал служеа сите трудници во ≥37 гестациска седмица кои во периодот 15.02.-28.02.2018 беа хоспитализирани во СБГА "Мајка Тереза". Студијата беше ретроспективна, а податоците се колектираа преку анкетен прашалник.
Дополнително, беа ретроспективно анализирани сите пациентки кои во 2017 година биле хоспитализирани во СБГА "Мајка Тереза" со дијагноза PIH/PE (pregnancy-induced hypertension/pre-eclampsia) за времето на поставување на дијагнозата.
Резултати. 22% "редовно контролираните" трудници нема ниту едно мерење на крвен притисок од страна на матичен гинеколог. Само кај 16,7% трудници дијагнозата е поставена рано т.е. пред појава на симптоми.
Заклучок. Свесноста на гинеколозите за рана (предсимптоматска) детекција на хипертензивните нарушувања во бременоста е ниска.

Клучни зборови: хипертензија во бременост, преeклампсија, рана детекција

Introduction

Hypertensive disorders in pregnancy (HDP) are serious conditions that occur in the second half of pregnancy. They may be present in various forms, such as: pregnancy-induced hypertension (PIH), preeclampsia (PE) or eclampsia, or may present with consequences like: placental abruption, acute renal failure, disseminated intravascular coagulation (DIC), cerebral hemorrhage that can seriously compromise the health and the life of a pregnant woman [1]. On the other hand, the fetus is also affected by diminished placental perfusion that can lead to fetal growth restriction [2] or even fetal

Correspondence to: Kristina Skeparovska, Special Hospital for Obstetrics and Gynecology "Mother Teresa"- Skopje, 1000 Skopje, Republic of North Macedonia; E-mail: kristina_skeparovska@yahoo.com

demise [3].This is why HDP, although rare, with an incidence of 3% [1], are one of the leading causes of maternal and perinatal morbidity and mortality [1].
Adequate management of this pathology in terms of providing the best possible outcome for mother and her baby implies early diagnosis of the condition that will allow enough time for preparations for term delivery or, if necessary, patient's transport to tertiary care hospital.
It is fundamental, for early diagnosis of this condition, which means diagnosis before onset of symptoms, regular check-up of the blood pressure [4]. This inexpensive, non-invasive, no-time consuming and highly efficient procedure, by current guidelines, is mandatory on every antenatal check-up [5].

Aim

The aim of this study was to estimate the awareness of out-hospital gynecologists (ob-gyn physician at primary care level) for early detection of hypertensive disorders in pregnancy through regular blood pressure measuring during antenatal visits.

Material and methods

This study comprised 205 pregnant women beyond 37 weeks of pregnancy admitted to the Special Hospital for Obstetrics and Gynecology "Mother Teresa"- Skopje for delivery during 15.02.2018 and 28.02.2018. Hypertensive pregnancy disorders, both actual and previous, were exclusion criteria.
All patients were offered the following questionnaire:

1. How many antenatal check-ups have you had by your primary care ob-gyn physician?
2. How many times your blood pressure was measured during these visits?
3. How many times have you measured your blood pressure at home?

Regarding the answers:

1. All women with at least 7 antenatal visits were considered as patients **with regular** medical check-ups.
2. The second question offered 4 options:

- On each visit
- Occasionally
- One or two times
- Not even once

3. The third question offered three options:

- More than 10 times
- One or two times
- Not even once

Additionally, all patients admitted to SHOG "Mother Teresa" during 2017 with diagnosis preeclampsia or pregnancy-induced hypertension, were checked whether the diagnosis was referral one from primary care gynecologist, or it was established upon patient arrival in the hospital.

Results

The following results were obtained:

- Of 205 consecutively admitted patients for delivery, 182 (88.8%) had regular antenatal visits (Figure 1).

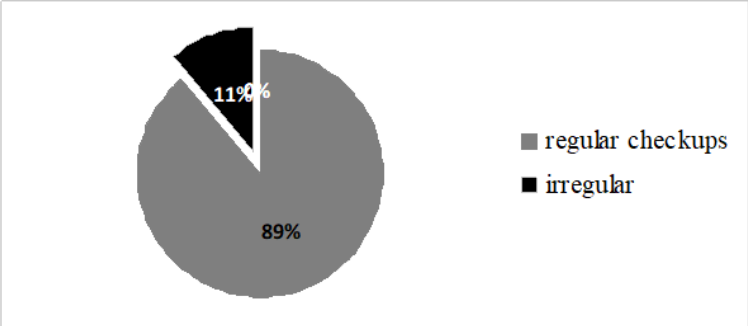

Fig. 1. Proportion of pregnant women with regular antenatal visits

- Of those with regular antenatal visits, only 94 women (51.6%) stated that their blood pressure was measured during each visit. Forty patients (22%) answered that their blood pressure was not measured even once, and additionally 7.7% declared once or two blood pressure controls by their primary care ob-gyn physician (Figure 2).
- Of these forty pregnant women whose blood pressure was never measuredby a primary care ob-gyn physician, 14(35%) did not measure the blood pressure even once by themselves at home, and 5 (12.5%) did that once or twice (Figure3).
- One or two blood pressure check-ups, either at the doctor's office or at home, had 19 out of 182, i.e. 10.4% of "regularly checked-up" patients.
- **7**.7% of pregnant women with "regular" antenatal visits did not measure the blood pressure either at home or at the doctor's office.
- Additionally, only 11 out of 69 patients admitted to our hospital with diagnosis of PE/PIH, came with the diagnosis previously established by a primary care gynecologist. In the remaining 58 patients, the diagnosis was made upon their arrival in the hospital (Figure 4).

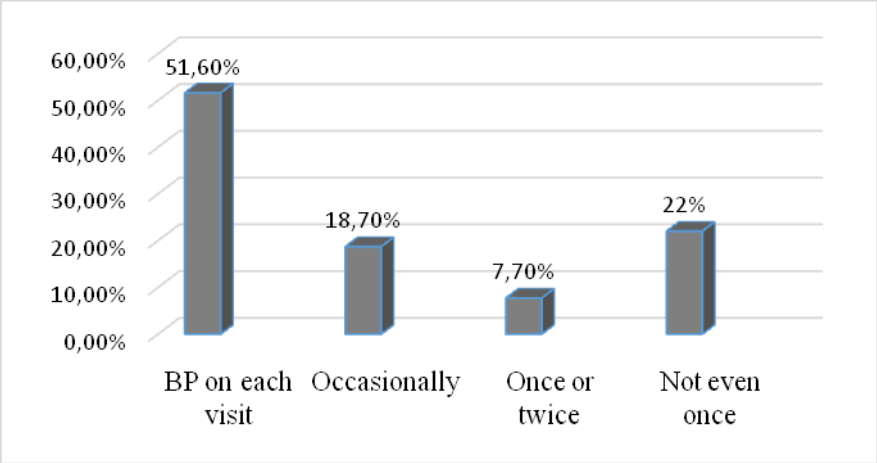

Fig. 2. Blood pressure measured by primary care ob-gyn physician

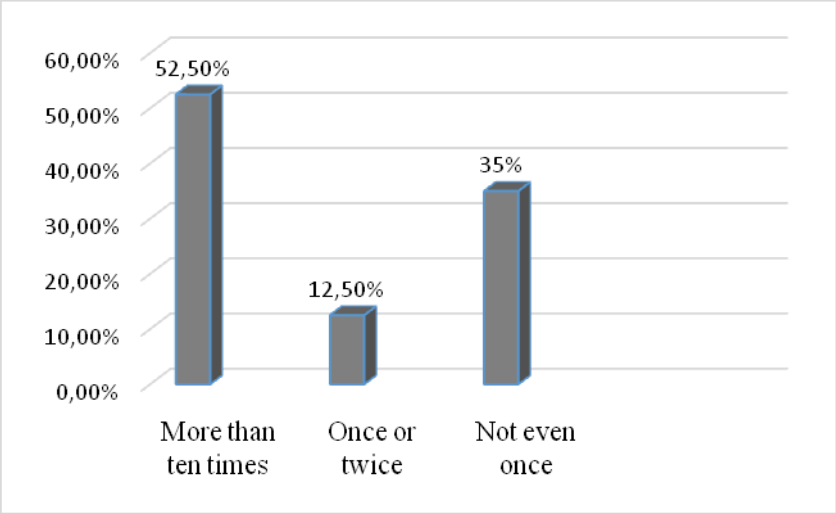

Fig. 3. Blood pressure measured at home by women without ob-gyn BP control

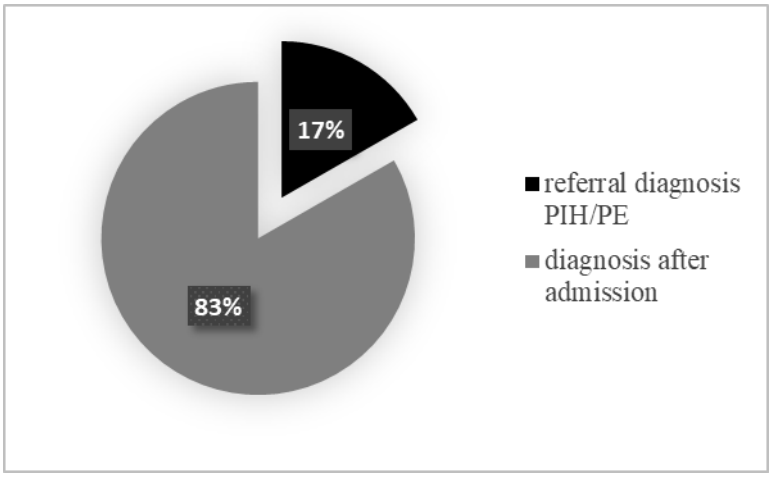

Fig. 4. PIH/PE referral or diagnosis after admission

Discussion

Even though nine out of ten women visit their gynecologist regularly, only in half of them blood pressure is measured during each visit. The remaining half do not have adequate screening for hypertensive disorders in pregnancy before symptoms onset.

The finding that every fifth pregnant woman **has no screening for HDP at all** is highly worrisome. Furthermore, every third woman whose physician doesn't

measure her blood pressure, does not measure it by herself either.

Additionally, one out of six women has diagnosis of PHI/PE established during antenatal check-ups by her primary care gynecologist. The remaining **83% of patients got a diagnosis upon their hospital admission,** which means it has been failed in early diagnosis, and consequently in opportunity of planned labor induction and/or in transporting the patient in a tertiary care institution.

Conclusion

Ob-gyn physicians at primary care level have low awareness for early (pre-symptomatic) detection of hypertensive disorders in pregnancy.

This finding together with the knowledge that current National Institute for Health and Care Excellence (NICE) guidelines for PE screening has failed (with sensitivity of about 40%) [6,7] in adequate recruiting of high-risk patients demanding closely antenatal surveillance, has a significant negative effect on perinatal outcome for both, the mother and her newborn.

Conflict of interest statement. None declared.

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Original article

INHERITED THROMBOPHILIA AND IMPLICATIONS IN PREGNANCY LOSS

НАСЛЕДНА ТРОМБОФИЛИЈА И ИМПЛИКАЦИИ ВО ГУБИТОКОТ НА БРЕМЕНОСТА

Elena Petkovikj[1], Rada Grubovic Rastvorceva[1] and Rozalinda Isjanovska[2]

[1]Institute of Transfusion Medicine - Skopje, [2]Institute of Epidemiology and Biostatistics with Medical Informatics, Medical Faculty, Ss. Cyril and Methodius University – Skopje, Republic of North Macedonia

Abstract

Introduction. Thrombophilia is a hypercoagulable condition with predisposition to thromboembolism. Recently, the inheritedthrombophilicmutations of the Factor V Leiden (FVL) G1691A gene, the methylentetrahydrofolate reductase (MTHFR) C677T gene and Factor II gene Prothrombin G20210A have been implicated in pregnancy loss. The **aim** of the study wasto evaluate the clinical characteristics and to examine the representation of thrombophilic mutations in women with pregnancy loss and healthy controls.
Methods. In a retrospective-prospective case-control study we evaluated 79women, divided in two groups. The study group included 43 women with history of pregnancy loss (missed abortion, blighted ovum, miscarriage in the first or second trimester,foetusmortus in utero). The control group included 36 women, age matched, who gave birth to at least one healthy baby without obstetric complications. Presence of gene mutations forprothrombin G20210A, FVL and MTHFR C677T was examined in both groups. Sociodemographic data, data from personal, family and obstetric anamnesis was collected with standard questionnaire.
Results. The average age of the study group was lower than that of the control group (median 30.7, range 20-41 *versus* median 32.8, range 23-44, respectively). Prothrombin G20210A heterozygous was found in 23.5% of the study group *vs.* 5.5% of the control group; FVL heterozygous was found in 23.5% of the study group *vs*. 2.8% of the control group; MTHFR homozygous was found in 48.8% of the study group *vs*. 5.5.% of the control group witha significant statistical difference ($p<0.05$).
Conclusion. The presence of thrombophilic mutations may predispose to pregnancy loss.

Keywords: thrombophilia, factor V Leiden, MTHFR, prothrombin, pregnancy loss

Апстракт

Вовед. Тромбофилија е состојбана хиперкоагулабилност со предиспозиција за тромбоемболизам. Неодамна, наследните тромбофилни мутации на генотза Factor V Leiden (FVL) G1691A, метилентетрахидрофолатредуктаза (MTHFR) C677T и Фактор II Протромбин G20210A се вмешани во губиток на бременоста.
Цел. Да се евалуираат клиничките карактеристики да се испита застапеноста на мутациите за тромбофилијакај жените со губиток на бременост и контролна група.
Методи. Во ретроспективно-проспективна студија на случај и контрола се евалуирани 79 жени, поделени во две групи. Во испитуваната група (ИГ) се вклучени 43 жени со историја нагубиток на бременоста (missed abortus, blighted ovum, спонтан абортус во прво или второ тримесечје, мртов плод). Во контролната група (КГ) се вклучени 36 жени на иста возраст, што веќе родиле, без акушерски компликации барем едно здраво дете. Кај жените е испитано присуство на мутации на генот за протромбин (G20210A), FVLиMTHFR C677T. Социо-демографски податоци, податоци од лична, акушерска и семејна анамнеза беа прибрани со стандарден прашалник.
Резултати. Просечната возраст на ИГ беше пониска од онаа на КГ (просек 30.7, опсег 20-41 наспроти просек 32.8, опсег 23-44, соодветно). Протромбин G20210A хетерозигот бил пронајден кај 23.5% од ИГ наспроти 5.5% од КГ, FVL хетерозигот бил пронајден кај 23.5% од ИГ наспроти 2.8% од КГ, MTHFR хомозигот бил пронајден кај 48.8% од ИГ наспроти 5.5% од КГ со сигнификантна статистичка разлика за $p <0.05$.
Заклучок. Присуството на тромбофилични мутации може да доведе до губиток на бременоста.

Клучнизборови: тромбофилија, фактор V Leiden, MTHFR, протромбин, губиток на бременост

Correspondence to: Elena Petkovikj, Institute of Transfusion Medicine -Skopje, Republic of North Macedonia E-mail: elena.petkovic@yahoo.com

Introduction

Thrombophilia occurs when the normal balance of the coagulation system is impaired. It can be inherited, i.e. a genetically determined predisposition for thromboembolism with a common occurrence at the age of 45-50 years, with tendency of frequent relapse and thrombotic incidents in unusual places [1]. The most common causes ofinherited thrombophilia are: deficiency of natural antagonist III antagonist III (ATIII), protein C (PC) deficiency, protein C (PS) deficiency, and factor V Leiden G1691A (FVL), factor II prothrombin G2010A and methylenetetrahydrofolate reductase C677T (MTHFR). The most common cause of acquired thrombophilia is the presence of antiphospholipid antibodies (APA) and lupus anticoagulant (LA).

The gene mutation for factor V Leiden G1691A is inherited in an autosomal dominant fashion. FVL is characterized by a weak anticoagulant response to activated PC, which is a natural anticoagulant protein that breaks down and inactivates Va and VIIIa, thereby preventing the further creation of thrombin.Leiden mutation produces PC resistance resulting in a prothrombotic condition that leads to a thrombosis risk [2-6]. This mutation is very common in the general population with a prevalence of 2-15%. The highest heterozygosity rate is found in Europe, while the mutation is very rare among Asian, African and Indigenous Australians [7].

Gene mutation for factor II Prothrombin G2010A is associated with an increased risk of thrombosis, complications and an unfavorable outcome of pregnancy [4-6,8]. The prevalence of heterozygotes is 2-6.5% in the European population [7].

Gene mutation for methylenetetrahydrofolate reductase C677T (MTHFR) results in decreased synthesis of 5-methyltetrahydrofolate, the primary methyl donor in the conversion of homocysteine to methionine. This results in increasing the plasma homocysteine concentrations, which then induces platelet aggregation by promoting endothelial oxidative damage and is a risk factor for thrombosis, atherosclerosis, recurrent pregnancy loss and fetal neural tube defects [4,6,9]. Mild and moderate hyperhomocysteinemia is autosomal dominant inherited present in up to 20% of the white European population [10].

Miscarriage is defined as the spontaneous loss of a fetus before it reaches viability and occurs in up to 15% of clinically recognized pregnancies[11].In the first trimester, the terms miscarriage, spontaneous abortion, and early pregnancy loss are used interchangeably, and there is no consensus on this terminology in the literature. Approximately 1 in every 10 pregnancies ends in early death of the embryo or the fetus (that is, before 20 weeks of gestation), and 1 in every 200 pregnancies ends in late fetal loss. Recurrent pregnancy loss (RPL) refers to three or more consecutive losses and occurs in 1% of couples trying to conceive [12]. The cause of RPL is not apparent and clarification of the cause is difficult due to the heterogeneity of the condition.Many different abnormalities including fetal chromosomal inversions or translocations, anatomic abnormalities of the maternal uterus, endocrinological abnormalities, and autoimmune disorders can result in recurrent fetal loss, but 50% of the causes for RPL remain unexplained [13]. Inadequate or abnormal placental vasculature may result in several complications that have potentially serious or even lethal consequences for the mother and her unborn child. These complications include preeclampsia, placental abruption, intrauterine growth retardation, miscarriage and stillbirth [7].

Recently, the inherited mutation of the Factor V Leiden G1691A gene, the MTHFR C677T gene, Factor II gene Prothrombin G20210A has beenimplicated in the loss of early pregnancy and*invitro* fertilization (IVF) failure by disrupting the initial vascularization process occurs during implantation, which is necessary for successful pregnancy.

The aimof this study was to evaluate the clinical characteristics and examinethe representation of thrombophilic mutations in women with pregnancy loss and healthy controls.

Materials and methods

This is retrospective-prospective case-control study conducted at the Institute of Transfusion Medicine – Skopje (ITM-Skopje). The study included 79 women divided in two groups. The data from the performed examinations and analyses in the outpatient clinic at ITM-Skopje in the period 2015-2018 were processed for the women with diagnoses according to the inclusion criteria.

Inclusion criteria:

- Women aged 18-45,
- Women with history of adverse pregnancy outcome: missed abortion, blighted ovum, miscarriage in the first or second trimester, fetus mortus in utero.

Exclusion criteria:

- Women who had a previous history of venous thromboembolism,
- Women with pre-existing causes of secondary thrombophilia: autoimmune disorders (such as systemic lupus erythematosus, rheumatoid arthritis, Hashimoto thyroiditis) positive AFA, positive LA, extreme obesity, dyslipidemia, nephrotic syndrome,
- Women who refused to participate in the study or gaveup at some point in the study.

In the study group, 43 women with a history of adverse pregnancy outcome (missed abortion, blighted ovum, miscarriage in the first or second trimester, foetusmortus) were included.

The control group included 36 women, age-matched, who gave birth to at least one healthy child without obstetric complications.

Presence of gene mutations for factor IIProthrombin G20210A, factor VLeidenG1691A and methylentetrahydrofolate reductase (MTHFR C677T) was examined in both groups. Sociodemographic data, data from personal, family and obstetric anamnesis werecollected with a standard questionnaire. Blood samples from the included women were examined in the Molecular Biology Laboratory at ITM - Skopje, with previously given informed consent before taking blood samples and using the results in the preparation of the study, approved by the Ethics Committee at the Medical Faculty - Skopje.

Method used to examine factor II factor G20210A, factor V Leiden G1691A and MTHFR C677T - molecular detection of point mutations using the Operon kit. It took 2ml venous blood taken with a vacutainer in K2EDTA.

Statistical analysis was performed with the statistical package STATISTICA 7.1; SPSS 13.0. Numerical series were analyzed with measures of central tendency and measures of dispersion of data. The Student's t-test (t) was used for testing the significance of difference between groups. A p-value less than 0.05 was considered as statistically significant.

Results

The representation of nationality in the studygroup and the control group was homogenous and according to the national structure in the Republic of Macedonia wasapproximately the same. Thirty-one women (72.1%) in the study group and twenty-five women (69.5%) in the control group were Macedonians, 20.9% of the women in the study group and 19.4% of the controls were Albanians, and 7% of the women in the studied group and 11.1% of the controls were of other ethnicity (Table 1).

The average age of the study group was lower than that of the control group (median 30.7, range 20-41 *versus* median 32.8, range 23-44 respectively), but the difference did not reach statistical significance (p>0.05).

Table 1. Ethnicity

Ethnicity	Patients N (%)	Controls N (%)
Macedonians	31 (72.1%)	25 (69.5%)
Albanians	9 (20.9%)	7 (19.4%)
Other	3 (7%)	4 (11.1%)
Total	43	36

The 43 women in the study group had a total of 125 pregnancies (mean 2.9±1.5) and the 36 women in the control group had a total of 77 pregnancies (mean 2.1±0.5) and the difference was statistically significant for p<0.05 (t-test=2.871773, p=0.005270). The average number of spontaneous abortions in the study group was 1.7±1.6 *versus* the control group 0.1±0.2; this difference reached a statistical significance for p<0.05 (t - test = 6.429524, p = 0.000000) (Table 2).

Table 2. Clinical features of pregnancy loss patients and controls

Age	Median	N	Std.Dev.	p
Patients	30.7	43	4.559317	>0.05
Controls	32.8	36	4.674398	
Number of pregnancies	**Median**	**N**	**Std.Dev.**	**p**
Patients	2.9	43	1.540160	>0.05
Controls	2.1	36	0.487136	
Number of spontaneous abortions	**Median**	**N**	**Std.Dev.**	**p**
Patients	1.7	43	1.559808	>0.05
Controls	0.1	36	0.232311	

Thirteen women (36.1%) in the control group and two patients (4.7%) in the study group had no thrombophilia. The percentage difference wasstatistically significant between the study and the control group for p <0.05 (Difference test, p=0.0008). F II prothrombin G20210A heterozygous was recorded in 10 patients (23.5%) of the study group *versus* 2 women (5.5%) of the control group and this difference reached a statistical significance for p<0.05 (Difference test, p=0.0269). Ten women (23.5%) with Factor V Leiden heterozygous were recorded in the study group and one woman (2.8%) in the control group. The percentage difference was statistically significant for p<0.05 (Difference test, p=0.0084). There was no statistical significance (p>0.05) between the two groups regarding the MTHFR C677T heterozygous genotype. Two women (4.7%) from the study

Table 3. Prevalence of thrombophilic mutation in patients and controls

Thrombophilic mutations	Patients		Controls		*P* value
	N	%	N	%	
Without mutation	2	4.7	13	36.1	p=0.0008
F II G20210A heterozygous	10	23.5	2	5.5	p=0.0269
FV Leidenheterozygous	10	23.5	1	2.8	p=0.0084
MTHFR C677T heterozygous	15	34.9	20	55.6	p>0.05
FV Leidenhomozygous	2	4.7	-	-	-
MTHFR C677T homozygous	21	48.8	2	5.5	p=0.0000
Total	43	100.0	36	100.0	

group had F V Leiden homozygous mutation and none of the healthy controls.MTHFR C677T homozygous mutation was recorded in 21 women (48.8%) of the study group and in 2 women (5.5%) of the control group. The percentage difference between the studyand the control group showed a high statistical significance($p < 0.05$) (Difference test, $p=0.0000$) (Table 3).

Discussion

Although many case-control studies have reported association between recurrent pregnancy loss (RPL) and inherited thrombophilia, the results are heterogeneous and the nature of this association has not been clarified, yet [14].

A statistical significance ($p<0.05$) was found between the groups regarding the absence of thrombophilic mutations. The differences between the two groups in our study showed a statistical significance for prothrombin G20210A heterozygous, Factor V Leiden heterozygous and MTHFR C677T homozygous, which are consistent with the literaturedata. In our study the most frequent mutation in the control groupwasfor MTHFR heterozigous, which is similar with the studies from other authors.

Kovac *et al*. in their study found that thrombophilia was considerably more common in women with pregnancy-associated complications in comparison with women with normal pregnancies, with 38% of the women with RFL and 54.5% of women with fetus mortus in utero had thrombophilia [15].

Jusic *et al.* investigated the association of FVL, prothrombin G20210A and MTHFR C677T in women with RPL. The results showed that FVL and MTHFR C677T were significantly associated with RPL [16].

Kovacheva *et al.* investigated the three gene mutations in 156 women with fetal loss in different trimester of pregnancy and 80 matched controls. They found that FVL was associated with a significantly increased risk for RFL in the second and third trimester; F II G20210A or MTHFR C677T was more common in a group of women with fetal loss in the first trimester compared to the controls [17].

Howard Carp *et al.* in a case-control study compared 108 women with recurrent miscarriage with 82 fertile parous control women without miscarriages and concluded that thrombophilia was not associated with recurrent pregnancy loss [18].

Martinelli *et al.* conducted a case-control study and included women with first unexplained late fetal loss and compared them with women with normal pregnancies. 16% of the study group had either FVL or prothrombin mutation, which was associated with an approximate tripling of the risk of late fetal loss, and 13% were homozygous for MTHFR [19].

Ozdemir *et al.* investigated the prevalence of 12 thrombophilic gene mutations in RPL couples. They found that homozygosity of MTHFR C677T genes in women with RPL, and heterozygosity of FVL in both parents play a crucial role and should be considered as a risk factor in RPL [20].

The findings from TREATS study have shown that thrombophilia is associated with increased risks of VTE and adverse pregnancy outcomes in women with thrombophilia during pregnancy. A selective screening based on prior VTE history is more cost-effective than universal screening [21].

Conclusion

In conclusion, our findings confirmed that the thrombophilic mutations: F II Prothrombin G20210A heterozygous, FVL heterozygous and MTHFR C677T homozygous are associated with a pregnancy loss and it can be implicated in the pathogenesis of the adverse pregnancy outcomes. This study demonstrates the potential to improve patient care through the use of anticoagulant drugs which are effective in the prevention of complications of pregnancy in thrombophilia carriers. However, further studies of the risk-benefit ratio of anticoagulant treatment are needed.

Conflict of interest statement. None declared.

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Original article

THE SIRS SCORE RELEVANCE FOR ASSESSMENT OF SYSTEMIC INFLAMMATION COMPARED TO C-REACTIVE PROTEIN IN PATIENTS WITH LIVER CIRRHOSIS

РЕЛЕВАНТНОСТА НА SIRS СКОРОТВО ПРОЦЕНКА НА СИСТЕМСКА ИНФЛАМАЦИЈА ВО СПОРЕДБА СО Ц-РЕАКТИВЕН ПРОТЕИН КАЈ ПАЦИЕНТИТЕ СО ЦРНОДРОБНА ЦИРОЗА

Elena Curakova Ristovska, Magdalena Genadieva-Dimitrova, Viktorija Caloska-Ivanova, Emilija Nikolovska, Nenad Joksimovic, Beti Todorovska, Urim Isahi and Ivana Milichevik

University Clinic of Gastroenterohepatology, Medical Faculty, University "Ss. Cyril and Methodius", Skopje, Republic of North Macedonia

Abstract

Introduction. Systemic inflammation is a key mechanism that determines the natural history and prognosis inpatients with liver disease. The presence of systemic inflammation is usually assessed through the presence of systemic inflammatory response syndrome (SIRS), but due to numerous morphological and hemodynamic abnormalities the application of SIRS criteria in patients with liver cirrhosis is difficult and not entirely relevant. The aim of the study was to determine the SIRS occurrence by applying different diagnostic criteria and to analyze the relevancy of the parameters included in the SCCM/ESICM/ACCP/ATS/SIS scoreby comparison to CRP cut-off value of 29 mg/L.

Methods. In patients with liver cirrhosis we estimated the occurrence of systemic inflammation by application of three SIRS criteria: the criterion of the International sepsis definitions conference of 2001 (SCCM/ESICM/ACCP/ATS/SIS), the modified SIRS score and the CRP cut-off value of 29 mg/L. The positive findings of the parameters included in the SIRS score were compared to the CRP cut-off value in order to analyze their relevance in the assessment of SIRS.

Results. Seventy-six patients were enrolled in the study, 60 males and 16 females with a mean age of 57±11 (31-84). The presence of SIRS was registered in 31 patients (40.79%) according to the first SIRS criterion, in 5 (6.58%) patients according to the second SIRS criterion and in 15 (27.63 %) patients according to the third SIRS criterion and the average CRP in the group was 21.61 mg/L±30.98 (0.5-158.90). The percentage difference in SIRS occurrence between the first and third SIRS criterion was statistically significant for p<0.05 {Difference test: Difference 21.05%[(6.45-34.49) CI 95%]; Chi-square=7.926;df=1 p=0.0049} in favor of a significantly larger number of patients with SIRS according to the first SIRS criterion and the percentage difference in SIRS occurrence between the second and the third SIRS criterion was statistically significant for p<0.05 {Difference test: Difference 13.16%[(2.33-24.12) CI 95%]; Chi-square=5.721; df=1 p=0.0168} in favor of a significantly larger number of patients with SIRS according to the third SIRS criterion.The percentage difference between the occurrence of positive finding of the analyzed parameters included in the SIRS score and the occurrence of positive finding of the same parameter in patients who fulfilled the third SIRS criterion was statistically significant for p<0.05for decreased partial pressure of CO2below 32 mmHg {Difference test: Difference 44.73%[(29.49-57.03) CI 95%]; Chi-square=30.98;df=1 p=0.0001}, for elevated respiratory rate above 20/min {Difference test: Difference 35.53% [(22.41-47.35) CI 95%]; Chi-square=25.87; df=1 p=0.0001}, for decreased leukocyte count below 4.000/mm³{Difference test: Difference 18.42%[(8.39-29.03) CI 95%]; Chi-square=12.271; df=1 p=0.0005} and for elevated heart rate above 90/min {Difference test: Difference 11.85%[(-1.71-22.34) CI 95%]; Chi-square=5.336;df=1 p=0.0209}. The percentage difference between the occurrence of positive finding of the analyzed parameters included in the SIRS score and the occurrence of positive finding of the same parameter in patients who fulfilled the third SIRS criterion was not statistically significant for p>0.05 for body temperature abnormalities and for elevated leukocyte count above 12.000/mm³.

Conclusion. When compared to the CRP cut-off value of 29 mg/L, the decreased partial pressure of CO2 below 32 mmHg, the elevated respiratory rate above 20/min, the elevated heart rate above 90/min and the low leukocyte count below 4.000/mm³ are not reliable SIRS indicators in patients with liver cirrhosis which make SCCM/ESICM/ACCP/ATS/SIS criteria not appropriate for assessment of SIRS occurrence in these patients.

Correspondence to: Elena Curakova Ristovska, University Clinic of Gastroenterohepatology, Medical Faculty, University "Ss. Cyril and Methodius", Skopje, Republic of North Macedonia; E-mail: elenacurakova@yahoo.com

Keywords: systemic inflammation, SIRS score, C-reactive protein, liver cirrhosis

Апстракт

Вовед. Системската инфламација претставува клучен механизам кој го детерминират екот на црнодробната болест и прогнозата кај овие пациенти. Нејзиното присуство вообичаено се проценува преку присуството на синдромот на системски инфламаторен одгоровор (SIRS), но поради бројните морфолошки и хемодинамски нарушувања примената на критериумите за SIRS кај пациените со црнодробна цироза е отежнато и нецелосно релевантно. Цел на студијата е да се одреди застапеноста на SIRS со примена на различни дијагностички критериуми и преку споредба со пресечната вредност на CRP од 29 mg/L да се анализира релевантноста на параметрите кои влегуваат во состав на SCCM/ESICM/ACCP/ATS/SISскорот во проценка на присуството на SIRS.

Методи. Кај пациенти со црнодробна цироза беше одредувана застапеноста на системска инфламација преку примена на три критериуми за SIRS: критериумот на интернационалната конференцијата за дефиниција на сепса од 2001 година (SCCM/ESICM/ACCP/ATS/SIS), модифицираниот SIRS скор и пресечната вредност за серумскиот CRP од 29mg/L. Застапеноста на позитивен наод на критериоумте кои влегуваат во состав на SIRS скорот беше компарирана со пресечната вредност на CRP за да се анализира нивната релевантност во проценката на SIRS.

Резултати. Во студијата учествуваа 76 пациени (60 мажи и 16 жени) со средна возраст од 57±11год (31-84). SIRS беше присутен кај 31 пациент (40.79%) според првиот, кај 5 пациенти (6.58%) според вториот и кај 15 пациенти (27.63%) според третиот критериум а средната вредност на серумскиот CRP во рамки на групата изнесуваше 21.61 mg/L±30.98 (0.5-158.90). Процентуалната разлика помеѓу застапеноста на позитивен наод при примененапрвиот и третиот SIRS критериум е статистички сигнификантна за p<0.05{Difference test: Difference 21.05% [(6.45-34.49) CI 95%]; Chi-square=7.926; df=1 p=0.0049} во прилог на значајно поголем број на позитивни наоди при примена на првиот SIRSкритериум, а процентуалната разлика помеѓу застапеноста на позитивен наод при примена на вториот и третиот SIRSкритериум е статистички сигнификантна за p<0.05{Difference test: Difference 13.16%[(2.33-24.12) CI 95%]; Chi-square=5.721;df=1 p=0.0168} во прилог на значајно поголем број на позитивни наоди при примена на третиот SIRS критериум. Процентуалната разлика помеѓу застапеноста на позитивен наод на анализираните параметри кои влегуваат во состав на SIRSскорот и застапеноста на позитивен наод на истите параметри кај пациентите кои го исполнија третиот SIRS критериум е статистички сигнификантна за p<0.05 за намален парцијален притисок на CO2 под 32 mmHg {Difference test: Difference 44.73% [(29.49-57.03) CI 95%]; Chi-square= 30.98; df=1 p=0.0001}, за покачена респираторна фрекфенција над 20/мин {Difference test: Difference 35.53% [(22.41-47.35) CI 95%]; Chi-square=25.87; df=1 p=0.0001}, за намален концентрација на леукоцити под 4.000/mm³ {Difference test: Difference 18.42% [(8.39-29.03) CI 95%]; Chi-square=12.271; df=1 p=0.0005} и за покачена срцева фрекфенција над 90/min {Difference test: Difference 11.85% [(-1.71-22.34) CI 95%]; Chi-square=5.336; df=1 p=0.0.0209}. Процентуалната разлика помеѓу застапеноста на позитивен наод на анализираните параметри кои влегуваат во состав на SIRS скорот и застапеноста на позитивен наод на истите параметри кај пациентите кои го исполнија третиот SIRS критериум не е статистички сигнификантна за p>0.05 за отстапувањата во телесната температура и за покачената концентрација на леукоцити над 12.000/mm³.

Заклучок. Во споредба со пресечната вредност на CRP од 29mg/L, кај пациентите со црнодробна цироза намалениотпарцијален притисок на CO2под 32 mmHg, покачената респираторна фрекфенција над 20/мин, покачената срцева фрекфенција над 90/мин и намалената концентрација на леукоцити под 4.000/mm³ не се релевантни индикатори на SIRS што укажува на тоа дека SCCM/ESICM/ACCP/ATS/SIS критеиумите не се соодветни и погодни за проценка на присуството на SIRS кај овие пациенти.

Клучни зборови: системската инфламација, системски инфламаторен одгоровор (SIRS), С-реактивен протеин, црнодробна цироза

Introduction

A large amount of evidence suggests that systemic inflammation (SI) is common in patients with advanced liver cirrhosis and portal hypertension and that SI is the key mechanism that determines the liver disease course and the prognosis inthese patients [1-6]. SI develops as a result of a persistent inadequate stimulation of the immune system and it is manifested by the presence of activated immune cells and elevated levels of inflammatory cytokines [7]. SI is usually a consequence of underlying bacterial infection, but in patients with liver cirrhosis SI can also exist independently of an infection and can still persist after the infection resolves [8]. The presence of SI is usually assessed through the presence of systemic inflammatory response syndrome (SIRS) which is confirmed by fulfilling certain diagnostic criteria.

The causes of SI in liver cirrhosis are different in different stage of the disease. In early, compensated cirrhosis there is arelease of ligands from the necrotic hepatocytesknown as damage-associated molecular patterns (DAMPs) that causeso called "sterile inflammation" [9]. This inflammationfollows the inflammation caused by a primary etiological agent (alcohol, virus, etc.) that leads to liver architectonics impairment and consecutive liver dysfunction. It is assumed that in more severe inflammation these particles can spill into the systemic circulation and cause immunological activation [7]. In advanced, decompensated cirrhosis, the leading mechanism that causes SI is the intestinal translocation of bacteria and bacterial products (lipopolysaccharides, lipopeptides, glycopolymers, methylated-DNA) into the systemic/splanchnic circulationcalled pathogen-associated molecular patterns (PAMPs) [7, 10-17]. These patterns stimulate leukocyteactivation and secretion of inflammatory cytokines, continuously activate the immune system and worsen the SI [7,18-21].
Not only that SI is involved in the pathogenesis of most manifestations and complications of liver cirrhosis and portal hypertension, but SI is also related to bacterial infection, hemodynamic derangement and inflammatory organ damage [7]. The activation of the intestinal immune system causes local release of NO andother vasodilators, leading to development ofhyperdynamic circulation and consecutive rennin-angiotensin system activetion, which consequentlyresults in ascites formation [15,17]. The inflammatory brain signaling and the migration of activated immune cells in the brain tissue activate the brain macrophages towards TNF-α production, modify the brain function and contribute to developmentof encephalopathy [22-24]. According to some studies, the renal damage in these patients is also mediated by specific inflammatory cytokines, PAMPs and DAMPs, which reduce the glomerular filtration rate and damage the tubular epithelium [25-27]. One study that analyzed the prognostic value of SI in patients with liver cirrhosis and acute renal failure, established that in these patients SI is a prognostic factor independent of the presence of infection [28].
Considering that in patients with liver cirrhosis the score calculation and the SIRS assessment can be quite difficult, the value of some biological variables that are considered surrogate markers of inflammatory stress is increasingly recognized. These include: CRP, procalcitonin, ferritin, serum free cortisol, copeptin, von-Willebrand factor, etc. [29]. Cervoni *et al.* evaluated the value of CRP as a surrogate marker of systemic inflammation and suggested that in patients with liver cirrhosis CRP can be more relevant SIRS indicator than the commonly used SIRS scores, especially when previously defined cut-off values are used[1].
The aim of the study was to determine the SIRS occurrence by applying different diagnostic criteria and to analyze the relevance of the parameters included in the SCCM/ESICM/ACCP/ATS/SIS score by comparison to CRP cut-off value of 29 mg/L.

Materials amd methods

Patients

In this cross-sectional study we enrolled outpatients and hospitalized patients with liver cirrhosis without other significant comorbidities. Inclusion criteria were: histologically proven liver cirrhosis or liver cirrhosis diagnosed based on clear clinical, morphological and biochemical parameters. Exclusion criteria were: age below 18 years, pregnancy, hepatocellular carcinoma or other extrahepatic neoplasm, significant organ insufficiency (cardiac, respiratory, renal), diabetes, active alcohol consumption (for one month or less), recent gastrointestinal bleeding (in less than a month), active infection. Prior to enrolment all patients signed the informed consent for participation in the study. The research and the study protocol were in line with the ethical principles of the Declaration of Helsinki.

Data collection and evaluation of participants

At enrolment in every patient we performed complete blood count, biochemical analysis of blood and urine sample, leukocyte count and biochemical analysis of ascites (in patients with ascites); we measured vital parameters (blood pressure, heart rate, respiratory rate, blood oxygen saturation), daily urine output, gas analysis from capillary blood sample. When there was a suspicion for a bacterial infection additional investigations were performed in order to confirm or exclude its presence. Finally we calculated the CTP and MELD score and we registered the presence of acute decompensation.

Systemic inflammation

The presence of SI was determined by using three SIRS criteria. The firstSIRS criterion was the criterion of the International sepsis definitions conference (2001 SCCM/ESICM/ACCP/ATS/SIS) [30] and the second criterion was a modification of the same SIRS score [31]. The presence of SIRS according to the first SIRS criterion was defined by the presence of two and according to the second by the presence of three of the same four parameters included in both SIRS scores:

1. body temperature> 38°C or < 36°C;
2. heart rate> 90 beats/minute;
3. respiratory rate (RR) >20 respirations/minuteor partial pressure of CO2 (Pa CO2) <32 mmHg orapplication of mechanical ventilation because of acute respiratory process;
4. leukocyte count >12.000/mm³ or <4.000/mm³ or presence of immature neutrophils >10%.

The third SIRS criterion was the presence of elevated CRP above 29 mg/L in three consecutive measure-

ments within two weeks since enrolment, a value for which Cervoni *et al.* established that is a relevant SIRS indicator in patients with liver cirrhosis and discriminates patients with SIRS from patients without SIRS [1]. By using the three SIRS criteria we determined and compared the occurrence of SIRS. In order to determine the pertinence of the separate parameters in the SIRS assessment in comparison to the CRP cut-off value, we calculatedthe percentage difference between the occurrence of positive finding of the parameters included in the SCCM/ESICM/ACCP/ATS/SIS score and the third SIRS criterion.

Results

Patients

Seventy-six patients were enrolled in the study, 60 males and 16 females. The mean age of patients was 57±11 (31-84). According to the CTP classification, 20 patients were in class A, 27 patients in class B and 29 patients in class C (mean CTP score 9). The mean MELD score was 19±9 (6-37) and acute decompensation was registered in 34 patients (44.74%). Regarding the etiology, 37 patients were diagnosed with alcoholic liver disease, 13 patients had chronic hepatitis B, 6 patients had chronic hepatitis C, 1 patient was diagnosed with primary biliary cholangitis, 6 patients with autoimmune hepatitis, 1 patient with non-alcoholic fatty liver disease and in 12 patients the liver cirrhosis was cryptogenic. Thirty-sevenpatients were hospitalized and 39 patients were enrolled during the outpatient follow-up. Eleven patients were hospitalized because of hepatic encephalopathy, 10 because of refractory ascites, 7 because of profound peripheral edemas, 6 because of hepatic failure, 3 because of jaundice and 2 patients because of impaired renal function.

Systemic inflammation and systemic inflammatory response syndrome

The presence of SIRS was registered in 31 (40.79%) patients according to the first SIRS criterion, in 5 (6.58%) patients according to the second SIRS criterion and in 15 (27.63 %) patients according to the third SIRS criterion. The average CRP in the group was 21.61 mg/L ± 30.98 (0.5-158.90). The percentage difference in SIRS occurrence between the first and third SIRS criterion was statistically significant for p<0.05 {Difference test: Difference 21.05%[(6.45-34.49) CI 95%]; Chi-square=7.926; df=1 p=0.0049} in favor of a significantly larger number of patients with SIRS according to the first SIRS criterion. The percentage difference in SIRS occurrence between the second and the third SIRS criterion was statistically significant for p<0.05 {Difference test: Difference 13.16% [(2.33-24.12) CI 95%]; Chi-square=5.721; df=1 p=0,0168} in favor of a significantly larger number of patients with SIRS according to the third SIRS criterion.

Diagnostic parameters included in SCCM/ESICM/ACCP/ATS/SIS score

We analyzed the occurrence of all parameters included in the first and second SIRS criterion. Elevated body temperature above 38˚C was registered in 2 patients, decreased body temperature below 36˚C in 6, leukocyte count above 12.000/mm³ in 4, leukocytes count below 4.000/mm³ in 16, heart rate above 90/min in 13, RR above 20/min in 32 and PaCO2below 32 mmHg in 59 patients. Ten patients fulfilled none of the four parameters included in the first and second SIRS scores, 35 patients fulfilled only one, 26 fulfilled two, 5 fulfilled three and not a single patient fulfilled all four criteria included in the first and second SIRS score. The percentage difference between the occurrence of decreased PaCO2 below 32 mmHg and decreased PaCO2 below 32 mmHg in patients who fulfilled the third SIRS criterion was statistically significant for p<0.05 {Difference test: Difference 44.73%[(29.49-57.03) CI 95%]; Chi-square=30.98;df=1 p=0.0001}in favor of a significantly larger number of patients with decreased PaCO2 below 32 mmHg. The percentage difference between the occurrence of elevated RR above 20/min and elevated RR above 20/min in patients who fulfilled the third SIRS criterion was statistically significant for p<0.05 {Difference test: Difference 35.53% [(22.41-47.35) CI 95%]; Chi-square=25.87; df=1 p=0.0001} in favor of a significantly larger numberof patients with elevated RR above 20/min. The percentage difference between the occurrence of decreased leukocyte count below 4.000/mm³ and decreased leukocyte count below 4.000/mm³ in patients who fulfilled the third SIRS criterion was statistically significant for p<0.05 {Difference test: Difference 18.42% [(8.39-29.03) CI 95%]; Chi-square=12.271; df=1 p=0.0005} in favor of a significantly larger number of patients with leukocyte count below 4.000/mm³. The percentage difference between the occurrence of elevated heart rate above 90/min and elevated heart rate above 90/min in patients who fulfilled the third SIRS criterion was statistically significant for p<0.05 {Difference test: Difference 11.85% [(-1.71-22.34) CI 95%]; Chi-square =5.336;df=1 p=0.0209} in favor of a significantly larger numberof patients with elevated heart rate above 90/min. The percentage difference between the occurrence of elevated body temperature above 38°C and elevated body temperature above 38°C in patients who fulfilled the third SIRS criterion was not statistically significant for p>0.05 {Difference test: Difference 1.31%[(-4.77-7.86) CI 95%]; Chi-square=0.335; df=1 p=0.5629}. The percentage difference between the occurrence of decreased body temperature below 36°C and decreased body temperature below 36°C in patients

who fulfilled the third SIRS criterion was not statistically significant for p>0.05 {Difference test: Difference 3.94% [(-4.26-12.61) CI 95%]; Chi-square=1.052; df=1 p=0.3050}. The percentage difference between the occurrence of elevated leukocyte count above 12.000/mm³and elevated leukocyte count above 12.000/mm³ in patients who fulfilled the third SIRS criterion was not statistically significant for p>0.05{Difference test: Difference 1.31%[(-6.41-9.25) CI 95%]; Chi-square= 0.147;df=1 p=0.7010}.

Discussion

The results obtained in our study have shownthat the SIRS occurrence significantly differs and depends on the applied criterion and that small change in the definition of SIRS results in a significant difference in the SIRS occurrence. Also, there was a statistically significant difference between the elevated CRP above the cut-off valueand the abnormalities in the respiretory function parameters, heart rate and low leukocyte count which indicates that these parameters are not relevant SIRS indicators when compared tothe CRP cut-off value. Considering the fact that three out of four criteria included in the SIRS score are not reliable SIRS indicators, we can conclude that SCCM/ESICM/ ACCP/ATS/SIS score is also not appropriate for assessment of SIRS occurrence and that it should not be used in the assessment of SI in patients with liver cirrhosis.

The diagnosticcriteria for SIRS were initially defined in 1992 by the American college of chest physicians and the Society of critical care medicine (ACCP/SCCM) [30]. Since these criteria were relatively poorly accepted by the clinicians, in 2001 the International Sepsis Definitions Conference (SCCM/ESICM/ACCP/ATS/SIS) performed a revision of the ACCP/SCCM criteria. Although they were evaluated as oversensitive and insufficiently specific, still they did not suffer a significant change [32]. Klouwenberg*et al.*analyzed the value of different diagnostic criteria and the SIRS incidence varied between 49% and 99% depending on the applied criterion. They concluded that small variations in the cut-off for different diagnostic criteria hada huge influence on the incidence of SIRS and sepsis, that the ACCP/SCCM criteria were overly sensitive, insufficiently specific and not particularly useful for clinical diagnosis of sepsis in the intensive care units [33]. Considering the fact that many studies estimated the ACCP/SCCM criteria as too liberal, Bernard in his study PROWESS applied a modification of the ACCP/SCCM criteria and defined the SIRS occurrence by the presenceof three instead of two out of four criteria [34]. Although most studies doubt their relevancy due to their oversensitivity and low specificity, ACCP/ SCCM criteria are still widely used especially as inclusion criteria mainly in a population of critically ill patients in the intensive care units.

When discussing the applicability of the SIRS criteria on a specific population of patients with liver cirrhosis, then the restrain related to their relevance is even more justified. Namely, liver cirrhosis is associated with many complex structural, hemodynamic and neurohumoral abnormalities that clearlyinterfere with the pathophysiological mechanisms of the systemic inflammatory response, which leads to inappropriate interpretation of the parameters that are considered SIRS representtatives. This is the reason why many researchers focused on identifying some biological variable that would be more precise SIRS indicator and indicate towards SIRS more precisely. Studies that have evaluated CRP value in this context established that the CRP level reflects the degree of SI regardless of the reason that led to it, that is, irrespectively of whether SIRS is caused by a bacterial infection or not [29]. Actually, the elevated CRP level can also persist after a resolution of an infection indicating that SI can become a persistent condition and act as an autonomic state [8]. It has been established that in patients with liver cirrhosis CRP is a precise marker of SIRS, it can predict six-month mortality [1] and that high CRP values are strongly associated with organ failure and lethal outcome, even in patients in whom a bacterial infection has not been established [35]. Cervoni*et al.* among others established that in patients with liver cirrhosis SI is a predictor of short-term mortality independent of age, MELD score and existing comorbidities and that the presence of CRP above 29 mg/L measured 15 days after the basic values is an indicator of prolonged SI that persists after the resolution of bacterial infection [1]. This is the reason why we decided to apply their cut-off value as our third SIRS criterion and to compare the positive findings of the separate criteria included in the SCCM/ESICM/ACCP/ ATS/SIS score to the CRP cut-off value in order to analyze their relevancy as SIRS indicators.

The abnormalities in the respiratory function parameters were the most frequent positive findingsamong other criteria within the SIRS score, but our analysis showed thatthey were also the least reliable ones. Decreased PaCO2 below 32 mmHg was present in 49 patients (64.47%) and elevated RRabove 20/minwas registered in 32 patients (42.11%). However, when we compared the positive finding of these parameters to the presence of the CRP cut-off value, we discovered that the percentage difference between both, the elevated respiratory rate and the decreased PaCO2 in patients that fulfilled the third SIRS criterion was statisticaly significant for both parameters{Difference test: Difference 44.73% [(29.49-57.03) CI 95%]; Chi-square=30.98; df=1 p=0.0.0001} for PaCO2 below 32 mmHgand {Difference test: Difference 35.53% [(22.41-47.35) CI 95%]; Chi-square=25.87; df=1 p=0.0001 for RR above 20/min}. This indicates that in a substantial number of cirrhotic patients there is anabnormality in the respiratory func-

tion parameters that is not in line with the presence of systemic inflammation and the CRP rise. Also, in a large number of patients the respiratory function criterion within the SIRS criterion, especially the decreased PaCO2 below 32 mmHg, was falsely positive, mainly as a consequence of the present hepatic encephalopathy [38], which was the cause for increased RR and decreased PaCO2.

Not only the leukocyte elevation, but the decreased leukocyte count below 4.000/mm³ is also considered a SIRS indicator. However, low leukocyte count below 4.000/mm³is a common finding in patients with liver cirrhosis and portal hypertension due to the coexisting enlarged spleen and hypersplenism. In our study a leukocyte count below 4.000/mm³ was registered in 16 patients (14.93%) and also, all 16 patients had a significantly enlarged spleen. This means that in all cirrhotic patients with enlarged spleen and consecutive low leukocyte count this criterion would be falsely positive. In patients with low leukocyte count a potential leukocyte rise in terms of systemic inflammation could result in a leukocyte count that would remainwithin the normal range resulting in a falsely negative criterion. This explains why in this population of patients the leukocyte count below 4.000/mm³ is not a SIRS representative which was also confirmed by the percentage difference between the occurrence of positive finding of this criterion and the occurrence of positive finding of the same criterionin our patients who fulfilled the third SIRS criterion {Difference test: Difference 18.42% [(8.39-29.03) CI 95%]; Chi-square=12.271; df=1 p=0.0005}.

The elevation of NO and other vasodilatatory molecules in cirrhotic patients lead tosplanchnic arterial vasodilatation and consecutive hyperdynamic circulation, which is related to low mean arterial pressure and elevated heart rate. On the other hand, the frequent usage of non-selective beta blockers in patients with gastroesophageal varices reduces the heart rate and in certain way moderates the hemodynamic reaction to inflammatory stress. Our study has shown a statistically significant difference betweenthe occurrence of positive finding of elevated heart rate and the occurrence of positive finding of the same criterion in patients who fulfilled the third SIRS criterion {Difference test: Difference 11.85% [(-1.71-22.34) CI 95%]; Chi-square=5.336; df=1 p=0.0209}, which suggest that the coexisting hyperdynamic circulation disables the elevated heart rate to be observed as a relevant SIRS indicator.

The study has several limitations. The small sample size might interfere with the data interpretation. Also, the measurement of the vital parameters was not fully standardized. In some patients the measurements were performed by the cardiorespiratory monitor, while in stabile patients the measurements were mainly performed manually. In most patientsthe measurements were performed at one time, i.e. we did not take into account the multiple daily variations. The level of the PaCO2 within the SIRS criteria refers to the value measured in the arterial blood. However, in our study the PaCO2 was measured in the arterialized capillary blood. This was justified by the results from meta-analysis and many studies that compared the values of the gas analyses in the arterial blood to those in the arterialized capillary blood. The results have proved a high level of similarity between both values suggesting that for the pH and PaCO2 the value obtained in the capillary blood from earlobe is an appropriate alternative to the value obtained in the arterial blood [37].

Conclusion

In conclusion, when compared to the CRP cut-off value, the respiratory function abnormalities, elevated HR and low leukocyte count are not reliable SIRS indicators which suggest that the SCCM/ESICM/ACCP/ATS/SIS criteria are not appropriate for SIRS assessment in patients with liver cirrhosis. Additional research is needed in order to create diagnostic criteria for SIRS that would be appropriate for usage in this population of patients and to define new biological variables that could be applied as surrogate markers of inflammatory stress.

Conflict of interest statement. None declared.

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Original article

ASSOCIATION OF GLYCEMIC CONTROL, BODY WEIGHT AND BODY FAT DISTRIBUTION WITH SELECTED SOCIO-DEMOGRAPHIC FACTORS IN TYPE 2 DIABETES PATIENTS AT FIRST REGULAR STRUCTURED VISIT

ПОВРЗАНОСТ НА ГЛИКОРЕГУЛАЦИЈАТА, ТЕЛЕСНАТА ТЕЖИНА И ДИСТРИБУЦИЈАТА НА МАСНО ТКИВО СО СЕЛЕКТИРАНИ СОЦИО-ДЕМОГРАФСКИ ФАКТОРИ КАЈ ПАЦИЕНТИ СО ДИЈАБЕТЕС ТИП 2 НА ПРВА РЕДОВНА СТРУКТУРИРАНА ПОСЕТА

Biljana Chekorova Mitreva[1], Katarina Stavrikj[1], Vesna Velikj Stefanovska[2], Magdalena Genadieva Dimitrova[3], Bekim Ismaili[4], Rajna Rashkova[5], Spasko Djurchinoski[6], Irena Nikolova[7], Marija Mihajlova[8], Maja Katrandjiska Dzonlaga[9], Zoran Valaski[10], Monika Jarikj-Bojkoska[11], Ljupcho Zahariev[12], Gabriela Gulevska[13], Olga Stojkovska[13], Djordji Stanoevski[14] and Dragan Djordjievski[15]

[1]Centre for Family Medicine, Medical Faculty, Skopje, [2]Institute of Epidemiology and Biostatistics, Medical Faculty, Skopje, [3]University Clinic of Gastroenterohepatology, Skopje, [4]PHI"Bekim-I", Tetovo, [5]PHI "Medi Plus", Kochani, [6]PHI "Dr. Spasko Djurchinoski" Makedonski Brod, [7]PHI "Biomedikus", Kavadarci, [8]PHI "SEMED Dr. Marija Mihajlova", Skopje, [9]PHI "Maja Katrandjinska Dzonlaga", Strumica, [10]PHI "Dr. Dimitar Alachki", Strumica, [11]PHI "Ortomedika", Prilep, [12]PHI "Intermedika", Radovish, [13]PHI "Golema Bogorodica", Bitola, [14]PHI "Dr. Ana", Skopje, [15]PHI "Dr. Svetlana A. Stojkovska", Skopje

Abstract

Introduction. Maintaining optimal glycemic control and weight management is crucial for successful diabetes management. Deeper understanding of possible influencing factors is inevitable. The aim of this study was to investigate the association between glycemic control, body weight and body fat distribution with selected socio-demographic factors in type 2 diabetes patients at first regular structured visit.

Methods. This is a cross-sectional clinical study performed in the period 2016-2017 at a primary health care level in the Republic of North Macedonia. Data on socio-demographic parameters (age, gender, place of residence, ethnicity), diabetes duration, anthropometric indices (BMI, waist circumference) and HbA_{1c} measurement were collected from 338 type 2 diabetes patients.

Results. With respect to HbA_{1c} value, it was found that older age, urban residence and Macedonian ethnicity were significantly associated with lower HbA_{1c} (R=-0.1449; p=0.0002 and p=0.0042, respectively), whereas longer diabetes duration was significantly associated with higher HbA_{1c} values (R=0.1448). Higher BMI was found in female subjects (p=0.0213), whereas older age and Albanian ethnicity were significantly associated with lower BMI (R=-0.1734 and p=0.0001, respectively). Female gender and Albanian ethnicity were associated with central obesity as per North American cut-off values (p=0.0001 and p=0.0026, respectively). Lower waist circumference values were found in Macedonians (p=0.0001).

Conclusion. According to the results obtained in this study, it can be concluded that certain socio-demographic factors can play a role in the management of glycaemia and weight in type 2 diabetes patients in North Macedonia.

Keywords: socio-demographic factors, HbA_{1c}, BMI, waist circumference, type 2 diabetes

Correspondence to: Biljana Chekorova Mitreva, Phone: +389 70 36 71 94; E-mail: bcekorovamitreva@yahoo.com

Апстракт

Вовед. За успешно справување со дијабетесот потребно е разбирање на факторите кои влијаат на гликорегулацијата и телесна тежина. Целта на оваа студија беше да се испита поврзаноста на гликемиската контрола, телесната тежина и дистрибуцијата на масно ткиво со одредени социо-демографски фактори кај пациенти со дијабетес тип 2 при прва редовна структурирана посета.

Методи. Ова истражување претставува пресечна студија спроведена во периодот 2016-2017 на примарно ниво на здравствена заштита во Северна Македонија. Од 338 пациенти со дијабетес тип 2 беа собрани податоци за социо-демографските карактеристики (возраст, пол, место на живеење, етничка припадност), времетраење на дијабетесот, антропометриски индекси (ИТМ, обем на половина) и мерења на HbA_{1c}.

Резултати. Во однос на вредностите на HbA_{1c}, беше најдено дека постарата возраст, урбаната сре-

дина и македонската етничка припадност беа сигнификантно асоцирани со пониски вредности на HbA_{1c} (R=-0,1449; p=0,0002 ир=0,0042 соодветно). Подолгото времетраење на дијабетесот беше сигнификантно асоцирано со повисоки вредности на HbA_{1c} (R=0,1488). Повисок ИТМ беше најден кај женските испитанички (p=0,0213), додека постарата возраст и албанската етничка припадност беа сигнификантно асоцирани со понизок ИТМ (R=-0,1734 и p=0,0001соодветно).
Женскиот пол и албанскиот етникум беа асоцирани со централна дебелина според Северноамериканскиот праг (p=0,0001 и p=0,0026 соодветно) и пониски вредности за обем на половина беа најдени кај Македонците (p=0,0001).
Заклучок. Од резултатите од оваа студија може да се заклучи дека одредени социо-демографски фактори може да имаат улога во справувањето со гликемијата и телесната тежина кај пациенти со дијабетес тип 2 во Северна Македонија.

Клучни зборови: социо-демографски фактори, HbA_{1c}, ИТМ, обем на половина, дијабетес тип 2

Introduction

Optimal glycemic control and weight management are one of the foundation pillars for successful type 2 diabetes management. Glycemic control can be evaluated by fasting plasma glucose and postprandial glucose levels; nevertheless, glycated haemoglobin-HbA_{1c} is considered the gold standard. Current treatment guidelines define optimal glycemic control using this parameter [1,2]. The level of HbA_{1c}<7% is generally accepted as a level for satisfactory glycemic control. Body mass index (BMI) derived from the relation between body weight and body height [weight (kg)/height$(m)^2$] is used to define ranges of normal body weight and other body weight categories, such as obesity. In addition to BMI being widely used for definition of obesity, waist circumference measurement is used to define central (abdominal) obesity. Abdominal obesity is strongly linked with insulin resistance and consequent metabolic disturbances. The role of abdominal obesity in the development and management of metabolic diseases, such as diabetes is of particular importance [3,4]. Waist circumference is the most common and accepted measure for abdominal obesity. HbA_{1c}, BMI and waist circumference results vary widely between individual type 2 diabetes patients. There are many factors that can potentially influence glycemic control, body weight and body fat distribution, making the management of type 2 diabetes more challenging. Studies have been conducted across the globe to investigate these potential factors, including socio-demographic, however it is difficult to draw a general conclusion regarding all of them [5-10]. To the best of our knowledge, no such study has been conducted in North Macedonia so far.
The aim of this study was to investigate association of selected socio-demographic variables (age, gender, ethnicity, place of residence-rural/urban) and diabetes duration with HbA_{1c}, BMI and waist circumference in type 2 diabetes patients in North Macedonia at their first regular structured visit. The study was approved by the Ethics Committee of the Medical Faculty, University Ss. Cyril and Methodius in Skopje.

Materials and methods

This research was part of a quantitative, prospective, longitudinal clinical study performed in the period 2016-2017. Twenty specialists in family medicine from different regions in the Republic of North Macedonia (Skopje, East and West) were initially included in the study. Each of the physicians was expected to collect data from minimum 20 patients with diagnosed diabetes at baseline and during regular structured visits during one year follow-up period. This cross-sectional analysis was done based on the data collected at the first regular structured visit. Inclusion criteria for selection were: patients with diagnosed type 2 and type 1 diabetes for at least one year, age >18 years, signed informed consent. For the purpose of this analysis only data from type 2 diabetes patients were analysed. Exclusion criteria were: age <18 years, diabetes in pregnancy and during breastfeeding, gestational diabetes and patients refusing therapy.
Socio-demographic data (age, gender, ethnicity and place of residence-rural/urban), data on diabetes duration and HbA_{1c}, BMI and waist circumference measurement were collected for each of the patients. Collected data were adequately entered into respective e-forms in online database. By the time this analysis was done, the response rate was 84.5% or 338 patients in total were included in the study. HbA_{1c}, BMI and waist circumference were analysed in relation to age, gender, ethnicity, place of residence and duration of diabetes.
The universally accepted classification of weight status in 6 categories as per BMI ranges was used for the analysis: (1) underweight (<18.5 kg/m^2); (2) normal weight (18.5-24.9 kg/m^2); (3) overweight (25-29.9 kg/m^2); (4) moderate obesity–class I (30-34.9 kg/m^2); (5) obesity -class II (35-39.9 $kg.m^2$); (6) severe (morbid) obesity-class III (>40 $kg.m^2$)[11-12].
Waist circumference (measured at a level of umbilicus) was used for definition of central obesity according to current guidelines classification for men and women accordingly: (а) normal values (<94 cm *vs*.<80 cm); (б) central obesity-Europid cut-off values (>94 cm *vs*.>80 cm)-moderate central fat accumulation; (в) central obesity-North American cut-off values (>102 cm *vs*.>88 cm)-high central fat accumulation[13-14].

Statistical analysis

Data was statistically analyzed in SPSS software package, version 22.0 for Windows (SPSS, Chicago, IL, USA). Qualitative series were processed by determining the coefficient of relations, proportions, and rates, and were shown as absolute and relative numbers. Quantitative series were analyzed with measures of central tendency (average, median), as well as with dispersion measures (standard deviation, standard error). Chi square test, Fisher Exact Test and Fisher Freeman Halton Exact Test were used to compare certain characteristics between the two groups of subjects and to determine the association between certain characteristics in the groups of subjects. To test the difference between two or four independent groups, Mann Whitney U test or Kruskal-Wallis H test was used appropriately. The correlation between two variables was tested with Spearman Rank Order Correlation. P value <0.05 was used for statistical significance.

Results

A total of 338 patients with diagnosed type 2 diabetes were included in this study. Male and female were equally distributed with 169 subjects in each gender group (50%) with mean age of 60.2±10.2 [95% CI (59.1-61.4)] years. 241(71.6%) of the subjects were of Macedonian ethnicity, 71(21%) of Albanian and 25 (7.4%) were of other ethnicities. The number of subjects from urban *vs.* rural place of residence was 197(58.9%) *vs*. 141(41.7%) accordingly. Mean duration of diabetes was 6.9±5.2 [95% CI (6.3-7.5)] years.

Mean HbA_{1c} value in male *vs.* female was 7.7±1.8, Median (IQR)=7.2 (6,4-8,6) *vs*.7.3±1.4 Median (IQR)=7 (6.4-8.1) accordingly. No statistically significant difference with respect to mean HbA_{1c} value was observed between the genders (Mann-Whitney U test: Z=1.2641; p=0.2062). A statistically significant linear weak negative correlation between age and HbA_{1c} (Spearman Rank Order Correlation: R=-0.1449; p<0.05) was found (Figure 1).

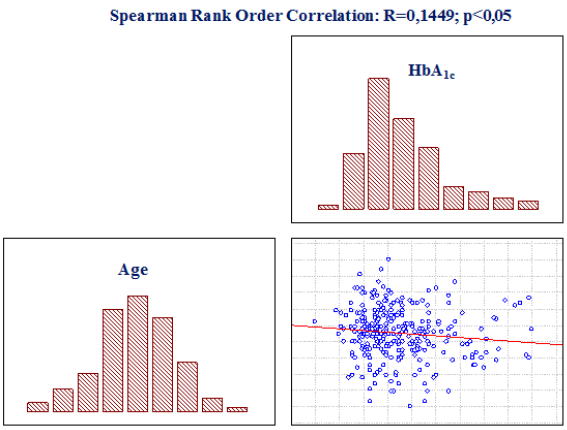

Fig. 1. Non-parametric correlation between HbA_{1c} andage

HbA_{1c} values were lower at older age. Duration of diabetes was seen to have a significant positive correlation with HbA_{1c} value (Spearman Rank Order Correlation: R=0.1488; p<0.05) (Figure 2). Mean HbA_{1c} value in Macedonians, Albanians and other ethnicities was 7.3±1.5, Median (IQR)=7 (6.3-8) *vs*. 8.2±1.8 Median (IQR)=7.9 (6.8-9.6) *vs*.7.7±1.9 Median (IQR)=7.2 (6.7-8.4) accordingly, with significantly lower HbA_{1c} value in Macedonians (Kruskal-Wallis H test, $X^2(2)=10.9227$; p=0.0042). Mean HbA_{1c} value in subjects from urban *vs.* rural place of residence was 7.2±1.5, Median (IQR)=6.9 (6.2-8) *vs.* 7.9±1.7 Median (IQR)=7.5 (6.7-8.8) with a significantly lower HbA_{1c} values in subjects from urban place of residence (Mann-Whitney U test: Z=-3.7156; p=0.0002).

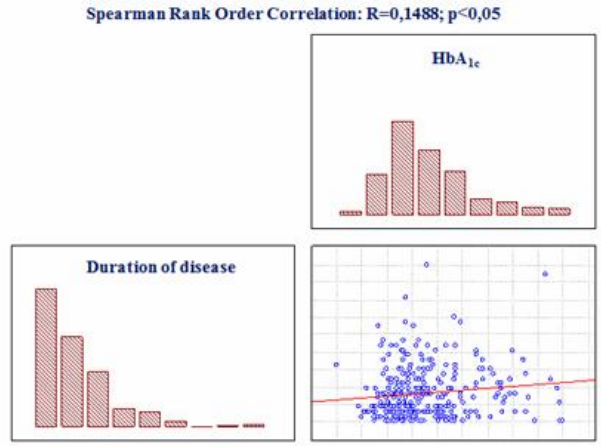

Fig. 2. Non-parametric correlation between HbA_{1c} and diabetes duration

Mean BMI in male *vs*. female subjects was 27.9±3.8., Median (IQR)=27.1 (25-30) kg/m^2 *vs.* mean 29±5.1, Median (IQR)=28.4 (26-31.6) kg/m^{2}accordingly. There was a significant difference between genders with regards to mean BMI (Mann-Whitney U test: Z=2.3034; p=0.0213), i.e. significantly higher BMI was found in female subjects. Association between gender and BMI categories was not statistically significant (Fisher Freeman Halton Exact test=0.259) (Table 1). Weak negative linear correlation was observed between older age and lower BMI (Spearman Rank Order Correlation: R=-0.1734; p<0.05). No significant association, i.e. linear insignificant negative correlation between duration of diabetes and BMI was found (Spearman Rank Order Correlation: R=-0.0458; p>0.05). Mean BMI in Macedonians, Albanians and other ethnicities was 28.8±4.6, Median (IQR)=28.1 (25.6-31.1) kg/m^2 *vs.* 27.1±3.9, Median (IQR) =26 (25-28) kg/m^2*vs*. 30.5±4.2, Median (IQR)=29.4 (27.8-32.1) kg/m^2, respectively. Between the three ethnic groups there was a significant difference with respect to BMI in favour of Albanians, with significantly lower BMI (Kruskal-Wallis H test, $X^2(2)=28.647$; p=0.0001). Significant association between ethnicity and BMI categories was found (Pearson Chi-square test=22.218,

df=8, p=0.004) (Table 1). There was no significant association between place of residence and BMI categories (Fisher Exact Test=0.927) (Table 1).

Mean waist circumference value in male *vs*. female subjects was 101.6±11.9, Median (IQR)=100 (94-108) cm *vs.*100.3±13.4, Median (IQR)=98 (90-110) cm, respectively. No significant difference between genders with respect to mean waist circumference was observed (Mann-Whitney U Test: Z=1.0298; p=0.3031). Significant association of gender with waist circumference ranges (normal, central obesity- Europid cut-off values and North American cut-off values) was found (Pearson Chi-square test=51.316. df=2. p=0.0001).i.e. significantly higher number of female subjects were found in the category of central obesity as per North American cut-off values (Table 2). An insignificant linear negative correlation between age of the subjects and waist circumference was determined (Spearman Rank Order Correlation: R=-0.0314; p>0.05). There was no significant association between duration of diabetes and waist circumference-an insignificant linear negative correlation was found (Spearman Rank Order Correlation: R=-0.00687; p> 0.05). Mean waist circumference value in Macedonians *vs*. Albanians *vs*. other ethnicities was 97.93±11.3, Median (IQR)=98(90-104) cm *vs*. 109.2±14.3, Median (IQR)=110(100-120) cm *vs.* 106.6±8.2, Median (IQR)=105(100-114) cm accordingly, with a significantly lower waist circumference value in Macedonians (Kruskal-Wallis H test. X2 (2)=36.902; p= 0.0001). There was a significant association between Albanian ethnicity and central obesity as per North

Table 1. Analysis of BMI and selected socio-demographic variables

Parameter		BMI (kg/m^2)						p*
		<18.5	18.5-24.9	25-29.9	30-34.9	35-39.9	>40	
Gender								
male	**N**	32	89	38	8	2	32	Fisher Freeman Halton Exact Test =0.259
	%	18.93%	52.66%	22.49%	4.73%	1.18%	18.93%	
female	**N**	29	74	45	14	7	29	
	%	17.16%	43.79%	26.63%	8.28%	4.14%	17.16%	
Ethnicity								
Macedonians	**N**	44	106	68	18	6	44	Pearson Chi-square test=22.218. df=8. p=0.004*
	%	18.18%	43.80%	28.10%	7.44%	2.48%	18.18%	
Albanians	**N**	16	45	6	3	1	16	
	%	22.54%	63.38%	8.45%	4.23%	1.41%	22.54%	
other	**N**	1	12	9	1	2	1	
	%	4%	48%	36%	4%	8%	4%	
Place of residence								
urban	**N**	70	36	23	8	4	70	Fisher Exact Test =0.927
	%	49.65%	25.53%	16.31%	5.67%	2.84%	49.65%	
rural	**N**	93	47	38	14	5	93	
	%	47.21%	23.86%	19.29%	7.11%	2.54%	47.21%	

*significant for p<0.05

Table 2. Analysis of waist circumference and selected socio-demographic variables

Parameter		Waist circumference – central fat accumulation			p**
		normal*	moderate *	high *	
Gender					
male	**N**	42	53	74	Pearson Chi-square test=51.316. df=2. p=0.0001**
	%	24.85%	31.36%	43.79%	
female	**N**	10	22	137	
	%	5.92%	13.02%	81.07%	
Ethnicity					
Macedonians	**N**	43	62	137	Pearson Chi-square test=11.87. df=2. p=0.0026**
	%	17.77%	25.62%	56.61%	
Albanians	**N**	9	9	53	
	%	12.68%	12.68%	74.65%	
other	**N**	0	4	21	
	%	0%	16%	84%	
Place of residence					
urban	**N**	30	40	127	Pearson Chi-square test=1.079. df=2. p=0.5831
	%	15.23%	20.30%	64.47%	
rural	**N**	22	35	84	
	%	15.60%	24.82%	59.57%	

*male/female: (a) normal range(<94 cm *vs*. <80 cm); (b) moderate central fat accumulation (90-101.9 cm *vs*. 80-87.9 cm) central obesity- Europid cut-off values (>94 cm *vs*.>80 cm), excluding overlapping subjects with North American cut-off values; (c) high central fat accumulation-central obesity- North American cut-off values (>102 cm *vs*. >88 cm); **significant for p<0.05

American cut-off values (Pearson Chi-square test=11.87. df=2. p=0.0026) (Table 2). There was no significant association between place of residence and waist circumference category (Pearson Chi-square test=1.079. df=2. p=0.5831) (Table 2).

Discussion

This research conducted on 338 type 2 diabetes patients in the Republic of North Macedonia revealed that some socio-demographic factors were associated with glycemic control, body weight and body fat distribution.
When evaluating factors contributing to glycemic control we found that age could have an impact on HbA_{1c} value, where HbA_{1c} values were lower at older age, although the correlation was weak (R=-0.1449). On the contrary, diabetes duration was shown to negatively influence glycemic control, i.e. longer duration was associated with higher HbA_{1c} values (R=0.1448). Ethnicity seems to play certain role in glycemic control, where significantly lower HbA_{1c} values were observed in patients of Macedonian ethnicity *vs*. those of Albanian ethnicity and other ethnicities (p=0.0042). Urban *vs*. rural place of residence was also significantly associated with lower HbA_{1c} values (p=0.0002). No association between gender and HbA_{1c} was found (p=0.2062). Some of our results related to glycemic control are consistent with findings from other studies, which is the case for diabetes duration [15]. Having in mind the progressive nature of diabetes, characterized by a decline in β-cell function and worsening of insulin resistance, this comes as no surprise. However, it is well known that despite the pathophysiological changes, the course of the disease can be altered by timely diagnosing diabetes and proper diabetes management. It has been demonstrated that aging in general population correlates with increased HbA_{1c} levels, but this seems not to be necessarily true in diabetic patients, as was also shown in our study [16,17]. Differences in lifestyle and compliance to treatment regimen among different age groups might be one of the reasons behind that and need to be further analysed. But, hypoglycaemia can also be a major contributing factor to lower HbA_{1c} values, which must be accessed, particularly having in mind that elderly patients are more susceptible to it. Results from other studies evaluating the influence of gender, ethnicity and place of residence on glycemic control are not consistent, demonstrating that this is locally specific and that is particularly true for ethnicity that could not be translated into our research [18-22]. Urban areas in North Macedonia have better access to care, that is likely contributing to better glycemic control. Nevertheless, other factors such as differences in lifestyle, level of education, adherence to treatment etc. between residents in urban *vs*. rural areas might also have their impact. Disparity in glycemic control between ethnicities in North Macedonia requires more profound analysis in identifying differences in dietary habits, level of education, adherence to treatment etc.
The analysis conducted for factors associated with body weight and body fat distribution in our study demonstrated that there was an association of some socio-demographic factors with BMI and waist circumference. Gender was significantly associated with BMI (p= 0.0213), where higher BMI was found in female subjects. Older age was significantly associated with lower BMI (R=-0.1734), but no association was seen for diabetes duration (R=-0.0458, p>0.05). Albanian ethnicity was associated with significantly lower BMI (p=0.0001). Ethnicity was also associated with BMI categories (p=0.004). No difference was observed between urban *vs.* rural residents with respect to BMI categories. There was no difference between genders with respect to mean waist circumference values (p=0.3031), but such difference was seen for central obesity, where more women *vs.* men were found in the category of central obesity as per North American cut-off values (p=0.0001). Age and diabetes duration were not significantly associated with waist circumference (R=-0.0314 and R=-0.00687, respectively). Significantly lower waist circumference values were found in Macedonians *vs*. other ethnicities (p=0.0001), but Albanian ethnicity was associated with central obesity as per North American cut-off values (p=0.0026). Place of residence and waist circumference category did not correlate (p=0.5831).
BMI tendency to increase with age in adults up to 5th or 6th decade of life and then to progressively decline has been observed in general population and this is not much different in diabetic population. But, this trend differs in different ethnicities and nations [23-25]. Findings from our study support the declining trend with increasing age. We did not evaluate the cut-off point at which BMI starts to decline. However, declining trend of BMI does not mean decline in adiposity, since age-dependent body fat redistribution favors enhanced visceral adipose tissue accumulation. Therefore, waist circumference is considered as more valuable prognostic factor than BMI for characterizing obesity in the elderly. Results from other studies in general population have demonstrated that older age significantly correlates with higher waist circumference values [26]. In our study we did not find such correlation, but having in mind the specificity of the diabetic population where majority of the people are centrally obese, which makes them susceptible to diabetes, this can be expected. In our study 84% of the subjects were centrally obese as per Europid cut-off values or 62% as per North American cut-off values. Gender-related differences in waist circumference in general population are well noted and translated into different cut-off values for central obesity for male *vs*. female gender (14 cm difference for both Europid and North American cut-offs). In our study we did not find a significant difference in mean waist circumference between genders (only 1.3

cm). Consequently, more women were categorized as centrally obese. Other studies also confirm that abdominal obesity is more prevalent among female *vs*. male diabetes patients, especially in those in post-menopausal period [27]. Racial or ethnic differences in body weight and body fat distribution worldwide are well acknowledged imposing different cut-off values for central obesity [13]. Likewise, we did find significant disparities. Interestingly, Albanian ethnicity was associated with lower BMI, but also with high central fat accumulation (central obesity as per North American cut-off values). Subjects from Macedonian ethnicity were associated with lower waist circumference values. We do not have data on general population for comparison to see whether there are genuine body shape differences between ethnicities in North Macedonia or maybe waist circumference plays a bigger ethnicity specific role when it comes to susceptibility to diabetes. Deeper understanding of underlying cause for such difference and analyzing dietary habits is required. Having in mind the values for waist circumference for all analyzed ethnicities in North Macedonia, it seems that Europid cut-off values for central obesity are underestimated in our diabetic population, but we cannot conclude this for the general population due to lack of evidence. Some studies report on higher BMI in rural residents [28]. We did not find such correlation, suggesting that rural dietary patterns in our country might not differ much from urban ones.

Study limitations

This study evaluated solely the association between selected socio-demographic factors and glycemic control, body weight and body fat distribution without multivariate adjustment for other very important contributing factors (antidiabetic treatment, nutrition, physical activity, hypoglycemia). Such an analysis might shed additional light on the current findings. Also, the study did not evaluate the cut-off point at which age BMI starts to decline in our type 2 diabetes patients.

Conclusion

This study revealed some important associating factors to glycemic control and weight management. That could help in better understanding the complexity of achieving optimal glycemic control and weight management and in creating tailor-made treatment strategies for diabetes patients in our country. Further analyses in this direction would be of great benefit.

Conflict of interest statement. None declared.

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ММР

Original article

RISING TREND OF USING LAPAROSCOPY IN THE TREATMENT OF COMPLICATED APPENDICITIS IN OUR INSTITUTION DURING JANUARY 2017-MAY 2019

НАГОРЕН ТРЕНД НА УПОТРЕБАТА НА ЛАПАРОСКОПИЈАТА ВО ТРЕТМАНОТ НА КОМПЛИЦИРАН АПЕНДИЦИТИС ВО НАШАТА УСТАНОВА ЗА ПЕРИОД ЈАНУАРИ 2017-МАЈ 2019

Andrej Nikolovski[1], Gjorgji Stavridis[1], Igor Fildishevski[1], Irina Pavlovska[2], Svetozar Antovic[3], Biljana Cvetanovska-Ilievski[1], Angelina Krsteva[1], Darko Dimitrovski[1], Burim Elezi[1], Valjon Saliu[1], Senol Tahir[1], Stefan Arsenkov[1] and Dragoslav Mladenovic[1]

[1]University Clinic for Surgery "St. Naum Ohridski", Skopje, [2]Institute for Epidemiology and Biostatistics with Medical Informatics, Medical Faculty, Skopje, [3] University Clinic for Digestive Surgery, Skopje, Republic of North Macedonia

Abstract

Introduction. Laparoscopic appendectomy was performed for the first time in the University Clinic for Surgery "St. Naum Ohridski" back in 2003 by the pediatric surgeons. At the moment it is still unrecognized by many senior surgeons as a reliable and safe alternative procedure for acute appendicitis. The end-point of this study is to present the rising trend of using laparoscopy in the treatment of complicated appendicitis.
Methods. In the period between January 2017 and May 2019 a total number of 403 patients were operated on due to a preoperative diagnosis of acute appendicitis (270 with open and 133 with laparoscopic appendectomy) and were retrospectively analyzed.
Results. Simple appendicitis was diagnosed intraoperatively in 248 patients and complicated appendicitis was diagnosed in 141 patients. The rising trend for overall use of laparoscopy for acute appendicitis was seen during the study period (20.9%, 32.2% and 63.3% in 2017, 2018 and 2019, respectively). In terms of complicated appendicitis, a drastic positive trend followed in favor of laparoscopy (8.9%, 24.6% and 36.7% in 2017, 2018 and 2019, respectively). The negative appendectomy rate with other intraoperative finding was 3.46% (14 cases). The conversion rate was 2.25%.
Conclusion. We can finally conclude that the laparoscopic appendectomy is recognized as an effective and safe alternative in the treatment of complicated appendicitis in our institution.

Keywords: acute appendicitis, complicated appendicitis, open appendectomy, laparoscopic appendectomy

Correspondence to: Andrej Nikolovski, University Clinic for Surgery "St. Naum Ohridski", 1000 Skopje, R. N. Macedonia, E-mail: andrejnikolovski@ymail.com

Апстракт

Вовед. Лапароскопска апендектомија е изведена за прв пат во 2003 година во ЈЗУ Универзитетска Клиника по Хируршки болести "Св. Наум Охридски"-Скопје од страна на детските хирурзи. Во сегашно време сé уште не е препознаена од повеќе постари хирурзи како сигурна и безбедна алтернативна процедура во третманот на акутниот апендицитис. Крајна цел на оваа студија е да го прикаже растечкиот тренд на употребата на лапароскопијата во третманот на комплициран апендицитис.
Методи. Во период од Јануари 2017-мај 2019 година вкупно се оперирани 403 пациенти со предоперативна дијагноза на акутен апендицитис (270 со отворена метода и 133 со лапароскопска апендектомија) и се анализирани ретроспективно.
Резултати. Едноставен (некомлициран) апендицитис се најде интраоперативно кај 248 пациенти, а комплициран кај 141 пациент. Растечки тренд во целокупната употреба на лапароскопијата за третманот на акутен апендицитис е забележана за време на студијата (20,9%, 32,2% и 63,3% во 2017, 2018 и 2019 соодветно). Во услови на комплициран апендицитис, забележан е драстичен позитивен тренд во корист на лапароскопијата (8,9%, 24,6% и 36,7% во 2017, 2018 и 2019 соодветно). Стапката на негативна апендектомија со друг интраоперативен наод беше 3,46% (14 случаи). Стапката на конверзија беше 2,25%.
Заклучок. Конечно можеме да заклучиме дека лапароскопската апендектомија е препознаена како ефикасна и безбедна процедура во третманот на комплициран апендицитис во нашата установа.

Клучни зборови: акутен апендицитис, комплициран апендицитис, отворена апендектомија, лапароскопска апендектомија

Introduction

The first laparoscopic appendectomy (LA) was performed back in the 20th century, in 1983 by a German gynecologist [1]. Since then the number of laparoscopically performed appendectomies raised through the years. In the beginning it was used in cases of simple (non-complicated) appendicitis and over time it has shown its superiority in terms of better surgical outcome [2]. The question whether laparoscopy should be used in cases of complicated appendicitis (CA) appeared to be logical [3-5].

Laparoscopic appendectomy was performed for the first time in the University Clinic for Surgery "St. Naum Ohridski" back in 2003 by the pediatric surgeons. Technical obstacles were among the major causes and it took long time before laparoscopy became a routine procedure for acute appendicitis treatment in our institution. At the moment, it is still unrecognized by many senior surgeons as a reliable and safe alternative procedure for acute appendicitis. Our recent data has shown that only 14.5% of patients with acute appendicitis are operated on by laparoscopy in the past 5 years [6]. However, the younger general and abdominal surgeons and the residents of general and abdominal surgery changed this devastating trend in our institution in this era of modern laparoscopy.

Materials and methods

This retrospective study analyzes the rising trend of the use of laparoscopy in cases of complicated appendicitis operated on in our Clinic in the period of January 2017-May 2019. All patients with preoperative diagnosis of acute appendicitis were included for analysis and according to the intraoperative finding were divided into three groups: patients with simple (non-complicated) appendicitis, patients with complicated appendicitis and a group with other intraoperative finding. The preoperative diagnosis was established by physical examination, blood test with complete blood count, CRP, serum bilirubin, ALT and AST analysis. Abdominal sonogram was the next diagnostic step. If a negative or inconclusive sonogram finding was revealed, a contrast enhanced CT of the abdomen was indicated.

The choice of the operative procedure was left to the patients with previous explanation of both methods. Of course, a choice was not offered by surgeons that operate appendicitis with the open method only. The operated patients were divided in two groups (laparoscopic and open group). Open appendectomy (OA) was performed with the McBurney muscle splitting access or with right low pararectal laparotomy. Laparoscopic appendectomy was performed with the standard three-port access. Patients received a single prophylactic dose of a third generation cephalosporine prior to surgery. It was continued in the postoperative period with intraoperative addition of metronidazole in cases of complicated appendicitis. Drainage was not a routine and depended on surgeons' choice. Postoperative follow-up period was 30 days.

Results

In the period of January 2017-May 2019 a total number of 403 patients were operated on due to a preoperative diagnosis of acute appendicitis (270 with OA and 133 with LA). Open appendectomies were performed in 133, 112 and 25 patients during 2017, 2018 and 2019 (Jan-May) respectively. Laparoscopic appendectomies were performed in 35 (20.9%), 53 (32.2%) and 45 (63.3%) patients during 2017, 2018 and 2019 (Jan-May), respectively (Table 1).

Table 1. Total number of performed appendectomies (OA and LA)

Year	OA	LA	Total
2017	133	35	168
2018	112	53	165
2019 (Jan-May)	25	45	70
Total	270	133	403

Simple (non-complicated) appendicitis was diagnosed intraoperatively in 248 patients (158 in the open group and 90 in the laparoscopic). Complicated appendicitis (appendiceal gangrene, appendiceal perforation/rupture, periappendiceal abscess and diffuse peritonitis) was diagnosed in 141 patients (104 in the open and 37 in the laparoscopic group).

Negative appendectomy rate with other intraoperative finding was 3.46 % (14 cases), 8 in the open and 6 in the laparoscopic group (Table 2).

Table 2. Distribution of intraoperative findings

Finding	OA	LA	Total
Simple appendicitis	158	90	248
Complicated app.	104	37	141
Other finding	8	6	14

Conversion to open appendectomy was performed in 3 cases (2 with complicated appendicitis and one with other intraoperative finding). The conversion rate in our study was 2.25%.

The rising trend for overall use of laparoscopy for acute appendicitis was seen during our study. In 2017 only 35 (20.9%) laparoscopic appendectomies were performed (mostly for non-complicated appendicitis) out of 168 procedures. In 2018, the number grew to 53 (32.2%) laparoscopic procedures, while in 2019, more than half of the patients were treated with LA (63.3%) (Figure 1).

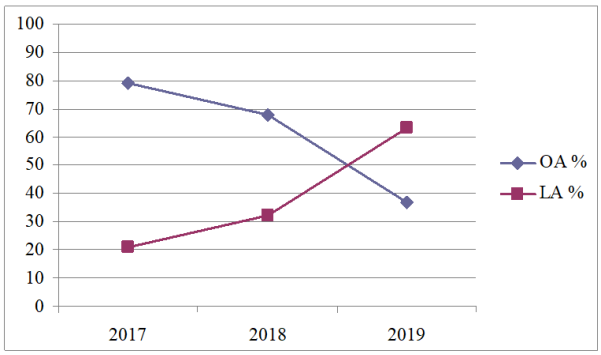

Fig. 1. Overall percentage of OA and LA performed for preoperatively diagnosed acute appendicitis

A total number of 141 patients were diagnosed with a form of complicated appendicitis (45, 69 and 27 for 2017, 2018 and 2019, respectively) (Table 3). A drastic positive trend followed in favor of laparoscopy usage for complicated appendicitis during the study period. Namely, only 4 cases (8.9%) were operated with LA in 2017. The numbers in 2018 and 2019 rose to 17 (24.6%) and 16 (59.2%), respectively (Figure 2).

Table 3. Distribution of patients with CA per year

Year	OA	LA	Total
2017	41	4	45
2018	52	17	69
2019 (Jan-May)	11	16	27

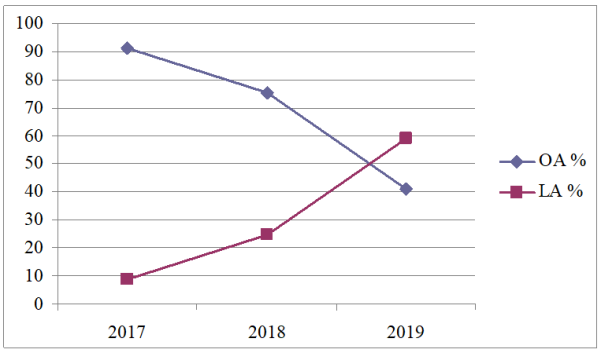

Fig. 2. Percentage of OA and LA performed for complicated appendicitis

Discussion

Since its introduction, the LA gained popularity and overtook the primate of the method of choice in the treatment of non-complicated appendicitis [7-10]. Back in that time, laparoscopy was contraindicated in terms of perforated appendicitis, but the proper training of surgeons resulted in using this method in CA [11].

The number of laparoscopically performed appendectomies varies worldwide. According to GlobalSurg Collaborative Organization, the type of surgical management of acute appendicitis varies depending on the level of country's income and the level of Human Development Index (HDI) [12]. In terms of country income, according to World Bank, Macedonia is ranked as upper middle economy in the region of Europe and Central Asia [13]. In 2018, United Nations Development Programme (UNDP) ranked Macedonia at position 80 out of 189 countries and regions with a HDI value of 0.757 [14]. Real data on the type of intervention (open and laparoscopic) for all appendectomies performed in Macedonia lacks and could be an aim of future studies. Reports for the rate of conversion vary up to 10% [15]. Our conversion rate of 2.25% could be explained by the low number of procedures for complicated appendicitis (37) out of 133 laparoscopic appendectomies. Also, all the surgeons and residents previously mastered the learning curve of 20 laparoscopic appendectomies.

Conclusion

LA is a well-established procedure in treatment of complicated appendicitis. Hence, it is recommendable to be performed by surgeons/residents that mastered the learning curve of at least 20 laparoscopic appendectomies and have experience with previous laparoscopic appendectomies in simple (non- complicated) appendicitis. We can finally conclude that the laparoscopic appendectomy is recognized as an effective and safe alternative in the treatment of complicated appendicitis in our institution.

Conflict of interest statement. None declared.

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ММР

Case report

COMPLEX SCALP DEFECT RECONSTRUCTION - A CASE REPORT

ПРИКАЗ НА СЛУЧАЈ ЗА РЕКОНСТРУКЦИЈА НА КОМПЛЕКСЕН ДЕФЕКТ НА ПОГЛАВИНА

Elizabeta Mircevska Zogovska[1], Vladimir Mircevski[2], Igor Peev[1], Ginoski V[1], Lazo Noveski[1], Boro Dzonov[1], Vladimir Rendevski[2] and MM Mircevski[2]

[1]University Clinic for Plastic and Reconstructive Surgery, [2]University Clinic for Neurosurgery, Medical Faculty, Ss. Cyril and MethodiusUniversity, Skopje, Republic of North Macedonia

Abstract

Introduction. Acquired cranial full thickness defects occur due to infections, trauma or after tumor resection in the region. There are many options for reconstructions, from spontaneous healing to free flaps. Regarding soft tissue coverage, usage of local flaps seems most reasonable and feasible. However, sometimes bone has to be reconstructed as well, and these complex defects are really challenging for specialists in plastic surgery and neurosurgery as it is in brain vicinity.
Case report. In this paper we describe a two-stage reconstruction of an extensive bone and soft tissue defect of the cranial vault in a 26-year-old female, using a polymethylmethacrylate (PMMA) implant and large local rotational skin flap after initial tissue expansion. Reconstruction was needed since infection appeared after the initial neurosurgical treatment. It was an interdisciplinary approach involving specialists inneuro- and plastic surgery. Complete and stable healing with no implant exposure as well as an esthetically pleasing cranial vault shape was achieved.
Discussion. Scalp reconstruction has two major aims: protection of the brain and restoration of harmonious skull contours with hair bearing tissues in order to achieve a good functional and aesthetic outcome. Scalp tissue can be expanded to a substantial degree. PMMA is the most widely used alloplastic material in cranioplasty. Reconstruction of complex skull defects requires collaboration between neurosurgeons and plastic surgeons to choose the most appropriate procedure.
Conclusion. By ppplyingmodern surgical techniques with usage of alloplastic materials and tissue expanders, a successful cranial reconstruction can be achieved.

Keywords: scalp, cranium, reconstruction, tissue expansion, rotational flap

Correspondence to: Elizabeta Mircevska Zogovska, University Clinic for Plastic and Reconstructive Surgery, Medical Faculty, Ss. Cyril and MethodiusUniversity, Skopje, Republic of North Macedonia; E-mail: elizabetamircevska@yahoo.com

Апстракт

Вовед. Стекнати кранијални дефекти со целосна дебелина се јавуваат поради инфекции, траума или после ресекција на тумор. Постојат многу опции за реконструкции, од спонтано зараснување до слободни резени. Во однос на покривањето со меки ткива, користењето на локалните резени сечини дека е најразумно и изводливо.Сепак, понекогаш икоскени структури треба да се реконструираат, и овие комплексни дефекти се навистина предизвикувачки запластичните и неврохирурзите, поради близина на мозокот.
Приказ на случај. Во овој труд ние ја опишуваме двостепената реконструкција на екстензивен ко дефект на коскено и на меко ткиво на кранијалниот свод кај 26-годишна жена, користејќи имплант на полиметилметакрилат (ПММА) и големата локална ротациона кожата по иницијалното експандирање на ткивото. Реконструкцијата беше потребна по првичниот неврохируршки третман кога следела инфекција. Тоа беше интердисциплинарен пристап кој опфати невро- и пластичен хирург. Целосно и стабилно покривање без изложеност на имплантот, како и естетски пријатна форма на кранијалниот свод беше постигнато.
Дискусија.Реконструкцијата на скалпот има две главни цели: заштита на мозокот и враќање на хармонизирани контури на черепот со ткива кои имаат влакна со цел да се постигне добар функционален и естетски резултат. Ткивото на скалпот може да се експандира до значителен степен. ПММА е најшироко користен алопластичен материјал за краниопластика. За реконструкција на сложени дефекти на черепот потребна е соработка меѓу неврохирурзи и пластични хирурзи за да се избере најсоодветната процедура.
Заклучок. Современите хируршки техники ни овозможуваат да употребуваме алопластични материјали и експанзија на ткивата.

Клучни зборови: поглавина, калварија, реконструкција, ткивна експанзија, ротациона резенка.

Introduction

Starting from the uppermost, anatomy of the scalp comprises: thick skin (with hair folliclesandsebaceous glands); hypodermal adipose tissue and dense connective tissue with abundantnetwork ofarteries, veins, lymphatics, and sensory nerves;fibromuscular layer called galeaaponeurotica (contiguous with the fascia of the frontalis muscle and the temporoparietalfascia), loose areolar layer (which is regularly surgical plane of cleavage-fascia innominata) and the last layer is the pericranium or periosteum of the calvarium. The calvariumis composed of the superior segmentsof the frontal bone and occipital bone, and both parietal bones and has three layers: internal and external tables or layers of compact bone, separated by diploë (medullary space of cancellous bone). The dura is situated under the internal layer of compact bone and it has two lamellae: the superficial (periosteal) and the deep (meningeal) lamella. Five paired arteries with many interconnections are responsible for the vascularization of the scalp (the supratrochlear and supraorbital arteries, and the superficial temporal, posterior auricular and occipital arteries) [1].

Acquired complex scalp defects can be due to infection, after neoplastic resection or after trauma. The dimension, depth and complexity of the scalp defect are the major factors that determine the method of reconstruction.On the other hand, full thickness com plex scalp defect seeksclever and creative reconstructtive technique, and it is often quite a challenge. Soft tissue reconstructive options comprise of primary closure for defects up to 3 cm in diameter, spontaneous closure, skin grafts, local scalp flaps (either partial or full thickness flaps) for defects with a diameter of 3 to 9 cm, tissue expansion, regional flaps, and free tissue transfer for scalp defects greater than 9 cm in diameter. Nevertheless, tissue expansion can be used in coverage of larger defects [1].

Although the genesis of modern-day tissue expansion is credited to Radovan and Austad, the technique takes some of its roots from early lessons in distraction osteogenesis [1,2].

Reconstructive options for the bone include: preferably the original “bone flap”, autogenous bone grafting and alloplastic materials. The ideal implant material would be biologically inert, osteoconductive, and biomechanically compatible. Currently titanium meshes and plates, polymethylmethacrylate (PMMA), hydroxylapatite (HA), polyethylene (PE), polyetheretherketone (PEEK), calcium phosphate and glass fiber–reinforced composite (FRC) are the most used materials [1,3,4].

In this paper, we describea two-stage reconstruction of an extensive bone and soft tissue defect of the cranial vault in a 26-year-old female, using a polymethylmethacrylate (PMMA) implant and a large local rotational skin flap after initial tissue expansion.

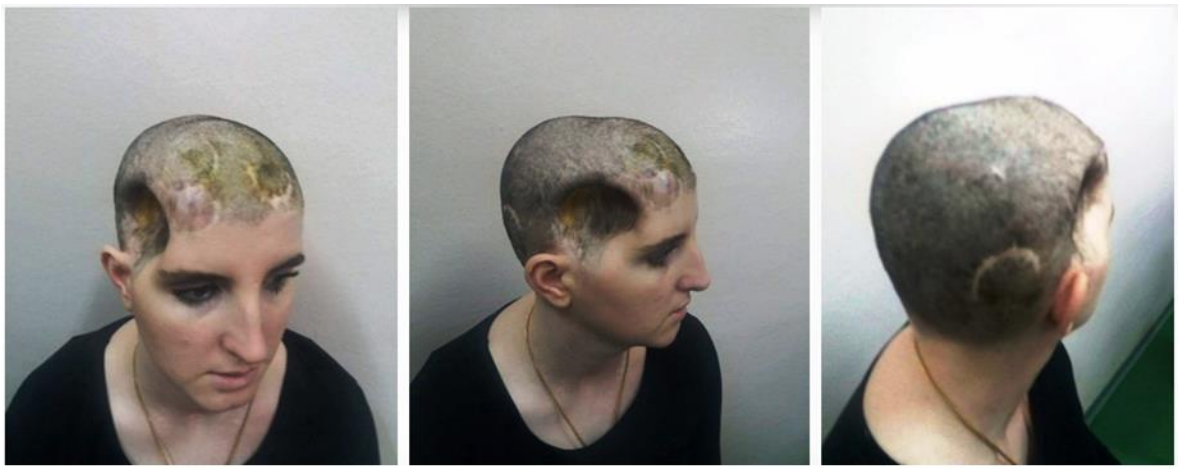

Fig. 1. Initial presentation

Case report

In this paper we present a case of complex reconstructtion of the scalp in a 26-year-old woman.Five years before the reconstruction, she had ruptured aneurysm of the anterior communicating artery with subarachnoid hemorrhage, resolved by clipping aneurysm and ventriculoperitoneal shunt on the right side.After the intervention, a local infection of the wound with osteomyelitis of the bone flap occurred with meningoencephalitis. The patient was then treated in an intensive care unit.Two years after the first operation, the patient had a new surgery due to the occurrence of osteocutaneous fistula, when revision intervention and sequestrectomy of bone structures due to osteomyelitis was performed. After one year, a new left ventriculoperitoneal shunt was placed due to dysfunction on the right. In 2017, the patient first appeared for consultation with a plastic surgeon due to a defect on the scalp. In collaboration with the neurosurgeon a two-step reconstruct-

tion was planned. Reconstruction of the scalp and the bone defects wasperformed in our center 24 months after initial neurosurgical treatment, approach including neurosurgery and plastic surgery teams. At the time of surgery, no skin infection was noted and stable coverage by fibrous tissues had been achieved. A bone defect was located in the rightfrontotemporoparietal region. The size of the defect, quality ofthe tissues, and patient's initial condition required a 2-stage approach.

The bone defect, situated on the right frontotemporoparietal region, was 60 cm^2 [Figure 1]. Under general anesthesia during the first operation, a 125 cc tissue expander-elliptical was placed in the right temporoparietoccipital region [MENTOR Smooth Elliptical Tissue Expander with Remote Injection Dome]. The tissue expander wasfully filled for a period of 4 weeks in order to obtainthe maximum expansion of the soft tissues of the scalpand overfilling up to 200cc was maintained [Figure 2]. The pseudotumor had dimensions 12x25 cm with the margin very closeto the primary defect.Six weeks later, the second operation followed, again undergeneral anesthesia.Secondary cranioplasty with methylmethacrylate and reconstruction of the bony vault of the calvarium with implantation of the PMMA was performed. Strengthened with aVicryl net of the dura was also performed.Covering the defect with soft tissue was performed with a large rotation flap, of the expandedskin. Complete and stable healing with no implantexposure as well as an esthetically pleasing cranial vaultshape was achieved [Figure 3, 4 and 5].

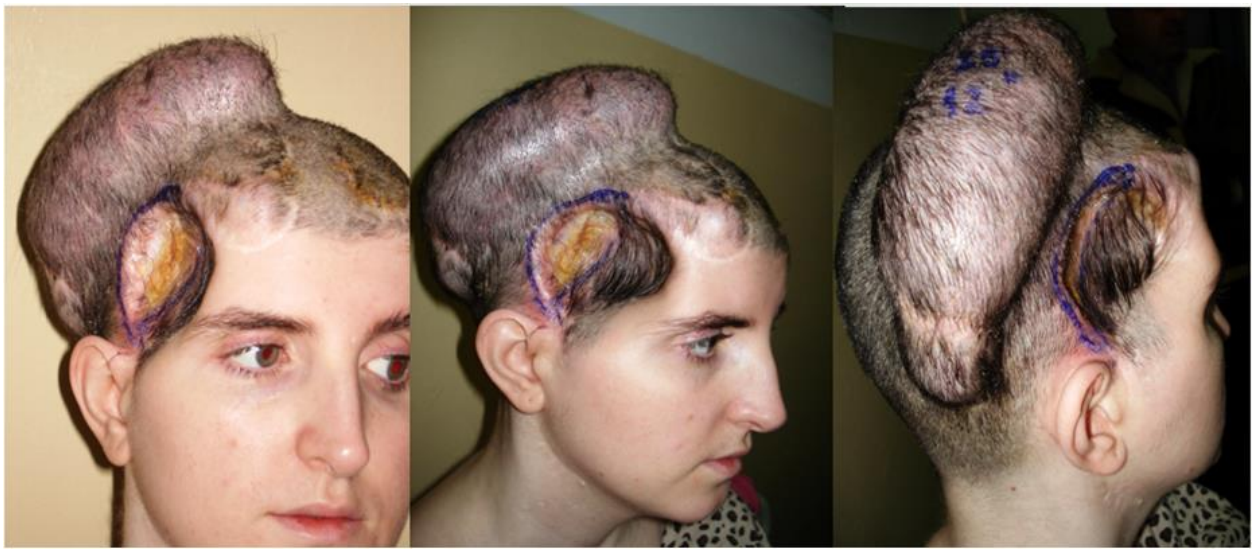

Fig. 2. After expansion

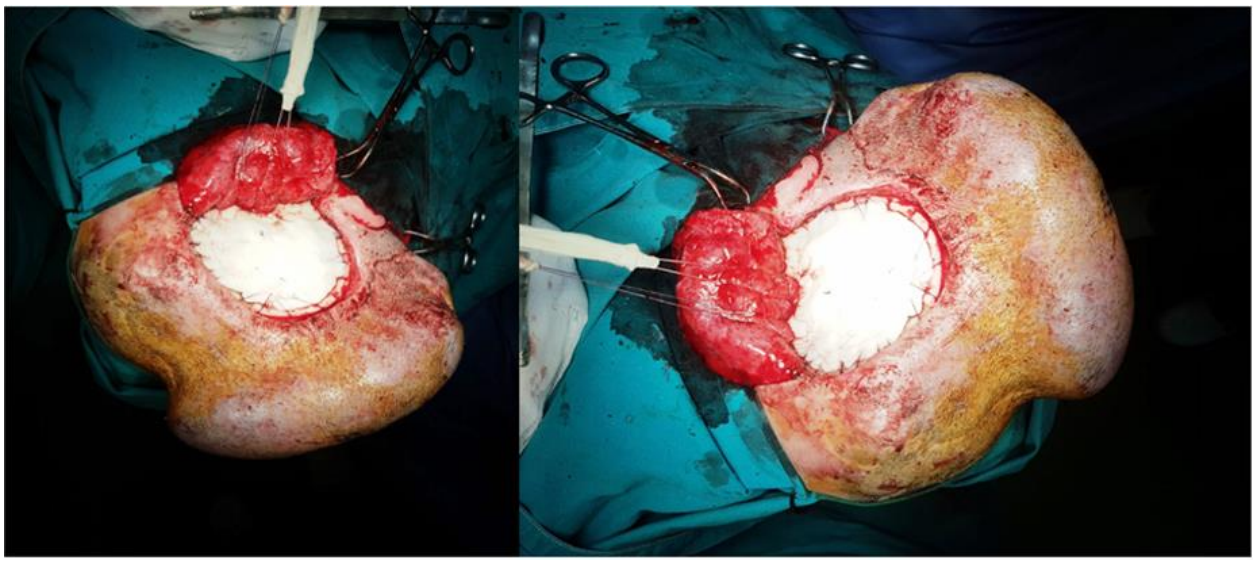

Fig. 3. Naslov

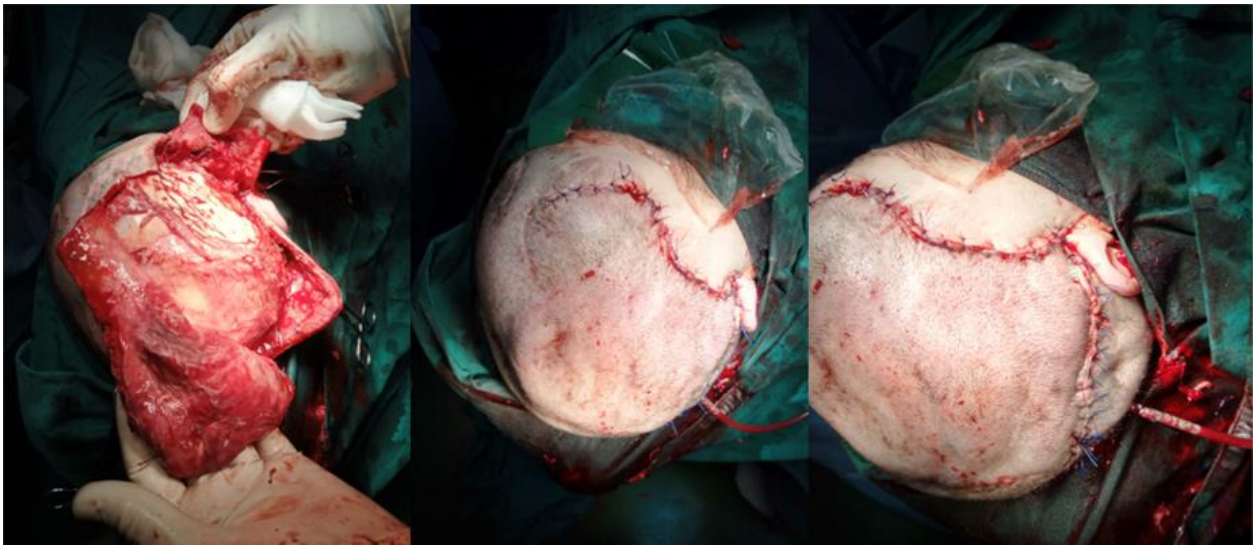

Fig. 4. Flap coverage

Fig. 5. End result

Discussion

Significant planning aspects in scalp reconstruction are the location, size, depth and shape of the defect, quailty of the surrounding tissues and overall health, level of function, compliance, and personal preference of the patient and doctor. Reconstruction of complex skull defects requires collaboration between neurosurgeons and plastic surgeons to choose the most appropriate procedure [1,3]. Bony defects, in this case calvarium, add complexity to reconstruction by dealingwith structural support, contour, and function [5].

Scalp reconstruction has twomajor aims: protection of the brain and restoration of harmonious skull contours with hair bearing tissues. Tissue expansion meeting these two criteria should be favored whenever possible and represents an invaluable asset in scalp reconstruction, allowing the replacement of like with like. Tissue expansion is aneffective method for enlarging tissues and achieving adequatecoverage with large rotation local flaps, and in most cases the procedure has satisfactory functional and aesthetic outcomes. A major advantage of scalp expansion is the potential to use expanded hair-bearing tissue, therefore, avoiding alopecia or treating existing alopecia.When given enough time, scalp tissue can be expanded to a substantial degree. The patient needs to be well informed and preoperatively screened in regard to social support, medical compliance, status of the underlying disease and its treatment course, and the will to endure the lengthy expansion period, the consequent physical deformity, and the multi-stage reconstruction. Approximately 50% of scalp can be reconstructed with expanded scalp tissue. It does require staged operations with a lengthy interval period and is potentially associated with expander complications, which vary from 6 to 25%. Complications of tissue expansion are: infection, implant extrusion, mecha-

nical failure, hematoma or seroma, pain, nerve dysfunction, tissue necrosis, bone resorption and flap failure [1,6].

Calvarial bone reconstruction for cerebral protection is commonly required, when the underlying dura is exposed. Cranioplasty is the surgical reconstruction and repair of an acquired or congenital defects or deformity of a cranium. Contemporary indications for secondary cranioplasty are reconstruction and reestablishment of the aesthetic and harmonious contour of the calvarium after loss of bone flaps from infection after craniotomy, to provide security and protection for the cerebral structures and cranial contents and to offer a definitive management for "syndrome of the trephined" [1,6-8].

Polymethylmethacrylate (PMMA) is a synthetic polymer of acrylicacid, capable of processing levelsof stress analogous tothatofnativebone.When mixed, it starts as a soft paste, which when cooled shapes to fit a defect. It is a stable inert substance with minimal local reaction to the meninges. Polymethylmethacrylate is a polymeric powder, which whenmixed into a paste causes an exothermic reaction. This cancause dangerous burns to local tissues, and during placement, the implant must constantly be irrigated with cool saline [7]. PMMA is the most widely used alloplastic material in cranioplasty. PMMA does not integrate, which helps facilitate removal in revision surgery when compared toother alloplastic implants. The purpose of these composite materials isto mimic natural bone and assist in restoring function (structurally and aesthetically) to the human skull. Of these properties, infection remains a core concern in regards to implant failure and patient health. Thus, it is fundamental than any implantable reconstruction solution aims to mitigate infection risk potential to the greatest possible extent. There are many contributing factors which canimpact the potential infection risk for a patient. Overall complication rates are relatively high in cranioplasty procedures, with a typical range of 20% to 30%. Contour deformities and infection being the most common, followed by exposure, hematoma, and seroma. *Staphylococcus aureus* is the most common organism isolated in cranioplasty infections, which may occur up to 6 or 7 months after surgery [1,6-8].

Conclusion

The purpose of all reconstructions is to accomplish the best potential functional and aesthetic results. If possible, replacing tissue with similartissue is the best option. However, in thecircumstanceof scalp reconstruction, tissue is often scarce. Nevertheless, modern surgical techniques allow us to surpass these obstacles by using alloplastic materials and tissue expansion.

Conflict of interest statement. None declared.

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ММР

Case report

PERIPHERAL EXUDATIVE HEMORRHAGIC CHORIORETINOPATHY - PEHCR

ПЕРИФЕРНАЕКСУДАТИВНА ХЕМОРАГИЧНА ХОРИОРЕТИНОПАТИЈА

Milena Golubovic Arsovska, Natasa Trpevska Shekerinov and Jana Nivichka Kjaeva

University Clinic of Ophthalmology, Medical Faculty, Skopje, R. North Macedonia

Abstract

Introduction. Peripheral exudative hemorrhagic chorioretinopathy is a serious disease characterized by subretinal hemorrhage and exudates. Although the disease may beasymptomatic, the classical clinical signs and symptoms are subjective difficulties due to visual decrease, onset of floaters, phenomenon of photopsia or metamorphosia.

The aim of this study was to present an explicit case of this disease, to stress its importance andto raise awareness concerning this disease, which would be important in the education of doctors involved in the pathology of the posterior eye segment.

Case report. A 56-year-old female was presented with decreased visual acuity involving both eyes, more prominent in the right eye. Medical history revealed that her first symptoms appeared 10 years ago, with difficulty focusing on objects that are up close.

On examinationthe visual acuity in the right eye was BCVA 0.02 cc, and in the left eye BCVA 0.5 cc. Bilateral intraocular pressure was 14.6 mmHg, and biomicroscopy of the anterior segment showed a normal finding.

Macula lutea in the fundus was with prominent atrophic changes of pigment epithelium and tiny hyperpigmentations, with few drusen, atrophic changes of choriocapillaris with exposition of the large choroidal blood vessels. Atrophic choroidal lesions with whitish drusen-like changes were observed in pre-equatorial segment periphery and in the equator circumferentially, especially visible temporally. In the peripheral fundus, near the equator as well as anteriorly, large hemorrhagic zones were seen located subretinally with zones of subretinal fibrosis shaped as grey-whitish plaques or strip-shaped that easily elevated the retina, but zones of serious retinal detachment were also present.

Optical coherence tomography (OCT) showed distinct atrophy of pigment epithelium and choriocapillaris with choroidal hyperreflexia and visible lacunar spaces in the large blood vessels. No vascular changes in the retina and choroid or newly formed blood/vascular network were observed on OCT angiography.

It is important to point out that the patient has got hypertension ang has been undergoing dialysis for 8 years.

Conclusion. A case with a rare, unusual disease that can pose a significant diagnostic problem has been presented. This disease is also a common cause for visual acuity impairment and there is still no standard approach to its treatment. Therefore, having in mind the presented dilemmas, awareness of this entity is of substantial importance in clinical ophthalmology practice. This paper, by presenting this case report is beneficial for the doctors dealing with this pathology.

Keywords: peripheral exudative hemorrhagic chorioretinopathy (PEHCR), age-related macular degeneration (ARMD), polypoidal choroidal vasculopathy (PCV), anti-VEGF

Correspondence to: Natasa Trpevska Shekerinov, University Clinic of Ophthalmology, Medical Faculty, Skopje, R. N. Macedonia; E-mail: n_trpevska@yahoo.com

Абстракт

Вовед. Периферна ексудативна хеморагична хориоретинопатија е сериозно заболување кое се карактеризира со субретинални крварења и ексудати. Иако заболувањето може да се јави незабележително, класично во клиничката слика, се манифестира со субјективни тегобизаради намалување на видот, појава на мушички, феномен на светкање или метаморфопсии.

Цел на трудот е експлицитен приказ на случај со ова заболување, да се насочи вниманието на истото, што би имало едукативно значење за лекарите кои се занимаваат со патологија на задниот сегмент на окото.

Приказ на случај. Жена на 56 год.возраст, дава податок за намален вид на двете очи, повеќе изразен на десното око. Анамнестички првите проблеми почнале од пред 10 години, со намалување на видот на близина.

На преглед најдобрата корегирана видна острина на десното око (BCVA) 0,02 cc; и на левото око BCVA 0,5 cc. Интраокуларниот притисок обострано беше 14, 6 mmHg, а биомикроскопијата на преден сегмент со уреден наод.

На очното дно макула лутеа со изразени атрофични промени на пигментен епител и ситни хиперпигментации, со ретки друзи, атрофични промени

на хориокапилариси со експозиција на големите крвни садови на хороидеа. Во преекваторијалниот предел и на екватор, посебно темпорално видили се атофични промени на хороидеа со присуство на беличести друзеновидни промени. На периферија на очното дно, во предел на екватор како и антериорно, видливи се големи хеморагични зони локализирани субретинално со зони на субретинална фиброза во облик на сиво беличасти плажи или со тракаст изглед кои лесно ја надигнуваат ретината, а присутни се и зони на серозно одлепување на ретината.
На ОЦТ пресек (OCT Topcon 3D 2000) присутна е изразена атрофија на пигментниот епител и хориокапиларис со хиперрефлексија на хороидеа и видливи лакунарни простори на големите крвни садови. На ОЦТ ангиографијата (OCT-A Topcon Atlantis) не се забележани васкуларни промени на ретината и хороидеа или новосоздадена крвна мрежа. Значајно е дека пациентката се лечи од хипертензија од 2002 година, а од пред осум години е на дијализа.
Заклучок. Прикажан е случај со ретко, невообичаено заболување, кое може да претставува значаен дијагностички проблем. Истовремено заболувањето е честа причина за нарушување на видната острина, за кое се уште нема стандардизиран пристап во неговото лекување. Оттука, имајки ги во предвид наведените дилеми, препознавањето на овој ентитет е од посебно значење во офталмолошката пракса. Овој труд, преку приказ на случај со изложена документација е од посебно значење за лекарите кои се занимаваат со оваа патологија.

Клучни зборови: периферна ексудативна хеморагична хориоретинопатија (PEHCR), дегенерација на макулата врзана за возраста (ARMD), полипоидна хороидална васкулопатија (PCV), анти ВЕГФ (anti-VEGF)

Introduction

Peripheral exudative hemorrhagic chorioretinopathy (PEHCR) is a rare disease which is manifested by subretinal hemorrhage and exudates. The lesions to a certain level resemble those manifested in age-related macular degeneration, but in this case they appear in the peripheral segments of chorioretina. It is an unusual degenerative process in the retinal tissue, which has to be taken into consideration versus vasoproliferative masses, melanomas or similar changes in chorioretina.

Case report

A 56-year-old woman was referred to the University Clinic of Ophthalmology due to decreased visual acuity involving both eyes, more prominent in the right eye. The best corrected visual acuity was BCVA 0.02 in the right eye and BCVA 0.5 in the left eye. Intraocular pressure was measured by Schioetz and its value was 14.6 mmHg in both eyes. Biomicroscopy of the anterior segment showed a normal finding. Corpus vitreum was with prominent degenerative changes, and blood elements diffusely spread were visible in the right eye.
The Optic Nerve Head (PNO) in the fundus was with normal color at retinal level. Vascular arcades had significant sclerotic changes and signs of arterial hypertension. Macula lutea was with distinct atrophic changes in the pigment epithelium and tiny hyperpigmentations, with few drusen, atrophic changes in choriocappillaris with exposition of the large blood vessels. In both, the pre-equatorial segment and the equator, especially temporally atrophic choroid lesions with present whitish drusen-like changes were observed (Figure 1).

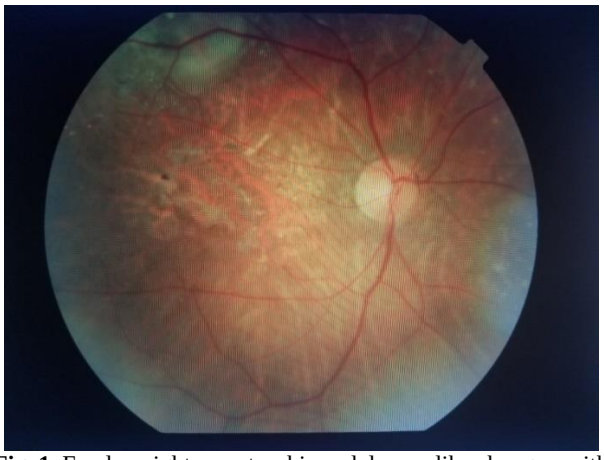

Fig. 1. Fundus, right eye-atrophic and drusen-like changes, with prominent large blood vessels in macula lutea

In the peripheral eye fundus, in the equator and anteriorly hemorrhagic zones were seen located subretinally with zones of subretinal fibrosis shaped as grey-whitish plaques or strip-shaped that easily elevated the retina, but zones of serious retinal detachment were also present (Figures 2 and 3).

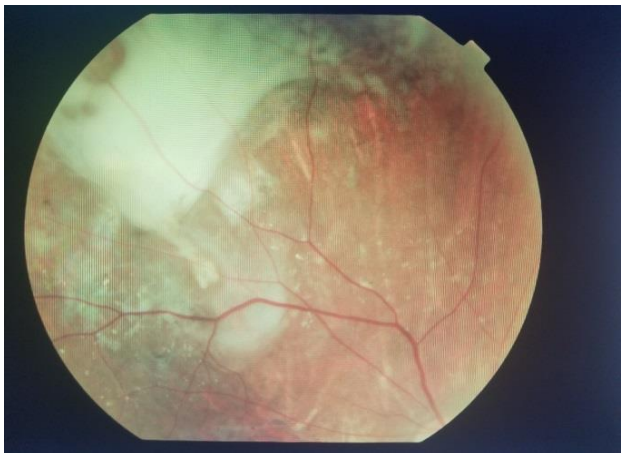

Fig. 2. Fundus, right eye, temporal sector - zones of subretinal fibrosis shaped as grey-whitish plaques or strip-shaped that easily elevated the retina, and atrophic changes

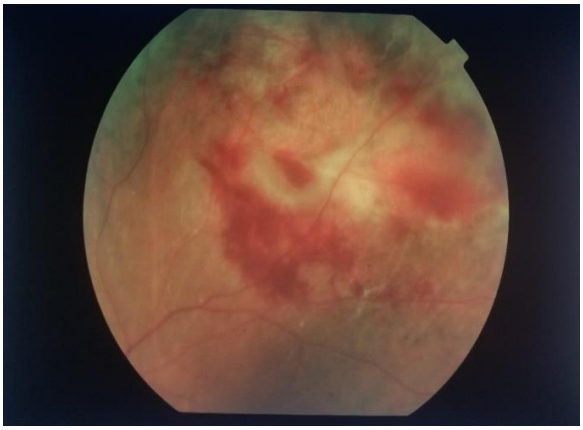

Fig. 3. Fundus, left eye, temporal sector-subretinal hemorrhagic zones

The choroid was with atrophic and drusen-like changes, with prominent large blood vessels.
Due to patient's kidney insufficiency, fluoroscein angiography was not realized. OCT of the posterior segment with angiography was made (Figure 4).
OCT section revealed distinct atrophy of pigment epithelium and choriocappillaris with hyperreflexia of the choroid and apparent lacunar spaces in the large blood vessels. In the left eye there were atrophic changes of neuroretinal layers andbroadening of foveal umbo were noticed in the right eye. In the left eye flattening of foveal curvature with discrete edema in the interplexiform cells and external granular layer with thickening of the internal limited membrane were observed (Figure 4).

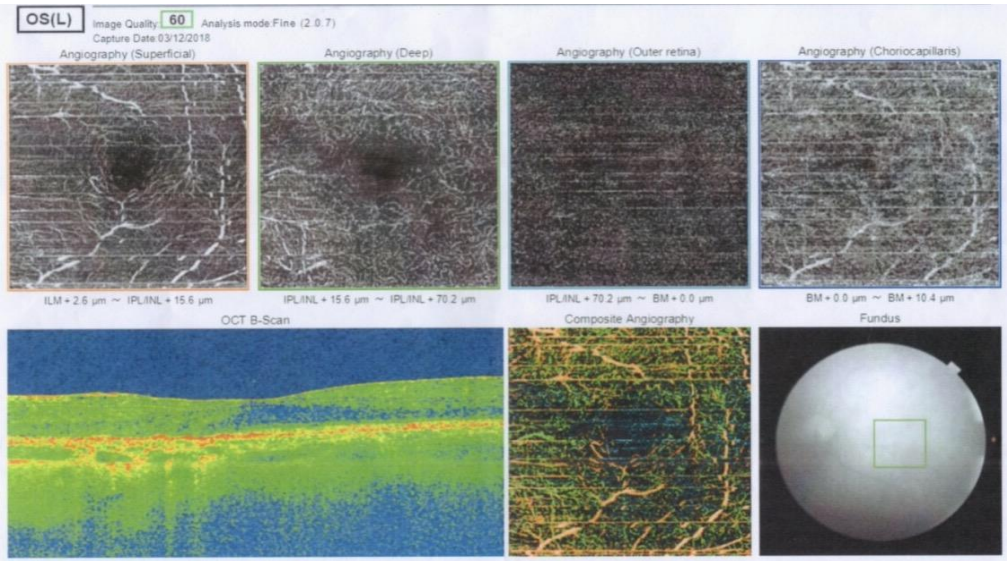

Fig. 4. OCT angiography of the posterior segment on left eye

OCT angiography revealed no vascular changes in the retina and choroid or in the neovascularnetwork (Figure 4).
OCT angiography revealed no vascular changes in the retina and choroid or existence of neovascularnetwork (Figure 4).
Medical history revealed that patient's first symptoms appeared 10 years ago, with difficulty focusing on objects that are up close. Eight years ago she experienced onset of floaters in her right eye, and 6 years ago a significant visual decreasein the left eye that was manifested as her seeing objects through a veil.
The patient has been receiving antihypertensive therapy since 2002, and systolic values ranged from 180 to 220 mmHg and diastolic from 90 to 110 mmHg. Since 2010 she has been undergoing dialysis, which is being conducted three times per week with anticoagulant heparin therapy. The patient informed us about the treatment of her sterility with hormone therapy that has been going on for 19 years.
In consultation with a specialist in internal medicine, the intra-arterial hypertension was treated and heparin was substituted with fraxipane. Due to the small edema in the macula of the left eye, therapy with anti-VEGF was given, intravitreal bevacizumab (avastin).
The control check-up showed significantly reduced hemorrhages with present large plaques and strip-like fibrotic lesions subretinally. Visual acuity in the right eye was BCVA 0.1 and in the left eye 0.6.

Discussion

Progressive exudative hemorrhagic chorioretinopathy was described for the first time in 1962 by Resse and Jones, and later this disease was also reported by other authors by presenting several caseseries [1-3]. It is a retinal degenerative process that develops in elderly population and in majority of patients it affects both eyes (30%). The disease is characterized by a symmetric process [4].
Changes are usually located in the periphery, temporally or in the lower segment of ocular fundus, but in severe progressive cases they can also appear in other sectors around fundus circumference. They are preva-

lent in the European population and in females/Caucasian females.

Some authors consider peripheral exudative hemorrhagic chorioretinopathy as the peripheral version of age-related macular degeneration, while othersbelieve it a variant of polypoidal choroidal vasculopathy (PCV) [5].

Although the disease may develop asymptomatic, the classical clinical manifestations are subjective discomfort with visual decrease, onset of floaters, phenolmenon of flashes or metamorphosia. Rarely the disease can be accompanied with pain as a result of glaucoma dueto angle closurethat arises frommassive peripheral hemorrhages [4,6].

The ophthalmological finding is a spectrum of changes that range from mild to more severe abnormalities, which affect the peripheral retina. Retinal pigment epithelial thinning with atrophy or hyperplasia of RPE is observed, as well as ablation of pigment epithelium with serous or hemorrhagic content, tears of the pigment epithelium, presence of subretinal hemorrhages and lipid exudates with consequent fibrosis. Sometimes vitreous hemorrhage appears. Changes are seen in peripheral retina, usually behind the equator involving several quadrants. However, sometimes they are so intense that can jeopardize the macula and can cause impairment of the central vision. A large number of authors have reported that these changes are very often associated with central changes includingage-related macular degeneration.

The severity and size of the changes in some distinct forms can easily be misinterpreted for tumor choroidal changes or for vasoproliferative tumors although they differ by localization and echographic characteristics.

The disease is of unknown etiology, but age is considered to be a risk factor, and it has been observed and presented in series of examined patients.

The medical history of systemic diseases and impairments in our patient revealed information on systemic hypertension and kidney insufficiency, and hence, the patient has been on dialysis with heparin anticoagulant therapy since 2010, three times per week.

Some authors emphasize the association of this disease with age-related macular degeneration (ARMD) [1,3]. In a substantial number of patients lesionswere found in ipsilateral eyesresembling macular degeneration, and hence, some retina specialists think that PEHCR is associated with ARMD because they share common risk factors, but still a large number of retina specialists make arguments against such relationship [1,3]. Some of the mentioned authors think that PEHCR is a variant of polypoidal choroidal vasculopathy (PCV). Based on analysis of cases, they support the attitude that individuals with PEHCR have PCV as an underlying disease [6]. Correlation with PCV has been shown in series of cases analyzed by Mantel *et al*. [3], where 50% had changes in the choroidal circulation, that is, choroidal vasculopathy and no cases of choroidal neovascularization were observed [3].

Due to unknown etiological factors of the disease and the expression of clinical signs and symptoms in prominent forms that might be related to life-threatening diseases, this disease has to be diagnosed and differentiated from these forms as in the case of malignant choroidal tumors or vasoproliferative tumors. Echographic finding has special characteristics in PEHCR, regarding the appearance, spreading and localization as well as echographic acoustic quality of the lesions and reflectivity of the lesions. Fluorescein angiography, if applicable, is important, and of particular importance is angiography with indocyanine green (ICG) in detecting abnormalities in choroidal vascular network.

Although there is no defined standard therapy for this disease, the applied method of management is anecdotal. The disease in certain cases that are less clinically manifested can resolve, and hence observation is the method of management of the patients. In case of vitreal bleeding vitrectomy can be made, and recentlythe affected eyes have been treated with intravitreal injections of anti-VEGF agents in cases of neovascular membrane with macular exudate, which is the cause of vision decrease [7,8].

Conclusion

We have presented a case of a very rare, unusual disease that can pose a diagnostic problem. At the same time, this disease is a common cause of visual acuity impairment that is difficult to be managed. Having in mind mentioned aspects, awareness of this entity is important in the ophthalmology practice. Presenting this explicitly documented case is of special importance for doctors who are involved in this type of eye pathology.

Conflict of interest statement. None declared.

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In memoriam

Проф д-р Владимир Цветанов
(1935-2019)

Проф. д-р Владимир Цветанов е роден 1935 година во Скопје, каде го завршува основното и средно образование. На Медицинскиот факултет во Скопје дипломирал во 1961 година. Од 1962 до 1965 година работи како општ лекар во Здравствената станица на рудникот Радуша. Во 1967 година ја завршува специјализацијата по медицина на трудот, а во 1970 година магистрира во Школата за народно здравје "Андрија Штампар"во Загреб со што станува прв магистер по медицински науки на Медицинскиот факултет во Скопје. Во 1979 година докторира на Медицинскиот факултет во Скопје на тема алергиски алвеолит, а неговата дисертација од некои скандинавски автори е наречена "македонска студија за алергискиот алвеолит". Во 1984 год. го добива звањето супспецијалист по алергологија и клиничка имунологија, а во 1993 супспецијалист по алергологија и пулмологија.

Проф. Цветанов е основоположник на Институтот за медицина на трудот (1972 година) и под негово раководство Институтот го добива новиот објект со оптимални услови за работа и станува наставна база на Медицинскиот факултет.

Повеќе дијагностички методи во областите на медицината на трудот, пулмологијата и алергологијата за прв пат кај нас се воспоставени од проф. Цветанов, а некои од нив и денес се применуваат. Во 1967 година ја воведува модерната функционална дијагностика на респираторниот систем, а сумираните искуства од "малата спирометрија" ги објавува во 1969 год. Резултатите, пак, од примената на кожните тестови со алергени од работно место во детекција на бронхијалната астма при експозиција на брашнена прашина ги објавува во списанието "Allergie und Asthma" во 1970 година. Во 1976 година го воспоставува тестот за одредување на преципитински антитела со двојна имунодифузија на гел-агар, во 1978 година индиректниот тест на базофилна дегранулација (во тоа време актуелен за пеницилинската и медикаментозна преосетливост), а ЛИФ тестот во дијагностиката на професионалниот контактен дерматит во 1980 година. Во 1991 година во Институтот за медицина на трудот отпочнати се аеропалинолошките истражувања, а 1993 година се публицирани и првите резултати за градот Скопје. Во 1994 година, пак, ја воведува риноманометријата како важен тест во дијагностиката на алергискиот ринит.

Од 1993 година е редовен професор на Катедрата по хигиена и медицина на трудот на Медицинскиот факултет во Скопје. Истовремено е вклучен во наставата на супспецијалноста по алергологија и пулмологија, како и на последипломските студии на медицинските факултети во Љубљана и Сараево. Во текот на својата академска кариера бил член на повеќе специјалистички комисии, како и ментор и член на комисии за одбрана на повеќе магистерски трудови и докторски дисертации на Медицинскиот факултет во Скопје.

Уредник и прв автор е на монографиите: "Здравствена состојба и работна способност" (1989), "Социјална медицина-Health promotion" (1995), "Алергиски болести-лекување" (1998), "Македонски национален консензус за алергиски ринит" (1999), "Специфична имунотерапија" (2001) и "Алергиските болести во Р. Македонија" (2006), издадени во Скопје. Тој е еден од авторите на "Македонскиот национален консензус за дијагноза и лекување на астма и хроничната опструктивна белодробна болест" (1999) и на учебникот "Клиничка алерголија" (Софија, 2001). Проф. Цветанов е носител на два проекта за епидемиологијата на алергискиот ринит (1993/1994), мулти-

центричната студија за бронхијална астма (1995/96) и Проектот бр. 400998 одобрен и финансиран од Министерството за образование и наука на Р. Македонија насловен како "Епидемиолошки карактеристики на алергискиот ринит во Р. Македонија во корелација со поленската микрофлора" (1998-2003). Автор или коавтор е на повеќе од 200 стручни и научни трудови презентирани или објавени во земјава и во странство.
Бил претседател на Првиот македонски имунолошки конгрерс (1996) и на Македонското здружение за базична, клиничка имунологија и алергологија (МЗБКИА) во пародот од 1996 до 2000 година.
Добитник е на највисокото признание на Македонско лекарско друштво за 1996 година.
Тешко е да се сфати фактот дека проф. Цветанов не е повеќе меѓу нас. Медицинскиот факултет засекогаш ќе му остане благодарен за се што направи со својата повеќедецениска истрајна и самопрегорна работа. Во исто време, почитуваниот и саканиот професор останува да живее во спомените и сеќавањата на неговите многубројни студенти, специјализанти, магистранти и докторанти.

Проф. д-р Јордан Минов

УПАТСТВО ЗА ПРИЈАВА НА ТРУД ОД СОРАБОТНИЦИТЕ НА ММП

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

Списанието ги има следниве рубрики и категории на трудови:

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

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

1. ТЕКСТ НА РАКОПИСОТ

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

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

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

Изворните трудови и **соопштувањата** го имаат следниов формален редослед: насловна страна, извадок на македонски јазик (вовед, методи, резултати, заклучок) со клучни зборови, извадок на македонски јазик со клучни зборови, вовед, материјал и методи, резултати, дискусија и заклучоци, литература и прилози (табели, графици и слики) и легенди за прилозите во еден фајл.

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

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

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

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

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

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

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

Заклучоците треба да не бидат подолги од 150 зборови.

2. ПРИЛОЗИ

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

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

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

Микрофотографиите може да содржат посебни ознаки во вид на стрелки или симболи. Покрај описот на сликата, мора да се наведе и зголемувањето и видот на боењето на препаратот (ако тоа веќе не е направено во секцијата *материјал и методи*).
Сите ознаки на фотографиите мора да бидат доволно големи, за да може јасно да се распознаат и по смалувањето во печатницата, при нивното вклучување во печатената страница на списанието.

3. ЛИТЕРАТУРА

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

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

б) заеднички автор

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

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

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

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

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

Адресата на Редакцијата
Даме Груев бр. 3
Градски ѕид блок II,
1000 Скопје,
Тел.: ++ 389 02 3162 577

Електронска адреса (Е-маил): mld@unet.com.mk

Известување за членовите на МЛД

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

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

Известување за рецензентите за ММП

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