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CONTENT - СОДРЖИНА

PUBLIC HEALTH

MORTALITY FROM MALIGNANT NEOPLASMS IN THE REPUBLIC OF NORTH MACEDONIA IN THE PERIOD FROM 2010 TO 2018

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Abstract

The aim of the paper was to provide data on the situation and the trend of the mortality rate from malignant neoplasms in the population of the Republic of North Macedonia (RNM) in the period 2010-2018 along with the most common causes of death from malignant neoplasms in 2018, with a special reference to the distribution of mortality by sex and age. Material and methods: A retrospective study was performed using epidemiological descriptive methodology. Data were statistically analyzed. The mortality rates for malignant neoplasms were estimated at 100,000 inhabitants. Data are displayed in tables and figures in total number for the Republic of North Macedonia. The data for the number of deaths were obtained from the State Statistical Office and processed and analyzed at the Institute of Public Health of RNM. Results: A total of 19,727 people died in RNM in 2018, and malignant diseases accounted for 18.9% of the total mortality and they were the second-rated cause of death behind the cardiovascular diseases, with 3,734 deaths or a rate of 179.8 deaths per 100,000 citizens. Of the total number of deaths from malignant neoplasms in RNM in 2018, a larger number of men died compared to women, and most of them (31.3%) died from malignant neoplasms of the bronchi and lungs. In 2018, in RNM, females mostly died from malignant breast neoplasms (18.3%) and 13.1% from malignant neoplasms of the bronchi and lungs. In the period 2010-2018, the mortality rate from malignant neoplasms in people aged 0-64 years decreased by 87.5 in 2010 to 79.2 in 2018 per 100,000 population. The same phenomenon was present in the population over the age of 65; it was 881.1 per 100,000 population in 2010 and 805.1 in 2018. Conclusion: Cancer is the second leading cause of death in RNM as well as globally. In 2018, 1 in 5 deaths were due to malignant diseases in RNM, while in the world 1 in 6 deaths were due to cancer. About one-third from cancer deaths are due to the five leading behavioral and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco and alcohol use.

ЈАВНО ЗДРАВЈЕ

МОРТАЛИТЕТ ОД МАЛИГНИ НЕОПЛАЗМИ ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА ВО ПЕРИОДОТ ОД 2010 ДО 2018 ГОДИНА

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Цитирање: Василеска Л, Ќосевска Е, Лековска-Стоицовска Т, Кардашевски А. Морталитет од малигни неоплазми во Република Северна Македонија во периодот од 2010 до 2018 година.

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Извадок

Целта на трудот беше да се прикаже состојбата и трендот на стапката на морталитет од малигни неоплазми во периодот 2010-2018 година кај населението во Република Северна Македонија (РСМ), најчестите причини за смрт од малигни неоплазми во 2018 година, со посебен осврт на дистрибуцијата на смртноста по пол и возраст. Материјал и методи: Беше изведена ретроспективна студија со примена на епидемиолошко-дескриптивниот меод на работа. Податоците беа статистички обработени. Добиените стапки на морталитет на малигни неоплазми беа пресметани на 100.000 жители. Податоците се прикажани табеларно и графички вкупно за РСМ. Податоците за бројот на умрени беа добиени од Државниот завод за статистика, а обработени и анализирани во Институтот за јавно здравје на РСМ. Резултати: Во РСМ во 2018 година починале вкупно 19.727 лица, а малигните заболувања учествувале со 18,9% во вкупниот морталитет и биле на второ место во структурата на причини за смрт по кардиоваскуларните заболувања со 3.734 починати лица или стапка од 179,8 починати на 100.000 жители. Од вкупниот број починати од малигни неоплазми во РСМ во 2018, регистрирани се поголем број починати кај машката популација отколку кај женската, а најголем дел од нив (31,3%) починале од малигни неоплазми на бронх и бел дроб. Кај женската популација, во 2018, најголем број починале од малигни неоплазми на дојка (18,3%), а 13,1% од малигни неоплазми на бронх и бел дроб. Во периодот 2010-2018 година стапката на морталитет од малигни неоплазми на возраст од 0-64 години бележи тренд на опаѓање, од 87,5 во 2010 до 79,2 во 2018 на 100.000 население. Истата појава е присутна и кај населението на возраст над 65 години, односно во 2010 изнесувала 881,1 на 100.000 население, а во 2018 е намалена на 805,1. Заклучок: Ракот е втора водечка причина за смрт во РСМ, како и на глобално ниво. Во 2018 година, 1 од 5 смртни случаи се должат на малигни заболувања во РСМ, додека глобално во светот 1 од 6 смртни случаи се должи на карцином. Околу една третина од смртните случаи од рак се должат на 5-те водечки ризици во однесувањето и исхраната: висок индекс на телесна маса, низок внес на овошје и зеленчук, недостаток на физичка активност, употреба на тутун и алкохол.

Introduction

Malignant neoplasms are one of the biggest socio-medical problems today due to the high frequency, high mortality, suffering of patients and their families caused by the disease and the great financial and social burden on the health care system and society as a whole.

According to the World Health Organization (WHO), more than 12 million people worldwide are diagnosed with malignant neoplasms each year, and 7.6 million die. In the total number of deaths in the world, malignant neoplasms as a cause of death account for 20-25%.

More than two-thirds of malignant neoplasms are caused by factors that are a result of the modern life style and are the cause of increased number of patients suffering from these diseases worldwide. More than 70% of malignant neoplasm deaths occur in low- and middle-income countries, where resources for the prevention, diagnosis, and treatment of malignancies are limited or non-existent. At the same time, WHO estimates the possibility of preventing one third of the existing malignancies, which risk factors widely cited as etiological factors of these diseases can be prevented. Also, about 30-50% of patients can be cured if the diagnosis is made in the early (initial) stage of the disease, and further treatment is appropriate. All these facts hypothetically confirm that every third patient suffers unnecessarily from a malignant disease, many people unnecessarily die prematurely and much more suffer. Many malignant neoplasms are curable if detected early and treated with appropriate diagnostic and therapeutic methods.

Fighting malignancies is a priority in many countries. It started in Europe in 1985 by implementation of the "Europe against cancer" program. In 2005, the World Health Assembly held its 58th session in Geneva and adopted Resolution Cancer Prevention and Control (WHA 58.22)[1], highlighting the growing problem of cancer worldwide. The resolution highlights the need to develop and strengthen comprehensive national cancer control programs, which include prevention, early detection, successful treatment and palliative care.

The aim of this paper was to provide data on the situation and the trend of the mortality rate from malignant neoplasms in the population of the Republic of North Macedonia (RSM) during the period 2010-2018 of, along with the most common causes of death from malignant neoplasms in 2018, with a special reference to the distribution of mortality by sex and age.

Material and methods

A retrospective study was performed using an epidemiologically descriptive method of work. The source of data was the State Statistical Office of RNM. The data was statistically analyzed at the Institute of Public Health of RNM. The resulting mortality rates for malignant neoplasms were estimated per 100,000 inhabitants. The data are presented in tables and figures in total number for the Republic of North Macedonia.

Results

Indicators of "negative" health are mortality indicators in the population. In 2018 in the Republic of North Macedonia, a total of 19,727 people died, of which 22.74% aged 0-64 years and 77.21% over 65 years (2,3) (Table 1).

Table 1. Deaths by sex and age in the Republic of North Macedonia, 2018

	Total	0-64	65+
Total	19727	4486	15232
Men	10339	2899	7432
Women	9388	1587	7800

Source: State Statistical Office
Processing: Center for statistical processing of health data and journalism

In 2018, 4,486 people aged 0-64 years died in the Republic of North Macedonia, 64.6% men and 35.3% women.

Mortality in the population over 65 years is a very important indicator of the health status of this population group. The health indicators of this age group are in fact indicators of all measures and activities undertaken in order to improve the health of the population up to 64 years of age. Out of 15,232 deaths in people over 65 years in 2018, 51.2% were men and 48.7% women (2,3,4,5).

The most common causes of death

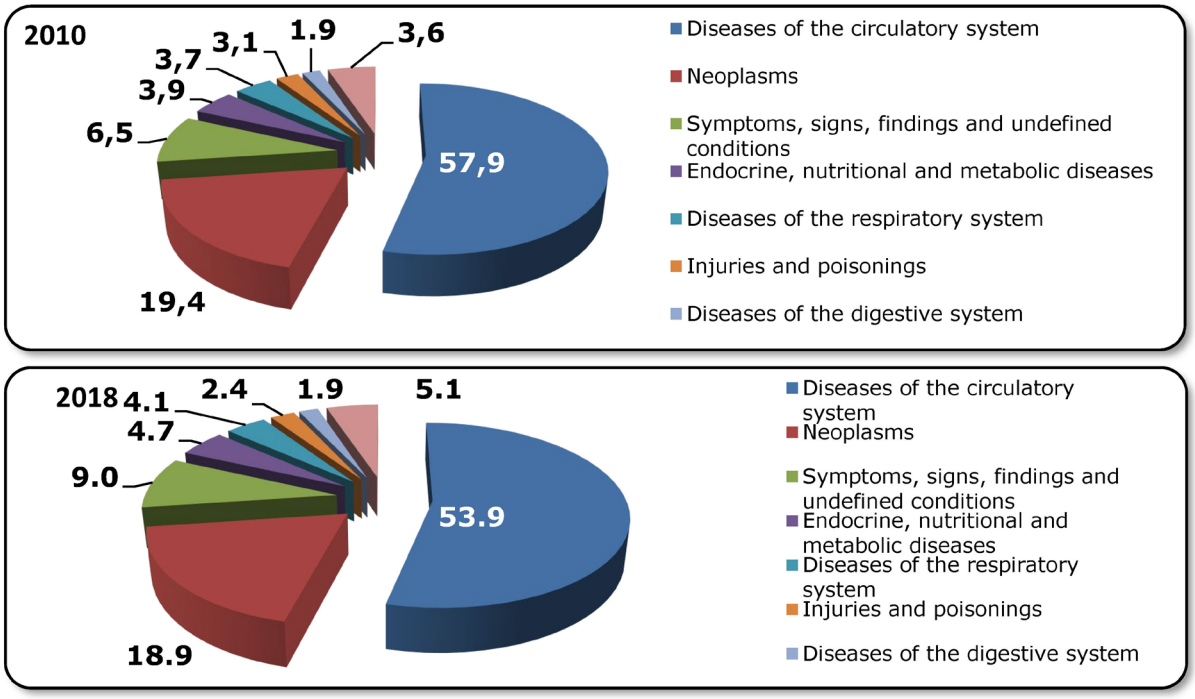

Figure 1 and 2 . Ten most common causes of death in the Republic of North Macedonia, 2010 and 2018

Source State Statistical Office
Processing: Center for statistical processing of health data and journalism

In 2018 in the Republic of North Macedonia, malignant diseases participated with 18.9%, and in 2010 with 19.4% in the total mortality and were the second-rated mortality cause of death, behind the cardiovascular diseases[2,3]. Mortality from malignant neoplasms decreased in 2018 compared to 2010.

Causes of death from malignant neoplasms by sex in the Republic of North Macedonia, 2018

Out of a total of 3,734 people who died from malignant neoplasms in the Republic of North Macedonia in 2018, 60% were men and 40% are women. (Table 2). A larger number of men died compared to women.

Table 2. Causes of death from malignant neoplasms by sex in the Republic of North Macedonia, 2018

MKB-10 Code	MALIGNANT NEOPLASM	Sex	2018	
			Number	rate /100 000
	Total deaths from malignant neoplasms	Total	3734	179.8
		m	2240	215.4
		f	1494	144.1
C16	Malignant neoplasms of the stomach	Total	257	12.4
		m	178	17.1
		f	79	7.6
C18	Malignant neoplasms of the colon	Total	240	11.6
		m	144	13.8
		f	96	9.3
C20	Malignant neoplasms of the rectum	Total	174	8.4
		m	103	9.9
		f	71	6.9
C22	Malignant neoplasms of the liver and intrahepatic bile ducts	Total	198	9.5
		m	119	11.4
		f	79	7.6
C25	Malignant neoplasms of the pancreas	Total	225	10.8
		m	128	12.3
		f	97	9.4
C32	Malignant neoplasms of the larynx	Total	63	3.0
		m	58	5.6
		f	5	0.5
C34	Malignant neoplasms of the bronchi and lungs	Total	895	43.1
		m	700	67.3
		f	195	18.8
C44	Other skin neoplasms	Total	27	1.3
		m	19	1.8
		f	8	0.8
C50	Malignant neoplasms of the breast	Total	281	13.5
		m	7	0.7
		f	274	26.4
C53 (2017) C54	Malignant neoplasms of the cervix	f	30	2.89
	Malignant neoplasms of the body of the uterus	Total	59	2.8
		m	0	0.0
		f	59	5.7

C56	Malignant neoplasms of the ovary	Total	73	3.5
		m	0	0.0
		f	73	7.0
C61	Malignant neoplasms of the prostate	Total	184	8.9
		m	184	17.7
		f	0	0.0
C71	Malignant neoplasms of the brain	Total	154	7.4
		m	82	7.9
		f	72	6.9
C67	Malignant neoplasms of the bladder	Total	120	5.8
		m	92	8.8
		f	28	2.7

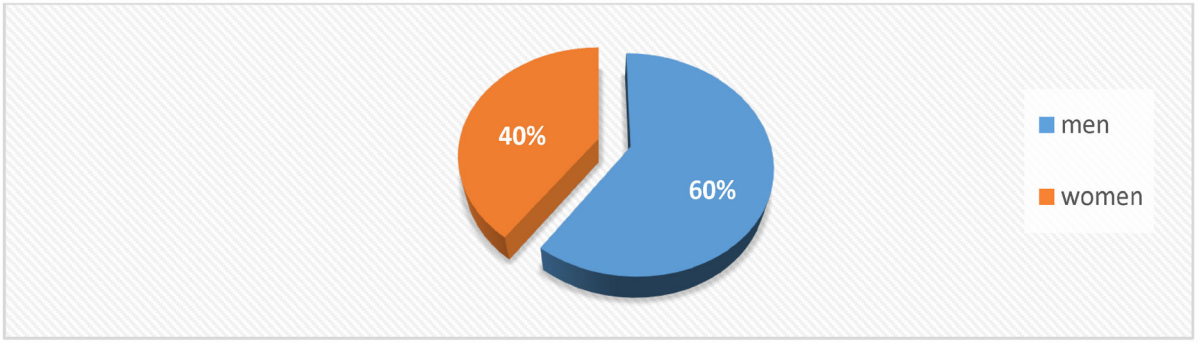

Figure 3. Structure of deaths from malignant neoplasms by sex in the Republic of North Macedonia, 2018

Out of a total of 2,240 men who died from malignant neoplasms in 2018 in RSM, the largest number died from malignant neoplasms of the bronchi and lungs, 31.3%. The second leading cause of death in men was prostate malignant neoplasm, from which 8.2% of men died.

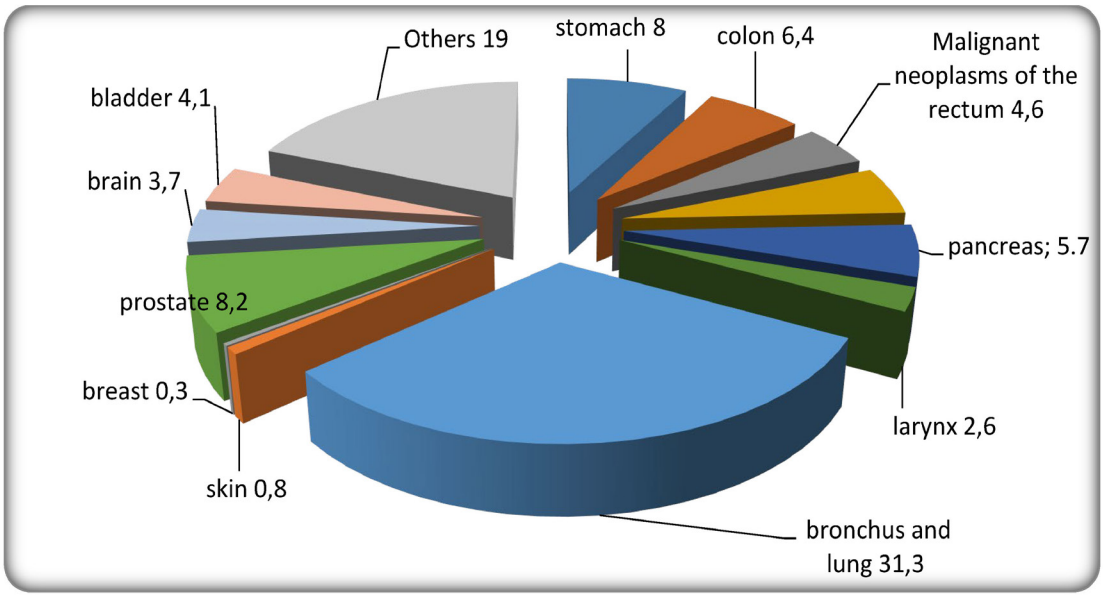

Figure 4. Causes of death from malignant neoplasms in men in the Republic of North Macedonia, 2018

Out of a total of 1,494 women who died from malignant neoplasms in 2018 in RSM, the largest number died of breast malignant neoplasms (18.3%), and 13.1% died from malignant neoplasms of the bronchi and lungs, as the second leading cause of death in women.

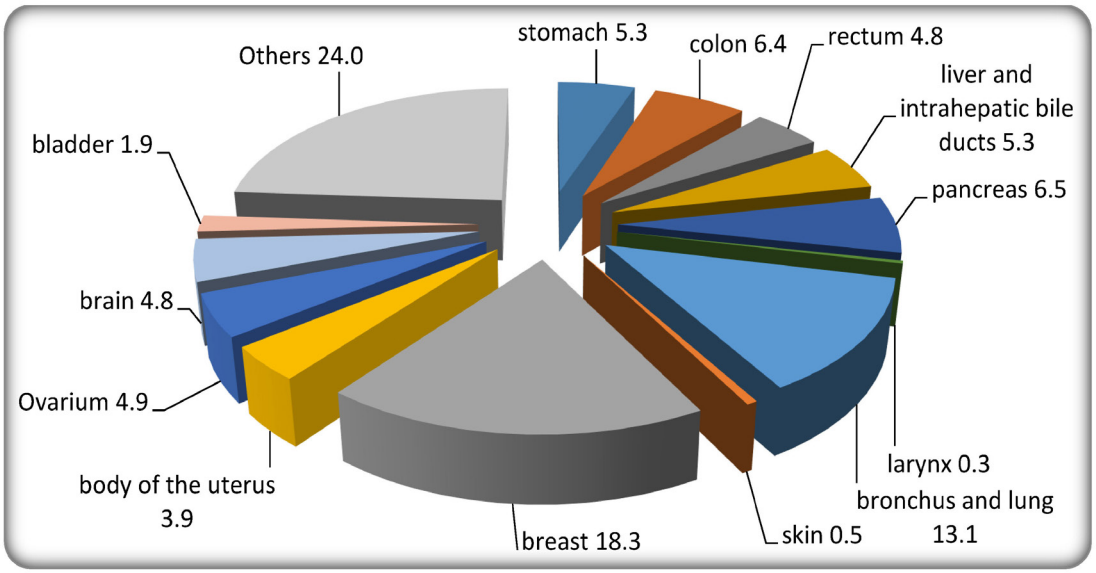

Figure 5. Causes of death from malignant neoplasms in women in the Republic of North Macedonia, 2018

Mortality rate from malignant neoplasms in RN Macedonia by sex and age, 2010 – 2018

In the analyzed period of 2010-2018, the mortality rate ranged from 180.3 per 100,000 population in 2010 to 179.8% in 2018. The mortality rate from malignant neoplasms was the highest in 2016 (187.3%), and the lowest in 2011 (172.5%) (Figure 6).

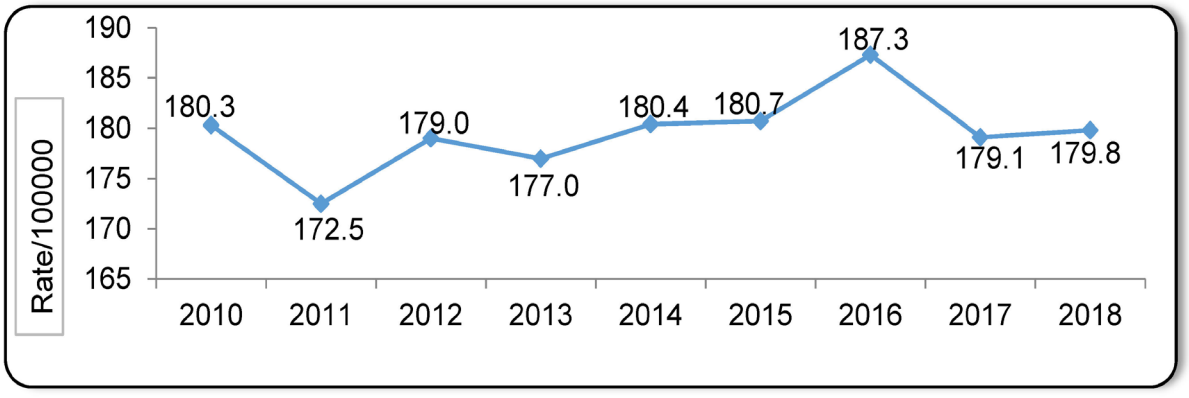

Figure 6. Mortality rate from malignant neoplasms in RN Macedonia, 2010 – 2018

In the analyzed period of 2010-2018, the mortality rate was higher in men than in women, starting from 2010 when the mortality rate was 215.4 for men and 145.1 for women, i.e., the number increased by 70. 3 index points for men compared to women, until 2018 when the mortality rate for men was 215.4

and 144.1 for women, with an increase of 71.3 index points for men compared to women. In 2016, the largest increase in the mortality rate from malignant neoplasms in both men (220.8) and women (153.7) was observed compared to the entire analyzed period (Figure 7).

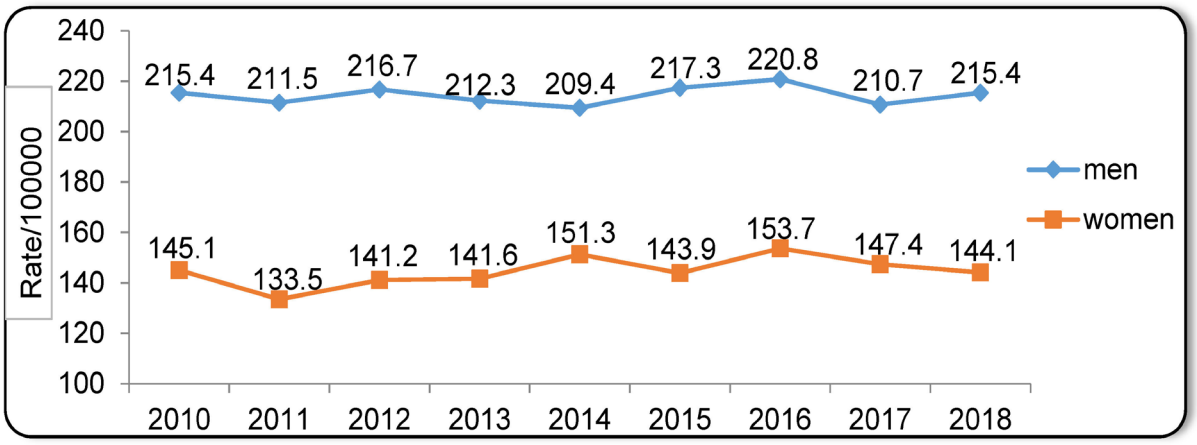

Figure 7. Mortality rate from malignant neoplasms in RN Macedonia, 2010 – 2018

Mortality from malignant neoplasms in people aged 0-64 years

In the period of 2010-2018, the mortality rate from malignant neoplasms in people aged 0-64 years declined and ranged from 87.5 in 2010 to 79.2 in 2018 per 100,000 population. The mortality rate in the analyzed period decreased by 8.3 index points.

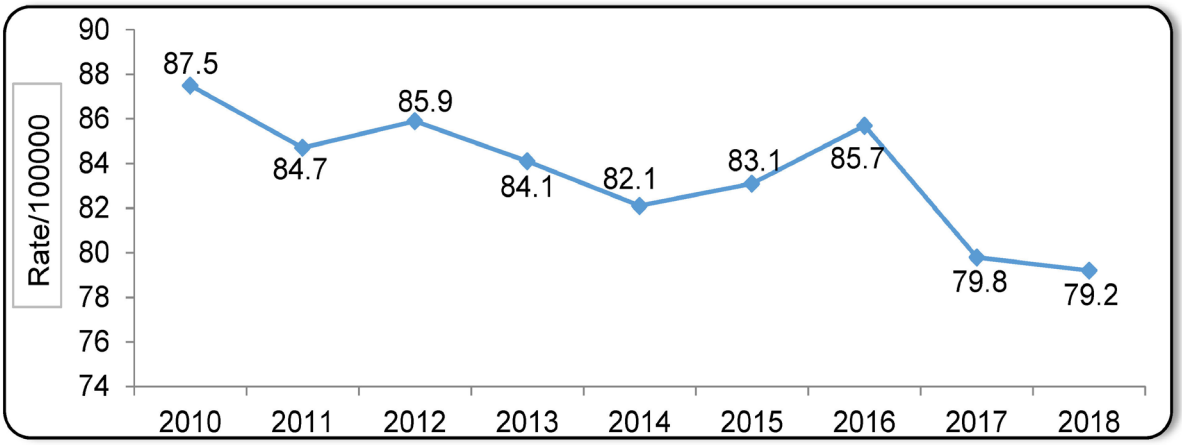

Figure 8. Mortality rate from malignant neoplasms in RN Macedonia in people aged 0 - 64 years, 2010 – 2018

The mortality rate from malignant neoplasms in the analyzed period in the age group 0-64 years was higher in men. Starting from 2010 when the mortality rate was 102.4 for men, it increased by 30.3 index points compared to the mortality rate for women, which was 72.1, until 2018 when the mortality rate for men was 89.5 and 68.4 for women, with an increase of 21.1 index points in men compared to women (Figure 9).

There was a downward trend in the mortality rate among men, which was 89.5 in 2018 compared to 102.4 in 2010, and among women, from 72.1 in 2010 to 68.4 in 2018.

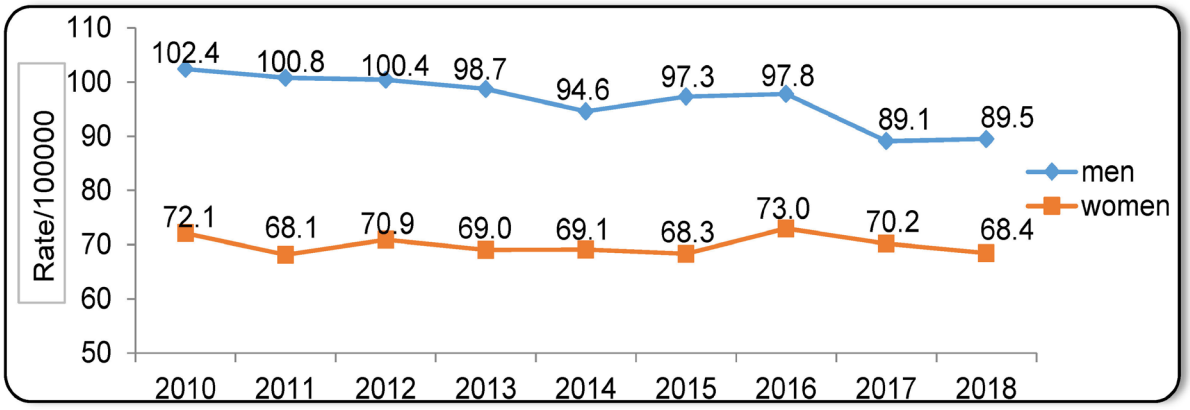

Figure 9. Mortality rate from malignant neoplasms in RN Macedonia in people aged 0-64 years by sex, 2010-2018

Mortality from malignant neoplasms in people over the age of 65 years

In the period 2010-2018, the mortality rate from malignant neoplasms in people over 65 years of age had a downward trend. In 2018, it was 805.1 per 100,000 population and was reduced by 76 index points compared to 2010 when the mortality rate from malignant neoplasms was 881.1.The mortality rate from malignant neoplasms in the age group 0-64 years was significantly lower than the mortality rate in people over the age of 65 years.

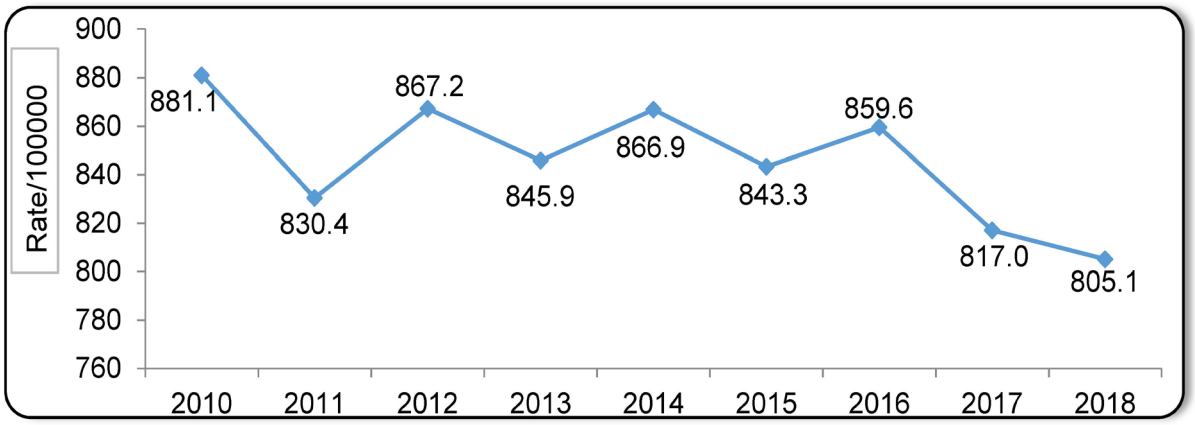

Figure 10. Mortality rate from malignant neoplasms in RN Macedonia over the age of 65, 2010 – 2018

The mortality rate from malignant neoplasms in the age group over 65 years was higher in men.

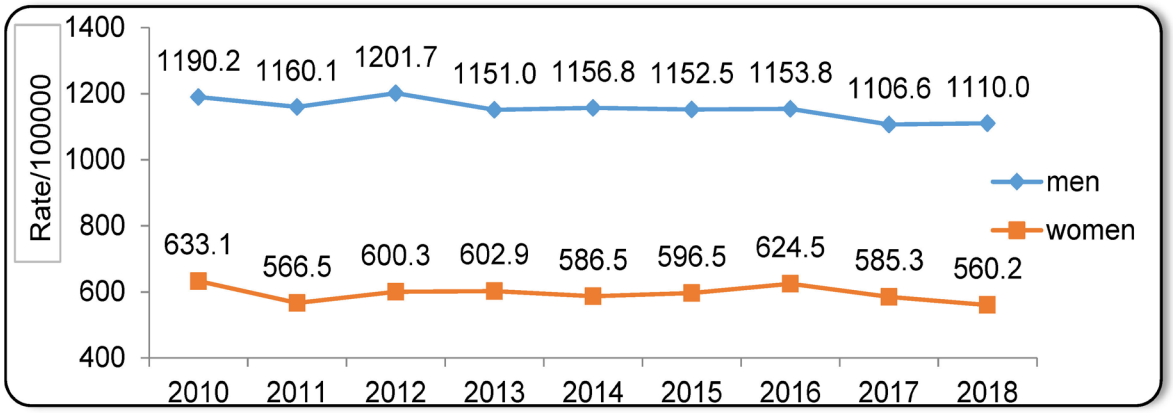

Figure 11. Mortality rate from malignant neoplasms in RN Macedonia over the age of 65 by sex, 2010 – 2018

The most common primary sites of malignant neoplasms

The most common cause of death from malignant neoplasms in men, with an increasing trend in the period 2010-2018, was malignant neoplasm of the bronchi and lungs with a mortality rate ranging from 64.8 in 2010 to 66.9 in 2014 and 67.3 per 100,000 men in 2018.

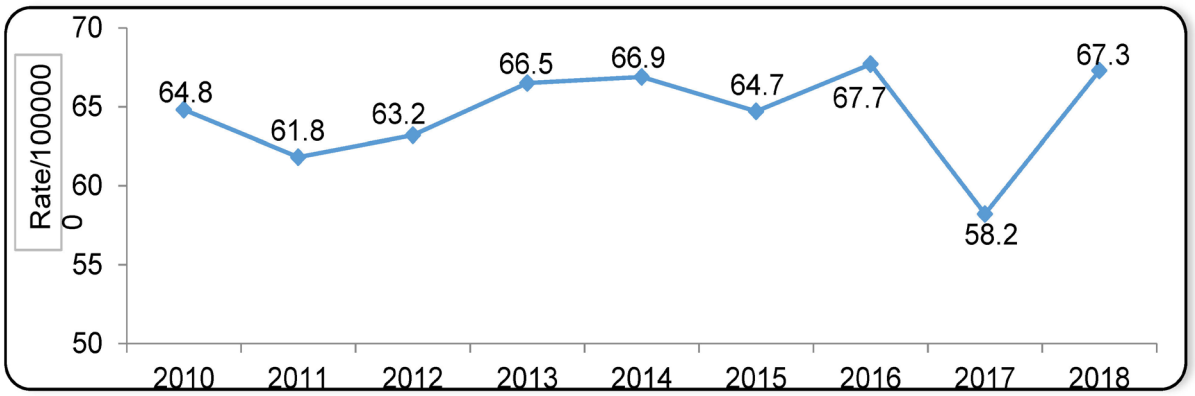

Figure 12. Mortality rate from malignant neoplasm of bronchi and lung in men in RN Macedonia, 2010 – 2018

In the period 2010-2018, the most common cause of death from malignant neoplasms in women was malignant breast neoplasm. The mortality rate ranged from 30.0 in 2010 to 26.4 in 2018 per 100,000 women. In the analyzed period, the mortality rate had a declining trend, with the exception of 2016 when the highest mortality rate of 32.7 index points was recorded.

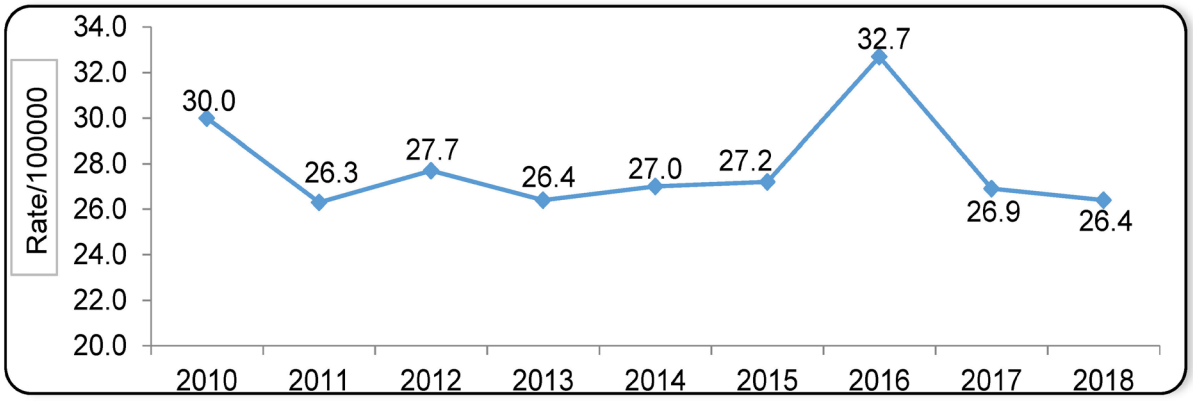

Figure 13. Mortality rate from malignant breast neoplasm in women in RN Macedonia, 2010 – 2018

Discussion

Among non-communicable diseases, malignant neoplasms are the most common causes of death in the world. Malignant neoplasms such as local, atypical, autonomic, intermittent, and inadequate tissue growth, together with cardiovascular diseases, are the leading cause of nearly three-quarters of all deaths in the European region.

In 2018, globally there were about 18.1 million new cases of cancer and 9.6 million deaths of cancer[4].

In 2018 in the Republic of North Macedonia , a total of 19,727 people died, of which 22.74% from 0-65 years old and 77.21% over 65 years, whereby in both age groups a larger number of deaths among men was recorded than among women.

In the same year, malignant diseases accounted for 18.9% of the total mortality and were the second-rated cause of death behind the cardiovascular diseases.

In 2018, there were 18.1 million new cases worldwide (17.0 million excluding the NMSC) and 9.6 million cancer deaths (9.5 million excluding the NMSC). For both sexes combined, it was estimated that nearly half of the world's cancer cases and more than half of all deaths occurred in Asia in 2018, as nearly 60% of the global population lives there.

Europe accounted 23.4% of all cancer cases and 20.3% of all cancer deaths, although it accounted for only 9% of the global population, followed by America with 21% of all cancer cases and 14.4% of deaths in the world. Unlike other regions, the share of cancer deaths in Asia (57.3%) and Africa (7.3%) is higher than the incidence rate (48.4% and 5.8%, respectively), due to different distribution of cancer types and higher mortality rate in these regions [5,6].

Globally, for both sexes, lung cancer is the most commonly diagnosed cancer (11.6% of all cases) and the leading cause of cancer death (18.4% of all cancer deaths), closely followed by female breast cancer (11.6%), colorectal cancer (10.2%) and prostate cancer (7.1%) incidence and colorectal cancer (9.2%), gastric cancer (8.2%) and carcinoma of the liver (8.2%) due to mortality. By sex, lung cancer is the most commonly diagnosed cancer and the

leading cause of cancer death in men, followed by prostate and colorectal cancer due to the incidence and liver and gastric cancer due to mortality. In women, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death, followed by colorectal and lung cancer for the incidence and lung cancer cause of death. Cervical cancer ranks fourth in both incidence and mortality. Overall, the top 10 cancers account for over 65% of newly diagnosed and malignant neoplasm deaths.

Of the total number of deaths from malignant neoplasms in RSM in 2018, there was a larger number of deaths recorded among the male population compared to the female, and most of them (31.3%) died from malignant neoplasms of the bronchi and lungs.

Out of a total of 1,494 women who died from malignant neoplasms in 2018 in RSM, the majority died from malignant neoplasms of the breast (18.3%), and 13.1% died from malignant neoplasms of the bronchi and lungs, as a second cause of death in women.

Cancer is the second leading cause of death globally, with about 1 in 6 deaths due to cancer.

About 70% of cancer deaths occur in low- and middle-income countries.

About one-third of cancer deaths are due to the top 5 behavioral and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco and alcohol use.

Tobacco use is the most important risk factor for onset of cancer and is responsible for about 22% of cancer deaths[7].

Cancer-causing infections, such as hepatitis and human papillomavirus (HPV), are responsible for up to 25% of cancer cases in low- and middle-income countries [8].

The economic impact of cancer is significant and increasing. The total annual economic cost of cancer in 2010 was estimated at approximately $ 1.16 trillion [9].

Only 1 in 5 low- and middle-income countries have the data needed to pursue a cancer policy[10].

In order to reduce the morbidity and mortality from malignant neoplasms in the Republic of North Macedonia, the Program for early detection of malignant diseases is being implemented. The program refers to:

I. Screening for prevention and early detection of cervical cancer which main goal is to reduce the incidence and mortality from cervical cancer in women in the Republic of North Macedonia.

II. Pilot screening of colorectal cancer in the Republic of North Macedonia in order to reduce the morbidity and mortality of the population from colon cancer.

III. Promotional campaign for prevention and early detection of prostate cancer organized by the Ministry of Health in order to raise awareness among the male population for prevention and early detection of prostate cancer. In addition, the goal is to encourage family doctors to recommend preventive examinations (at the secondary and tertiary level) for all men aged 50-55 years and those with a family risk from prostate cancer aged 40-50 years.

IV. Organized mammographic screening for early detection of breast cancer which main goal is early detection of breast cancer in women in the Republic of North Macedonia by conducting screening, following the European recommendations for implementation of organized screening.

Conclusion

Cancer is the second leading cause of death globally and was responsible for about 9.6 million deaths in 2018, about 1 in 6 deaths due to cancer.

In 2018 in the Republic of North Macedonia, a total of 19,727 people died, of which 22.74% from 0-65 years old and 77.21% over 65 years, whereby in both age groups a larger number of deaths was recorded in men compared to women.

Of the total number of deaths from malignant neoplasms in 2018, 60% were men and 40% women.

In 2018 in RSM, out of a total of 2,240 men who died from malignant neoplasms, the majority died from malignant neoplasms of the bronchi and lungs (31.3%), and 8.2% died from malignant prostate neoplasm, as the second leading cause of death.

In the same year, out of a total population of 1,494 women who died from malignant neoplasms, the majority died from malignant breast neoplasms (18.3%), and 13.1% died from malignant neoplasms of the bronchi and lungs, as the second leading cause of death in women.

The most common cause of death from malignant neoplasms in men with an increasing trend in the period 2010-2018, was malignant neoplasm of the bronchi and lungs with a mortality rate of 64.8 in 2010 to 67.3 per 100,000 men in 2018.

In women, the most common cause of death from malignant neoplasms in the period 2010-2018 was malignant breast neoplasm with a declining trend from 30.0 in 2010 to 26.4 in 2018 per 100,000 women.

In the period 2010-2018, the mortality rate from malignant neoplasms in people aged 0-64 years was declining, from 87.5 in 2010 to 79.2 in 2018 per 100,000 population. The same phenomenon was present in the population over the age of 65, i.e., 805.1 per 100,000 population in 2018 and 881.1 in 2010.

About one-third of cancer deaths are due to the top 5 behavioral and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco and alcohol use.

WHO estimates support opportunities to prevent one-third of existing malignancies by developing and strengthening comprehensive national cancer control programs, which include prevention, early detection, successful treatment, and palliative care. It will contribute in reducing the number of patients with malignant neoplasms, reducing the mortality from malignant neoplasms, reducing the suffering of patients and their families and improving the quality of life.

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PUBLIC HEALTH

SOME INTERNATIONAL EXPERIENCES FROM SCREENING FOR COLORECTAL CANCER

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Abstract

Colorectal cancer (CRC) is an important public health problem, especially in Europe. Every year approximately 435,000 new cases are being diagnosed with colorectal cancer. Half of these people die, which makes this type of cancer a second-rated mortality cause in Europe. The main aim of this paper was to make a literature search related to colorectal cancer with a focus on the developed Western European countries and countries close to the Republic of North Macedonia.

This paper also intended to provide a picture of the early screening for colorectal cancer as the most efficient method for prevention and early detection of colorectal cancer and its application in some developed countries. For achieving the objectives set out in this paper, a survey of the available literature (both electronic and print) as well as of the grey literature was made. A systematic search of the following databases was made: PubMed, European Commission, and Google Scholar. The inclusion criteria were studies conducted between 2008 and 2020, with an emphasis on the newest studies and those published in the neighboring countries. According to the WHO recommendations and practices in modern countries, colorectal cancer should be identified as a serious public health problem. This includes unclear cause of its occurrence, as well as all possible risk factors which make it almost possible to implement an adequate prevention program.

The most acceptable sensitive test for implementation of the screening program for colorectal cancer is the utilization of the FOB test. It is of great importance to follow-up patients with a positive FOB test as well as to offer easy access to health services, i.e., screening program to the population.

ЈАВНО ЗДРАВЈЕ

НЕКОИ МЕЃУНАРОДНИ ИСКУСТВА ОД СКРИНИНГ НА КОЛОРЕКТАЛЕН РАК

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Извадок

Колоректалниот карцином (КРК) претставува многу важен јавноздравствен проблем со 435.000 нови случаи годишно. Овој вид карцином е на второ место по смртност во Европа. Главна цел на овој труд беше да се изврши преглед на постојната литература поврзана со скринингот за колоректален карцином (КРК) во развиените западноевропски земји, како и во Република Северна Макединија и земјите од нејзиното опкружување. Трудот укажува на почетоците и развојот на скрининг програмата за КРК, како најефикасна метода за превенција и рана детекција на колоректалниот карцином. Бидејќи сè уште во целост не се познати причините за настанувањето на карциномот на дебелото црево, како и можните фактори на ризик, единствено можна превенција е избегнувањето на веќе познатите ризици како и скринингот за рано откривање. За остварување на целите поставени во овој труд беше направен преглед на достапната литература (во електронска и печатена форма), како и преглед на „сивата литература“ (grey literature). Како извори на податоци (бази на податоци) за електронско пребарување беа користени PubMed, WHO, European commission, Google Scholar. Во истражувањето беа вклучени стидии публикувани во периодот 2008-2020 година, при што предност им беше дадена на поновите студии како и на студиите кои се однесуваа на земјите од регионот на Република Северна Македонија. Како најмногу применуван и најсензитивен тест при скрининг за КРК е ФОБ тестот. Неопходно е да се олесни пристапот на населението кон раното откривање на колоректалниот карцином преку здравствена услуга во форма на бесплатен скрининг за КРК со ФОБ тест.

Introduction

Colorectal cancer (CRC) is a very important public health problem in Europe. Every year approximately 435,000 new cases are being diagnosed with colorectal cancer. Half of these people die, which makes this type of cancer a second-rated mortality cause in Europe[1]. According to WHO data, colorectal cancer is the third commonest cause of death from malignant diseases in men, and the fourth most common in women, responsible for 10% of overall death rate from malignant diseases in the developed countries.[3] CRC mortality rate in 27 Member States of the European Union varies, whereby Hungary takes the leading place and Cyprus is on the last place. This diversity in mortality is due to different life styles, screening models or the stage when the disease has been detected as well as to the range of sophisticated treatment and health care.

Colorectal cancer can be detected in its early stage. In the developed countries, approximately 40-50% of the population across lifetime develop one or more adenomas in the colorectal region1, and most of them do not progress to malignancy.[2] The average duration of the development of an adenoma to colorectal cancer has not been identified, but it is assumed to take at least 10 years.[3] This long latent phase provides an excellent opportunity for early detection of this disease. If it is detected in the phase of adenoma, its removal can prevent the incidence of colorectal cancer. But, even when cancer is detected in an earlier stage, prognosis is considerably better than in a more advanced stage.

Efficiently conducted screening technique can significantly reduce morbidity and mortality from CRC in the population. Several approaches for CRC control are available in healthy control subjects with or without familial or other risk of this disease. They include colonoscopy combined with sigmoidoscopy and FOB test. Screening with the FOB test is essential, but it is necessary to adequately implement it in practice, to have systems for appointment for early colonoscopy if there is a positive finding and to establish functional cancer registers.[4]

The main aim of this paper was to make a literature search related to screening for colorectal cancer with a focus on the developed Western European countries and countries close to the Republic of North Macedonia. The paper also describes the beginnings and development of CRC screening program as the most efficient method for prevention and early detection of colorectal cancer.

Material and methods

In order to accomplish the objectives, set out for this paper, a systematic review of the available literature (electronic and print) was conducted as well as a survey of the "grey literature". Retrieval of the following databases PubMed, European Commission, and Google Scholar was made. The paper included studies conducted between 2008 and 2020, with an emphasis on the recent studies and those published in the neighboring countries of North Macedonia. The following keywords were used for retrieval of the electronic databases: colorectal cancer, screening for colorectal cancer, FOB test, algorithm of screening for col-

orectal cancer. The search of the "grey literature" comprised retrieval of web sites of relevant national institutions (Health Ministries, academic institutions, doctors' associations, non-governmental organizations) and it consisted of reviews of national annual programs, reports on implementation of programs, protocols and professional consensuses, national projects, etc.

Results

In 2008, according to the WHO data, 450,000 newly diagnosed cases with colorectal cancer were registered and the estimated total number of deaths in the European Union was 232,000. About 65% of all new cases were in the high-income countries. The risk of onset of colorectal cancer across the lifespan depends on several factors such as age, eating habits/physical activity, personal and familial predisposition, and it ranges from 5% in patients with an average risk to more than 95% in patients with some hereditary/congenital syndromes.[5] It is important to stress the fact that one fourth of the diseased has a positive family history, of which 15% are first-degree relatives.[6]

According to the existing literature used for the needs of this paper, CRC is the third most common malignoma behind that in the lungs and prostate in the United Kingdom. It is the second most commonly diagnosed malignoma in women, right behind that of the breasts. CRC is always fatal if it is diagnosed in the advanced stage, but it can be cured, i.e., has a relatively long survival rate if it is diagnosed in the early stage.

In Europe, CRC is the second most common cause of cancer death in both men and women. It is the second most common malignoma encountered in women, right behind the breast cancer, and the third most commonly diagnosed cancer in men behind lung and prostate cancers. In the entire European Union, the death from colorectal cancer has decreased from 20.36/100,000 population in 1995 to 18.86/100,000 population in 2009.

Having in mind that in more than 90% of patients CRC develops based on previous existing benign adenomatous intestinal polyps by which removal carcinoma onset is prevented along with the fact that disease detection in the early phase results in a 5-year survival in more than 90% of patients, it is necessary to establish a preventive screening program for early detection of this disease.[7]

In 1968, WHO defined the first set of principles for population screening[8]: 1) its importance as a public health problem for the individual and for the community; 2) recognition of the latent or early symptomatic stage; 3) available facilities for diagnosis and treatment; 4) suitable screening tests; 5) promotion of tests among the populations; 6) adequate understanding of the disease history; 7) agreed policy for testing, treatment and care of patients diagnosed with this disease; and 8) financing of screening and treatment of CRC as a continuing process.

Accumulated knowledge for implementation of screening programs for cancer has been acquired through screening networks founded in the European Union and the ''Europe Against Cancer'' program.[9]

EU networks have shown that the entire outcome and quality from the screening depends on the performance of each and every step of the screening process. For achieving a potential benefit from CRC screening, the quality has to be optimal in every step of the process and has to include information, identification and personal invitation to the target population, adequate performance of the screening test, additional diagnostics of the lesions detected with the screening, treatment, surveillance and continuous care. This approach is essential regarding screening adjustment to those individuals who would benefit from it in terms of adequate monitoring, evaluation and subsequent improvement of its performance[10].

Later, all the above-mentioned principles were incorporated in the European Union policy about cancer screening and were embodied in the European Council Recommendations on Cancer Screening on 2nd December, 2003[11]. They showed that efficacy evaluation is an indispensable prerequisite for accepting the screening process by the population, but not sufficient by itself. Many other aspects such as adverse effects, cost and infrastructure should also be included in the screening process. Population screening is a process that starts with education of the population about the disease that is being screened and ends with follow-up of the disease and treatment of the patient if he/she tested positive.

Screening can have two approaches: opportunistic – when patients themselves pay a routine check-up to their family physician, and proactive – when a target group that is going to be subjected to screening is identified. There are several screening modalities for early detection of CRC. They include: fecal occult blood test (FOBT), flexible sigmoidoscopy, colonoscopy and computerized tomographic colonography. Since one of the leading symptoms of colon cancer is occult or overt bleeding along with impaired intestinal (gastric) emptying, screening with the FOBT is a method of choice in a large number of countries.

The risk of developing CRC significantly rises above the age of 40, and 91% of all cancers have been detected at this age and primarily in individuals older than 50 years. It is assumed that every person at the age of 50 bears a 4.8% risk of developing CRC by the age of 74, i.e., 2.3% risk that he/she will die from CRC. That is why, the European Union recommends FOB screening for colorectal cancer in men and women aged 50 to 74 years.

Screening tests are available, but with different degrees of sensitivity and specificity. Prior to implementation of the national program in the United Kingdom, several sensitive and specific screening methods were identified and patient acceptance and financial implications were also investigated. CRC screening was conducted by using the FOB tests. There is evidence that this modality saves lives in a similar manner as the breast screening program in the United Kingdom. Single flexible sigmoidoscopy is an alternative to the FOB test screening and pilot data show that this technique is being logistically realized in the United Kingdom. Currently, the FOB test and

flexible sigmoidoscopy are rewarding, but they differ in sensitivity and specificity. Programs for education of the population are essential for reaching the effectiveness.[12]

In recent decades, the principles of WHO have been expanded and elaborated in the implementation of the national screening programs in the Netherlands and has been concluded that initiation of treatment in the early phase has more benefit than delayed treatment. In the Netherlands, population screening for colorectal cancer stared in 2014, the target group being aged 55-75 years. According to the experts' opinion in the Netherlands, in long-term perspective the national screening program could help about 2,400 people per year that would otherwise die from colorectal cancer. In the years 2014 through 2018, about 76 of 100 people responded to the invitation to participate in the screening program[14].

In the developed Nordic/Scandinavian countries colorectal cancer is the most common type of malignoma, ahead of breast and prostate cancer. By application of CRC screening and in line with the results they obtained, these countries have reduced death from this cancer by 23%. Denmark decided to conduct a feasibility study to assess whether population/community-based screening would have the same effect as it was demonstrated in randomized controlled trials.[15] In Danmark, all citizens between 50 and 74 years of age were invited to make a colon cancer screening every second year. A screening program looks for cancer precursors and cancer in people who do not have symptoms. Without a screening program colon cancer is usually discovered late, because symptoms appear late. In Danmark around 5,200 people a year develop colon cancer. Colon cancer is one of the most widespread types of cancer in the population. Approximately 1,800 people die from colon cancer every year. A screening kit is sent to every person by mail. This test kit is used to collect a small sample, and then it is returned to a laboratory by mail. The sample is then checked under a microscope for hidden blood, i.e., tiny amount of blood. Hidden blood can be a sign of colon cancer or polyps.[16] The earlier colon cancer is diagnosed, the greater the chances of being cured. In Norway, the Government has accepted the non-formal screening of the population. The reason behind this lies in the fact that this country has one of the world's highest incidence rates of colon cancer, especially in people aged 55 years and older. This country plans to offer every citizen free colorectal cancer screening before he/she turns 55 years. The program was started in 2019 with an aim to cover the entire population within a five-year period.[17] It was estimated that during the period 2013-2017 the final effect of this policy were 500 death cases. In Finland, the implementation of the national screening program was gradually introduced by using the FOBT as a method for screening in 2014[18]. In August of 2021 the Finish Government amended the Government Degree on Screening. Colorectal cancer screening will be performed on national level from 2022 onwards. The screening will be made for both men and women aged 60-68 years. It will be expanded by age group and will cover the entire

target population, that is, all people 56 - 74 years old in 2031. The screening will be made every two years.[19]

The National system in Italy (Passi) is organized as a telephone-interview surveillance system that collects information on population health, monitors behavioral health risk factors and diffusion of preventive health interventions. From 2010 to 2013, more than 151,000 of the population aged 18-69 years were interviewed. During 2013, 136 out of 147 Italian local health authorities participated in the survey. Information regarding screening included: test uptake (PAP test, HPV, mammography, FOB test, colonoscopy), date of the last test, reason for not participating in screening, screening promotion and results from the screening. Individual information about socio-economic characteristics was also available.[21]

In analyzing the structure of the conducted screening programs in different regions of Italy, 38% of the participants aged 50-69 years reported having undergone CRC screening in the last two years prior to the interview. From 2010 to 2013, an increased coverage for all types of screening was registered: the trend was higher in the South of the country, and the increase was mostly due to the tests performed within the organized programs. In regions with people with a low level of education, economic problems and immigrants, a lower coverage of screening was observed. In regions with well-implemented organized screening programs, coverage for testing was higher. Also, differences regarding socio-economic factors were smaller than in regions with incomplete activation of the screening program. Between 2017 and 2020, about 47% of 50-69-years old in Italy underwent colorectal cancer screening. This statistic has highlighted regional variations. An obvious considerable geographic difference between the South and the North of the country was registered. In fact, in Northern regions, about 69% of residents underwent this kind of screening, while the average percentage in Southern regions was 27%. In Apulia, the prevalence rate of colorectal tests was as low as 10.6%.

With an aim to reduce death cases, CRC screening was established in the United Kingdom. The screening program was commenced in Northern Ireland in 2010, and then England and Scotland started its implementation. Its goal was to analyze and discuss the initial results from screening of the colon cancer in Northern Ireland and at the same time to compare data with other regions in the United Kingdom. The adenoma detection was higher than the expected one.[20]

A good example of a well-organized and effective colorectal cancer screening program from the region is the SVIT Program from Slovenia22 aimed for men and women aged 50 to 69 years. As a result of the screening program, each year in this country the number of new CRC cases is reduced for 300, and of death cases for 200. In the beginning, Slovenia conducted this CRC screening as a pilot project, which later proved to be very successful and hence was implemented on a national level.

In order to reduce CRC incidence and mortality, a population screen-

ing in the Republic of Serbia was organized. The goal was to assess the acceptability of the FOB test proposed by primary care physicians. From August to November 2013, a pilot study for CRC screening was realized. The screening was organized in individuals aged 50 to 74 years. Fifty primary healthcare centers from all 25 administrative regions of Serbia were included. A total of 50,894 individuals were invited to participate in the screening program. The participation rate was 67.8 and 3.4% of the FOB tests were positive. Of those with a positive test, 69.7% agreed to undergo colonoscopy. The positive prognostic value was 27.1% for adenoma and 14.6% for carcinoma. This was the first CRC screening program in the country and encompassed approximately one third of primary healthcare institutions in all regions across the country.[23]

According to the data of the National System for Electronic Health Records/Evidence – "My Term", the incidence of colorectal cancer in R. Macedonia in 2019 was 34.7/100,000 inhabitants, that is, 38.8/100,000 men and 30.6/100,000 women. In 2018/2019 the incidence of colorectal cancer in both genders was more than three times higher than in the period of 2015/2016. The prevalence of men was significantly higher compared to women (p=0.0001). The mean age was 64.7±10.9 years; the youngest diagnosed patient was 14 years old, and the oldest 94 years. The mean age of men versus women was 65.1±10.6 vs. 64.1±11.3, with a significant difference in favor of older age at first diagnosis in male patients (p=0.033). A total of 91.54% of diagnosed individuals were at the age ≥50 years. Diagnosis of colorectal cancer in younger age groups was significantly associated with life in the rural environment (p=0.0001). Since 2008, there is a national consensus on prevention, diagnosis, therapy and follow-up of CRC patients in R. North Macedonia. In a six-month period in 2012 (July – December), the first pilot CRC screening in the age group 50-74 years was organized. The results obtained showed that by using the FOB test there was a possibility of diagnosing this type of cancer in an early stage. In 2012, the first organized CRC screening was initiated, which in 2014 reached the highest coverage and fulfilled all steps of the screening program in R. North Macedonia. Screening and the need for its implementation in our country was included in the Strategy for Healthcare Development, Consensus on prevention, diagnosis, therapy and follow-up of patients with colorectal cancer in the Republic of North Macedonia has been made, and it is in line with the European recommendations against colorectal cancer as well as in line with the resolution on prevention and control of carcinomas adopted by the World Health Organization in Geneva in 2003.[24]

Discussion

Although the mechanism has not yet been defined, a large number of studies have pointed out to stimulation of the proliferation of the normal colon mycosis that can turn to adenoma and CRC, probably due to the direct genotoxic effect of local metabolites (free oxygen radicals and sulfur reactions) in the colon. Advances in knowledge about molecular and genetic mechanisms, which play a key

role in the CRC pathogenesis, have stressed the importance of prevention and early detection by screening of people from 50 to 70 years of age.

The implementation of screening programs includes also a structure responsible for delivery of services, quality of the service and evaluation. Population programs, in general, ask for a high level of organization in terms of identification and invitation of each and every individual that belongs to the target group. A large number of experts and professionals are undertaking further steps regarding the improvement of the screening standards.[25]

On 2nd of December 2003, the Health Ministers of the European Union unanimously adopted recommendations on cancer screening based on the evidence and experience of the "Europe Against Cancer" program.[25] The European Council Recommendations include fundamental principles of best practice in early detection of cancer and invites EU Member States to undertake joint actions in implementation of national colorectal cancer screening programs, with an organized population-based approach and with adequate quality assurance at all levels.

The adoption and subsequent implementation of the Council Recommendations on Cancer Screening has also been supported by various initiatives of the European Parliament and has been documented in resolutions of the Parliament.[26] Efforts for implementation of EU Council Recommendations also include continuous update of quality assurance guidelines suggested by the Council as a conclusion during the Slovenian Presidency.[27] The Council recommendations and European guidelines also stress the need for efficient communication with population groups, most commonly identified as persons with a limited access to screening or vulnerable social-economic groups. This, in return, should enable informed decisions about participation, based on objective, balanced information about the risks and benefits of the screening.[28]

Screening program efficacy is seen in the qualitative functioning of the individual components of the screening. The success of the program is seen not only in the impact on public health but also on the organization, implementation and adaptation. In order to determine the efficacy of the program, that is, its impact on morbidity and mortality, a continuous monitoring of the target population in defined timeframe is necessary. The key to evaluation of the population screening program is in the collection and timely and precise analysis of the data.

Short-term estimation on the success of conducting a screening program is evaluated by the population response, the speed of reporting a positive finding and referral to colonoscopy, the attitude of the people with a positive test towards further investigations, extent of the utilization of engaged resources (colonoscopy, analgosedation, endoscopic interventions – a successfully conducted examination, follow-up of the pathological finding and treatment).

Long-term estimation on the success of conducting a screening program refers to the decrease of mortality and morbidity rate from CRC.

Since 2007, several EU Member States

are in a process of implementation of a national population screening. This type of screening is being conducted in five countries: Finland, France, Italy, Poland and United Kingdom. Some of these countries are running non-population-based CRC screening program (Austria, Bulgaria, Czech Republic, Germany, Greece, Latvia, Slovak Republic). Other five countries have realized a pilot CRC screening program (Hungary, Cyprus, Portugal, Romania and Slovenia). Ten of these 17 countries have adopted the FOB test alone, 6 use a combined FOB test and endoscopy, and one uses colonoscopy, too. Ten of them have developed or upgraded the CRC screening program (Czech Republic, France, Ireland, Lithuania, Portugal, Slovak Republic, Slovenia, Spain, Sweden and United Kingdom). Danmark and the Netherlands are in the phase of implementation of the CRC screening program.[29]

Conclusions

According to the WHO recommendations and good practices in modern countries, CRC has to be identified as a public health problem. By applying a high-quality screening program that would comprise a large number of participants, the decrease in mortality percentage is generally accepted to be similar in all countries. Each country should give priority to the benefits of the CRC screening over the benefits of alternative programs. CRC incidence rate in Europe shows that the potential benefit from CRC screening is important for all European countries.

Currently, only the FOB test (for detection of occult bleeding) for men and women aged 50-74 years is recommended by EU as a valid screening test for early detection of CRC. Direct harmful effects related to this test are minimal. The guidelines, in general, contain information about establishing screening programs with excellent quality using the most common modalities in Europe, which are FOBT, flexible sigmoidoscopy and colonoscopy. Stool-based tests, such as FOBT and FIT (fecal immunochemical test), have been recognized as effective, but it is assumed that quantitative FIT is superior in terms of specificity and sensitivity. FOB tests should be repeated at annual or biannual basis or at least every three years if FIT is used. The guidelines emphasize the lack of high-quality evidence for assessment of colonoscopy. Nevertheless, according to the authors, current evidence supports the 10-year surveillance if colonoscopy is used, which indicates that the extended interval up to 20 years can be appropriate.

In the Republic of North Macedonia, the FOB test has been accepted for implementation in the screening program for early detection of CRC and hence European guidelines are met, but it has to be taken into consideration that upgrading is necessary for development of protocols and guidelines for screening.

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PUBLIC HEALTH

KNOWLEDGE OF HEPATITIS B AMONG THE HEALTHY POPULATION IN COMMUNITY

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Key words: hepatitis B, hepatitis B virus, knowledge, transmission

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Abstract

Hepatitis B is the world's most common blood-borne viral infection, accounting for 2 billion infections, 350 million carriers, and 6 lakh deaths annually. Aim of the paper was to determine the level of knowledge among healthy population in the Republic of North Macedonia regarding Hepatitis B virus infection. Material and methods: A community-based cross-sectional study was undertaken. Questionnaire was administered to 600 healthy individuals, who heard about hepatitis B. Data handled and analyzed by using statistical package SPSS. Results: The profile of those who give the correct answer regarding the cause of hepatitis B that it is a virus are women (65.3%), aged 40 to 49 (42.8%), by nationality are Macedonian, have higher education (52.8%), 92.8% live in urban areas, 74.3% are married, employed (79.2%) and have a moderate monthly income (68.9). About one-third of the sample said that loss of appetite, diarrhea, nausea/vomiting also associated with hepatitis B. There is a significant difference in knowledge related to early (prodromal) (symptoms such as cold and flu - fever, runny nose, cough) symptoms of hepatitis infection. Only 17.7% give the correct answer that they register, and 81.7% do not. Jaundice is one of the common symptoms of hepatitis, 32.2% give the correct answer, and 25.8% of the symptoms that are present and common are nausea, vomiting and loss of appetite. The percentage difference registered between the correct answers to the questions QP 18,19 and 20 versus the incorrect answers is significant for $p < 0.05$ ($p = 0.0000$) in favor of the incorrect answers. Conclusions: Important knowledge deficits about the routes of hepatitis B transmission/prevention were identified. Continued efforts should be made to develop and implement hepatitis B educational campaigns/health promotion for these communities.

ЈАВНО ЗДРАВЈЕ

ЗНАЕЊЕ ЗА ХЕПАТИТИС Б КАЈ ЗДРАВА ПОПУЛАЦИЈА ВО ЗАЕДНИЦАТА

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Извадок

Хепатитис Б е најчестата вирусна инфекција во светот која се пренесува преку крв, со 2 милијарди инфекции, 350 милиони носители и 6 милиони смртни случаи годишно. Цел на трудот е да се утврди нивото на знаење кај здравата популација во Република Северна Македонија во врска со инфекцијата со вирусот Хепатитис Б. Материјал и методи: Беше спроведена студија на пресек во заедницата. Прашалникот беше администриран на 600 здрави индивидуи кои слушнале за хепатитис Б. Податоците се анализираа со помош на статистички пакет SPSS. Резултати: Профилот на оние кои даваат точен одговор во однос на причината за хепатитис Б дека е вирус се жени (65,3%), на возраст од 40 до 49 години (42,8%), по националност се Македонки, со високо образование (52,8%), 92,8% живеат во урбани средини, 74,3% се во брак, вработени (79,2%) и имаат умерени месечни примања (68,9). Околу една третина од примерокот знаеле дека губењето на апетит, дијареа, гадење/повраќање се поврзани со хепатитис Б. Постои значајна разлика во знаењето поврзано со раните (продромални) (симптоми како настинка и грип - треска, течење на носот, кашлица) симптоми на инфекција со хепатитис. Само 17,7% даваат точен одговор дека се регистрираат, а 81,7% не. Жолтица е еден од најчестите симптоми на хепатитис, 32,2% го даваат точниот одговор, а 25,8% од симптомите кои се присутни и чести се гадење, повраќање и губење на апетит. Процентуалната разлика регистрирана помеѓу точните одговори на прашањата 18,19 и 20 наспроти неточните одговори е значајна за $p < 0,05$ ($p = 0,0000$) во корист на неточните одговори. Заклучоци: Идентификувани се важни недостатоци во знаењето за патиштата на пренос/превенција на хепатитис Б. Треба да се направат континуирани напори за развој и спроведување на едукативни кампањи за хепатитис Б/промоција на здравјето за овие заедници.

Introduction

About 240 million persons worldwide are chronically infected with hepatitis B virus (HBV)[1] with heterogeneous prevalence throughout the world. There is an intermediate to high prevalence in the Asia-Pacific region, representing three-quarters of chronic HBV-positive subjects worldwide.[2] In South-East Asia region, the estimated burden of chronic HBV infection is around100 million.[3] During HBV infection, an estimated 15%–40% of chronic hepatitis B patients would develop complications such as acute exacerbation, liver cirrhosis, and hepatocellular carcinoma.[4,5] The HBV is 50–100 times more infectious than HIV.[6-8]

Hepatitis B is a vaccine-preventable infection. Universal HBV vaccination in newborns has dramatically changed the epidemiology of chronic HBV infection.[1,9]

By knowing facts, having proper awareness, and attitudes the menace of this disease can be prevented to a great extent.[10]

In the present study, we have made an attempt to document the knowledge status among the general healthy population. It is part of bigger study of knowledge, awareness and practice of hepatitis B and HBV vaccine. This assessment will identify the gaps in knowledge and will be helpful in planning effective health education campaign for health care people.

Material and methods

Study setting

The time period is not limited, the study lasts until the fulfillment of the number, ie. sample size.

Study sample and sampling

An estimated sample size of 600 participants. Criteria for inclusion in the study is that the respondents are residents of the Republic of Northern Macedonia, to be older than 18, to be healthy, not to use any type of medication, not to be mentally and physically handicapped, and to participate voluntarily. They were interviewed through a KAP (knowledge, attitudes and practices) questionnaire. Information was obtained regarding socio demographic and knowledge variables. The method of data collection is through a paper questionnaire, smart phone, tablet, questionnaires sent via Google forms or Kobo toolbox specified on basis of feasibility of use. The study was conducted using a structured questionnaire consisting of two parts: I. sociodemographic data-8 questions and II. Knowledge - 25

The first part includes data on age, gender, education, nationality, area of residence, marital status, etc.

The second part includes 25 questions. Participants can choose between three predefined options which were (Yes), (No) and (I do not know). Every correct answer gets one point, and zero for incorrect and do not know answers. The range is from zero (minimum score) to 2 (maximum score). The questions are about the knowledge of hepatitis B about viral pathogenesis, modes of transmission, risk factors (blood transfusion, surgical or gynecological intervention, dental intervention, tattoos, piercing, intravenous drug users, hemodialysis, and occupational exposure), symptoms, diagnosis, and prevention of infection.

The results of knowledge are classified into three levels: poor, moderate, and good. The scale of classified levels of knowledge is: bad (poor) level of knowledge of <50%, moderate level of knowledge of 50% -75% points and good level of knowledge of> 75% points. Similar cut-offs are used in the literature points values for a good level of knowl-

edge. For example, "good knowledge" cut-off points vary in Indonesia studies 80%[11-15] and Nepal [16], or 75% points in Saudi Arabia [17-18], in Malaysia [19], or 70% in Yemen [20], and Vietnam [21].

Study analysis

Data obtained were entered and analyzed by using statistical package SPSS. Descriptive statistics was done to document the knowledge level, and Difference also performed to understand the significant difference ($P < 0.05$). The chi-square test was used to assess the statistical significance to different risk factors and the multiple logistic regression, was also used to get the most significant risk factors of hepatitis B. The logistic regression model was used to check the significant risk factors of hepatitis B, in which we considered knowledge about hepatitis B and the remaining variable such as age, sex, area, marital status, education, piercing, re-use of syringes, affected mother to child, multiple sexual relation, affected blood were considered as independent variables.

Results

A total of 600 subjects were involved in the study. Table-1 shows the details of descriptive statistics-the socio-demographic characteristics of the studied participants are summarized.

Table 1 . Overview of the socio-demographic characteristics of the respondents

age-years.	*број*	*%*
<=29	178	29.7
30 – 39	137	22.8
40 – 49	238	39.7
>-50	47	7.8
gender		
man	208	34.7
woman	392	65.3
nationality		
Macedonian	523	87.2
Albanian	65	10.8
Turkish	8	1.3
Roma	1	0.2
else	3	0.5
education		
elementary	8	1.3
high	266	44.3
higher	45	7.5
university	281	46.8
place of residence		
urban	553	92.2
rural	47	7.8

marital status		
no	167	27.8
yes	433	72.2
employment status		
employee	460	76.7
unemployed	42	7.0
student	98	16.3
monthly income		
Low	74	12.3
Moderate	406	67.7
High	58	9.7
Does not want to share this information / I do not know	62	10.3

All the participants were in the age between 20–67 years with a mean age of 36.7± 9.6 years. 39.7% participants belonged to age range 40-49 years, 29.7% less than 29 years and 7.8% above 50 years of age. Majority (65.3%) was females, while 34.7% were male. Seventy two percent were married, 27.8% unmarried. Regarding educational status, 44.3% had intermediate, 1.3% elementary, 46.8% graduate and postgraduate education. Most of the participants were employed (76.7%), they belong to the Macedonian nationality, 67.7% are with moderate monthly income and were from urban area.

Table 2 describes participants' responses to HB knowledge. Knowledge was assessed with questions focusing on the etiology of HB, signs, symptoms and transmission. The participants in the study showed a moderate level of knowledge-54% points (50% -75% points). Out of 600 participants, 439 (73.2%) were within the poor (poor) range of knowledge, while 1611 (26.8%) showed adequate knowledge of HB. Poor knowledge was evident in the answers to the questions related to the symptoms (questions 18-21), some of the questions related to the transmission of HB (questions 8.10) and the questions related to the consequences (Q18-19). The correct answers 89%, 87.2%, 83.7%, 81.5% were the highest in answer to questions 1, 2, and 9 respectively.

To the question "Have you heard of hepatitis B? (Q1) 89.0% of respondents answered positively - YES (heard before the study), and 66 (11.0%) respondents did not hear about hepatitis B. Correct answer, correct information to the question "Hepatitis B causes" virus have 83.7% of respondents, and 16.3% think it is a bacteria, the percentage difference is statistically significant for $p < 0.05$ ($p = 0.000000$)

The profile of those who give the correct answer regarding the cause of hepatitis B that it is a virus are women (65.3%), aged 40 to 49 (42.8%), by nationality are Macedonian, have higher education (52.8%), 92.8% live in urban areas, 74.3% are married, employed (79.2%) and have a moderate monthly income (68.9).

Knowledge about mode of transmission of hepatitis B

Results revealed that most of the respondents were unaware of the hepatitis B infection. The transmission by blood and blood products (74%), needles and sharps (75%), unprotected sex (67.7%) knowledge level found to be intermediate.

In terms of knowledge about the mode of transmission, the majority of respondents, i.e. participants in the study showed a moderate level of knowledge - 56.6% points (50% -75% points). Poor knowledge was evident in the answers to the questions related to the transfer question 8 (piercing-48.3%) and the question related to the transfer question 10 (cocaine sniffing - 21.0%). Correct answer in the study that showed a good level of knowledge was i.v. drug use 87.2% (Q 9).

Respondents rate the transmission of HBV through piercing or tattoo from 48.3% to 66.2%. Ignorance and negation of piercing and tattoo placement as a possible mode of transmission ranges between 51.7% (non-8.0% and 43.7% know) to 33.8% (non-8.0% and 25.8% know). More than half of the 54.5% of the respondents know that hemodialysis as a therapeutic method and its implementation can be transmitted and HBV. 57.3% of respondents give the correct answer that hemophilia as a disease in which blood and blood products are received is a possible transmission of HBV. The percentage difference registered between those who give the correct answer versus those who do not know or give the wrong answer is significant for $p < 0.05$ ($p = 0.0000$)

Half of the respondents (51.3%) know that frequent change of sexual partner is risky behavior and 67.7% of respondents know that unsafe sex is a risk for HBV transmission.

66.5% of respondents know that hygienic habits - using common utensils to maintain personal hygiene (for shaving, for dental hygiene - toothbrushes, for injecting drugs) is correct. The percentage difference that is registered between the correct answer, the incorrect answer and I do not know according to the Difference test is statistically significant for $p < 0.05$ ($p = 0.0000$).

Perinatal and sexual transmission of HBV were recognized by 52% and 51% of respondents

Table 2. Knowledge about HBV and mode of transmission (Q1-Q17)

Q1 have you heard of Hepatitis B.	***број***	***%***
yes	534	89.0
no	66	11.0
Q2 Hepatitis B causes		
virus/correct	502	83.7
bacteria/incorrect	98	16.3
Q3 Transfusion of infected blood and blood product		
correct	444	74.0
incorrect	65	10.8
I do not know	91	15.2
Q4 Surgery		

correct	355	59.2
incorrect	95	15.8
I do not know	150	25.0
Q5 Gynecological intervention		
correct	316	52.6
incorrect	148	24.7
I do not know	136	22.7
Q6 Dental intervention		
correct	355	59.2
incorrect	46	7.7
I do not know	199	33.2
Q7 tattoo		
correct	397	66.2
incorrect	48	8.0
I do not know	155	25.8
Q 8 piercing		
correct	290	48.3
incorrect	48	8.0
I do not know	262	43.7
Q9 i.v. drug use		
correct	523	87.2
incorrect	18	3.0
I do not know	59	9.8
Q10 cocaine sniffing		
correct	126	21.0
incorrect	331	55.2
I do not know	143	23.8
Q11 hemodialysis		
correct	327	54.5
incorrect	161	26.8
I do not know	112	18.7
Q12 hemophilia		
correct	344	57.3
incorrect	41	6.8
I do not know	215	35.8

Q13 hygiene habits - using common utensils to maintain personal hygiene		
correct	399	66.5
incorrect	31	5.2
I do not know	170	28.3
Q14 often changing sexual partner		
correct	308	51.3
incorrect	173	28.8
I do not know	119	19.8
Q 15 contaminated syringes and needles		
correct	450	75.0
incorrect	99	16.5
I do not know	51	8.5
Q 16 from a positive mother to a child		
correct	303	50.5
incorrect	67	11.2
I do not know	230	38.3
Q 17 through unsafe sex		
correct	406	67.7
incorrect	109	18.2
I do not know	85	14.2

Knowledge about symptoms of hepatitis B

About one-third of the sample said that loss of appetite, diarrhea, nausea/vomiting are also associated with hepatitis B. There is a significant difference in knowledge related to early (prodromal) (symptoms such as cold and flu - fever, runny nose, cough) symptoms of hepatitis infection. Only 17.7% give the correct answer that they register, and 81.7% do not. Jaundice is one of the common symptoms of hepatitis, 32.2% give the correct answer, and 25.8% of the symptoms that are present and common are nausea, vomiting and loss of appetite. The percentage difference registered between the correct answers to the questions QP 18,19 and 20 versus the incorrect answers is significant for $p < 0.05$ ($p = 0.0000$) in favor of the incorrect answers (Table 3).

18.5% of respondents know that patients with HBV often show no symptoms, the percentage difference between the correct answer to question 21 versus the incorrect answer is significant for $p < 0.05$ ($p = 0.0000$) in favor of the incorrect answer (Table 3).

Table 2. Knowledge about HBV and mode of transmission (Q1-Q17)

Q18 The early symptoms of hepatitis B are the same as the common cold and flu (fever, runny nose, cough)	***N***	***%***
correct	106	17.7
incorrect	490	81.7
I do not know	4	0.6
Q 19 Jaundice is one of the common symptoms of hepatitis B?		
correct	193	32.2
incorrect	404	67.3
I do not know	3	0.5
Q 20 Are nausea, vomiting and loss of appetite a common symptom of hepatitis B?		
correct	155	25.8
incorrect	440	73.3
I do not know	5	0.8
Q 21 Are there no symptoms of hepatitis B in some patients?		
correct	111	18.5
incorrect	480	80.0
I do not know	9	1.5

In the univariate analysis, age, marital status, educational level and family income were associated with good knowledge. Gender, ethnicity, and type of employment had no association with participants' knowledge. Higher HBV knowledge was statistically significantly associated with younger age ($p = 0.014$), higher education ($p < 0.0001$), place of living ($p < 0.00$), employment status-employee ($p < 0.00$) and monthly income-moderate ($p < 0.00$). Compared to the youngest age group (<29 years), participants aged 30-49 years had 2.2 times higher odds of having good knowledge (OR: 2.21; 95% CI: 1.39–3.50). Compared to individuals who had only completed primary school and high school increased odds observed among participants who had completed university diploma certificate (OR: 5.46). A moderate monthly income was also associated with good knowledge.

After excluding predictor variables with $P > 0.25$ from the analysis, the multivariate model revealed that age, ethnicity, education and family income were significant predictors of good knowledge. Having a postgraduate was the strongest predictor factor for good knowledge (OR: 3.20; 95% CI: 1.06–9.62) followed by individuals with the highest family income (OR: 1.87;95% CI: 1.15–3.06). They were positive predictor of higher HBV knowledge in our study. Nationality was not identified as a positive predictor of higher HBV knowledge in our study.

Discussion

Accurate knowledge is not only critical for decreasing the infection rate, but also important to dispel persistent myths, partial knowledge can

further perpetuate the risk of infection[22].

This study was a part of much bigger study to assess HBV knowledge, attitudes and practices.The current study sought to document the knowledge toward hepatitis B among healthy individuals. Results of the study demonstrated a "reasonable" level of HBV knowledge toward hepatitis B, majority of people still unaware about the disease and its vaccine .

HB is probably the most important chronic viral infection affecting people. However, despite the development of an effective vaccine against HBV, this infection remains a serious threat to public health in world and in North Macedonia, still.

A study was conducted to know the knowledge in community. Younger age was found to be a positive predictor of higher HBV knowledge in our study, a possible explanation is that the Internet is being utilized more frequently in recent years by younger individuals for health information[23].

Higher education was another positive predictor of higher HBV knowledge in our study. Such an association has been well documented in the literature[24, 25, 26-29, 30, 31–38].

This finding is comparable with previous studies in Malaysia. A study of community members, healthcare workers and university students found 39.1% of respondents had good knowledge (using a cut-off point of 73.3%). Among university students (undergraduate, master and PhD students), 50.3% of the respondents had good knowledge (using a cut-off point of the median score)[39]. In a population of people with chronic HB, the mean knowledge score was only 12.57/20 (62.85%)[31]. In this study, 38.8% of respondents are categorized as have good awareness. Low awareness towards HB has also been reported among community members [40,41] and among dentists[42] in Malaysia. Together, these figures indicate that knowledge[39-42] and awareness[41, 42] towards HB is low in Malaysia. The lack of knowledge is a major obstacle for putting forth an effective population /community agenda, and also has implications for the continued spread of the infection. Our findings of low knowledge highlight the need to improve public knowledge towards HB through the dissemination of information on HB to community members.

One of the strongest predictors for poor knowledge and awareness towards HepB is low education. The impact of education on good knowledge of HB has been reported in studies from Australia[43], British Columbia, Canada[44], Canada[45], China[46], Kenya [47], Malaysia[31], Poland[48], Singapore[49] , and among Cambodian Americans in the US[50].. There are at least two reasons for this finding. Firstly, HB is a complex disease with variations in natural history, progression and clinical management; individuals with low levels of education could have difficulty in understanding and interpreting information related to HB. Secondly, individuals with higher education have greater access to information related to HB from various sources and therefore are more likely to have better knowledge. These findings have two important implications. Firstly, community members with low educational attainment are the most appropriate group to be targeted in intervention programs to improve knowledge towards HB in Macedonia. Secondly, information related to HB being used in prevention programs needs to be simplified so that it is easy to

understand for households with low academic education.

Study conducted among health workers in White Nile state in Sudan, showed that the level of knowledge was significantly associated with occupation and educational degree[51].

These results indicate that there is a need for more HBV health promotion, targeted education, and training. Other studies reported that the level of the knowledge of hepatitis is low among different populations, in several areas worldwide[52-54].

Conclusion

Our findings revealed gaps in respondents' knowledge and understanding of the transmission risks of hepatitis B. Comprehensive hepatitis education strategies should be developed to address gaps in knowledge among the Macedonian public towards viral hepatitis

Important knowledge deficits about routes of hepatitis B transmission/ prevention were identified, though these health populations are aware of at least a symptom of HB. Continued efforts should be made to develop and implement hepatitis B educational campaigns/health promotion for these communities. Emphasis should especially be laid on awareness campaigns to educate the public that hepatitis B is vaccine-preventable disease and do not spread by polluted water or by sharing utensils and that it could be easily prevented by three simple, easily available, inexpensive shots of hepatitis B vaccine. There is an urgent need for community-based interventional study for improving the knowledge and awareness level of these healthy population regarding hepatitis B and its vaccine.

In summary, there is an urgent need to raise public awareness and knowledge of HBV in order to avert its perpetuation in the community.

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Public health

POLYMERASE CHAIN REACTION TEST FOR DETECTION OF *SARS-COV-2* VIRUS AND VARIANTS

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Abstract

The first human cases of coronavirus disease (COVID-19), a disease caused by the new coronavirus, was reported on December 31, 2019 in China for the first time. The virus was named temporarily as 2019 new coronavirus (2019 novel coronavirus-2019 -nCoV), or finally as *SARS-CoV-2*. The aim of this paper is to give an overview of the laboratory detection of *SARS-CoV-2* virus with reverse transcriptase - polymerase chain reaction (RT-PCR) in real time, as well as detection of viral mutations in the Laboratory for virology at the Institute of Public Health. The samples used in the study were taken from all geographical regions in North Macedonia, including the 10 regional Centers for Public Health throughout the country, from hospital patients, from COVID19 hospitals across the country and from the COVID19 checkpoint at the Institute of Public Health. All samples were tested using RT-PCR in real time. Additional assays were applied for identification of the circulating variants. The continuous surveillance of the variants of concern (VOC), as well as the newly emerged variants can allow the public health officials to modify their approach to disease control and management and intervene more effectively as well as in a timely manner in order to prevent major morbidity and mortality from COVID-19.

Јавно здравје

ПОЛИМЕРАЗНО ВЕРИЖНА РЕАКЦИЈА ЗА ДЕТЕКЦИЈА НА SARS COV-2 ВИРУС И ВАРИЈАНТИ

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Клучни зборови: *SARS-CoV-2* вирус, РТ-ПВР, варијанти на загриженост, варијанти на интерес.

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Извадок

Првите хумани случаи на болеста КОВИД-19 (coronavirus disease 2019- COVID-19), болест предизвикана од новиот коронавирус, за прв пат се пријавени на 31 декември 2019 година во НР Кина, кога вирусот го добил привременото име 2019 нов коронавирус (2019 novel coronavirus -2019-nCoV) или подоцна *SARS-CoV-2*. Целта на овој труд е да се прикаже процесот на лабораториска детекција на *SARS-CoV-2* вирусот со реверзна транскриптаза - полимеразно верижна реакција (РТ-ПВР) во реално време, како и протоколот за детекција на варијантите на *SARS-CoV-2* во Лабораторијата за вирусологија при Институтот за јавно здравје (ИЈЗ). Тестирани се примероци од суспектни пациенти за КОВИД-19 од територијата на цела држава за лабораториска детекција на *SARS-CoV-2*. Примероците пристигнуваат од 10-те регионални центри за јавно здравје (ЦЈЗ), од хоспитализирани пациенти од ковид болниците низ државата и од пунктот за ковид при ИЈЗ. Сите примероци се тестирани со примена на РТ-ПВР во реално време со детекција на различни гени на вирусот. Дополнителни анализи се прават за идентификација на циркулирачките варијанти. Континуираниот надзор на варијантите за загриженост (variants of concern - VOC), како и новонастанатите варијанти може да им овозможат на здравствените служби да го модифицираат својот пристап кон процесот на контрола и управување на болеста и да интервенираат ефикасно и навремено, со цел да се спречи голем морбидитет и смртност од КОВИД-19.

Вовед

Пандемијата со КОВИД-19 официјално е објавена од страна на Светската здравствена организација (СЗО) на 30 јануари 2020 година и предизвика зголемување на стапките на морбидитет и морталитет низ целиот свет.[1] Стратегиите за ограничување на пандемијата се потпираат на брзата и чувствителна лабораториска дијагноза за детекција на цели од вирусниот геном на *SARS-CoV-2* кај респираторни примероци. Еден од многуте фактори кои имаат влијание врз веродостојноста на дијагностичките протоколи може да е генетската варијабилност на *SARS-CoV-2* . Всушност, мутациите коишто се случуваат за време на геномската еволуција на *SARS-CoV-2* вирусот може да бидат во конзервирани региони за кои се дизајнирани повеќето комерцијални прајмери и проби. Имајќи ја предвид континуираната појава на нови варијанти, ситуацијата треба да се следи постојано, како и да се применуваат протоколи за лабораториска дијагностика кои се насочени кон повеќе целни гени на детекција.

Целни гени на детекција се четирите структурни протеини: трансмембрански гликопротеин - spike (S), протеин на обвивката - envelope (E), мембрански протеин - membrane (M), нуклеокапсиден протеин - nucleocapsid (N) и неструктурен протеин – (важен за формирање на комплексот репликаза транскриптаза) - open reading frame (ORF).[2] Вирусите имаат кратко генерациско време, особено РНК вирусите и имаат релативно високи стапки на мутација. Неопходно е да се следат циркулирачките варијанти со клучни мутации на *SARS-CoV-2* што се случуваат најчесто во рамките на S протеинот и кои можат да доведат до зголемување на трансмисибилната моќ на вирусот.[3] Повеќекратни мутации може да доведат до појавување на нови варијанти кои може да влијаат на текот на пандемијата и клиничката слика на заразените.

Зависно од тоа дали варијантите на *SARS-CoV-2* ја менуваат клиничката слика и сериозност, воспоставени се системи во СЗО за откривање на потенцијални варијанти на загриженост (variant of Concern - VOC) или варијанти на интерес (variant of interest - VOI) и истите се проценуваат врз основа на ризикот што го носат за глобалното јавно здравје.[3]

Цел на овој труд е да се прикаже процесот на лабораториска детекција на *SARS-CoV-2* вирусот со реверзна транскриптаза - полимеразно верижна реакција (РТ-ПВР) во реално време, како и протоколот за детекција на варијантите на *SARS-CoV-2* во Лабораторијата за вирусологија при Институтот за јавно здравје, како лабораторија одговорна за следење на вирусните заболувања со јавноздравствено значење, вклучително и *SARS-CoV-2*.

Материјали и методи

Примероци за лабораториска детекција на *SARS-CoV-2* се земаат од пунктот при Институтот за јавно здравје (ИЈЗ), пунктовите низ целата држава во центрите за јавно здравје, пунктовите при поликлиниките во Скопје и сите КОВИД болници и се транспортираат до Лабораторијата, по претходно дефинирани протоколи објавени на страната на ИЈЗ[4,5] и спроведен тренинг од страна на тим од ИЈЗ за сите КОВИД-болници.

Примерокот за анализа е најчесто комбиниран назо- и орофарингеален брис од еден пациент. Примероците се транспортираат следејќи го правилото „тројно пакување“.[6]

Во процесот на мануелна изолација користени се китови од различни

производители, но најчест метод кој се применува е QIAamp Viral RNA kit (од производителот Qiagen, GmbH, Германија).[7] Процесот на изолација на РНК е процес кој се извршува во кабинет за биобезбедна работа (КБР) од класа 2.

При автоматска изолација на РНК се користи технологијата со магнетни честички од различни производители (MagBind кит за екстракција на MaccuraBiotechnology,[8] AbGenix Viral Dna/Rna на AITbiotech,[9] M Sorb – S на Sacace за SaMag – 96 автоматски систем,[10] Applied Biosystems™ MagMAX™ Viral/Pathogen II Nucleic Acid Isolation Kit на апарат за автоматска изолација KingFisher™ Flex Magnetic Particle Processor with 96 Deep-Well Head),11 во согласност со препораките од производителот. Подготовката на примероците исто така се врши во КБР класа 2.

Добиената РНК се вклучува во реверзна транскриптаза – полимеразно верижна реакција (РТ-ПВР) во реално време за детекција на целните гени.[27]

Реакцијата на амплификација се одвива во апарати за ПВР во реално време – термосајклери, и тоа: CFX 96 (од производителот BioRad) и Quant Studio 5 (од производителот Applied Biosystem) и DNA Technology DTLite 5. Дополнително се користи Xpert® Xpress *SARS-CoV-2* од производителот Cepheid кој детектира N и E ген RT-PCR/поединечен тест, со време на изведба од 45 мин.[12]

Користени се молекуларни дијагностички тестови за откривање на вирусен генетски материјал на *SARS-CoV-2* достапни на Есенцијалната листа на китови од СЗО и Американската агенција за лекови(FDA) како што се: 2019-nCoV“ Allplex™,[13] BGI,14 Nucleic Acid Diagnostic Kit“ – Sansure Biotech,[15] Charite- Diagnostic detection of Wuhan coronavirus 2019 by real-time RT-PCR,[16] RealTime SARS-CoV-2“ – EUROIMMUN,[17] TaqMan 2019-nCoV Assay Kit v1,[18] *SARS-CoV-2* Fluorescent PCR“ – Maccura,[19] „TaqPath™ COVID-19 CE-IVD RT-PCR Kit“,[20] SARS-CoV-2/Influenza Multiplex на Dna –Technology,[21] Genrui *SARS-CoV-2* Detection Kit RT-PCR22 и се употребени во согласност со препораките на производителот.

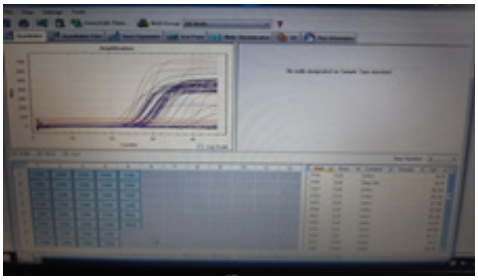
Следејќи ги препораките на СЗО и Европскиот центар за контрола на болести (ECDC), користени се и повеќенаменски молекуларни тестови со мулти-целен дизајн и следено е отсуство на S-ген кој е најчеста мета на мутација.[23] Примероците кај кои е детектиран недостаток (S gene dropout) или појава на S генот во доцен циклус со TaqPath или Genrui китовите, а позитивни на другите таргети до 25 циклус, дополнително се тестирани на Bio-Speedy® *SARS-CoV-2* Variant Plus RT-qPCR.[24]

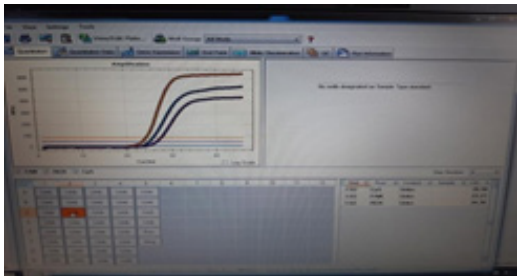
SARS-CoV-2 Variant plus RT-qPCR во реално време е тест во еден чекор, наменет за квалитативно диференцирање на B.1.1.7 (алфа варијанта), Б.1.351 (бета варијанта) и P.1 (гама варијнта) скрининг анализа за да се прикажат VOC (24). Паралелно респираторните примероци се тестирани на VirSNiP *SARS-CoV-2* Spike N501Y дијагностички тест базиран на точка на топење (melting curve), т.н. single nucleotide polymorphism (SNP) тест каде со примена на специфична проба се детектира 501Y мутацијата.[15,25]

Резултати

РТ-ПВР методот во реално време за детекција на *SARS-CoV-2* со детекција на E генот, RdRP и N генот е воведен во Лабораторијата за вирусологија на 2 февруари 2020 година. Првиот случај со КОВИД-19 е детектиран на 26 февруари 2020 година. Од детекцијата на првиот случај заклучно со 30 септември 2021 година анализи-

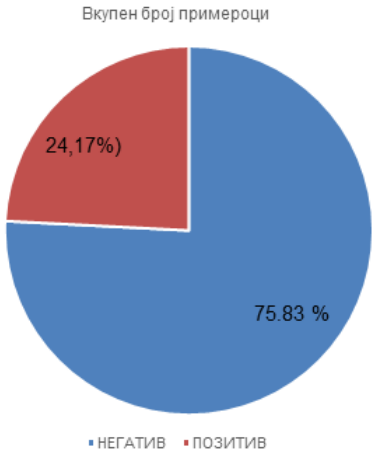
рани се 244.228 примероци од наведените COVID-19 пунктови. Позитивни примероци на *SARS-CoV-2* вирусот се 59.051 (24,17%) (графикон 1, слика 1 и 2).





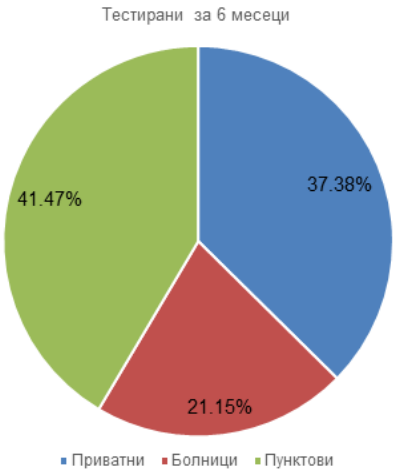
Слика 1 и 2. Амплификациски криви со РТ-ПВР во реално време

Графикон 1. Приказ на вкупно тестирани негативни и позитивни примероци



Во период од 6 месеци, односно од 01.04.2021 до 30.09.2021 година анализирани се примероци од центрите за јавно здравје и пунктовите во градот Скопје (22.589/41,47%), болнички примероци од сите болници низ државата (11.518/21,15%) и пациенти кои се тестирале на нивно барање (20.359/37,38%). Заклучно со месец септември оваа година направени се 244.228 тестирања со РТ – ПВР методот, од кои 59.051 биле позитивни за SARS-CoV-2(графикон 2).

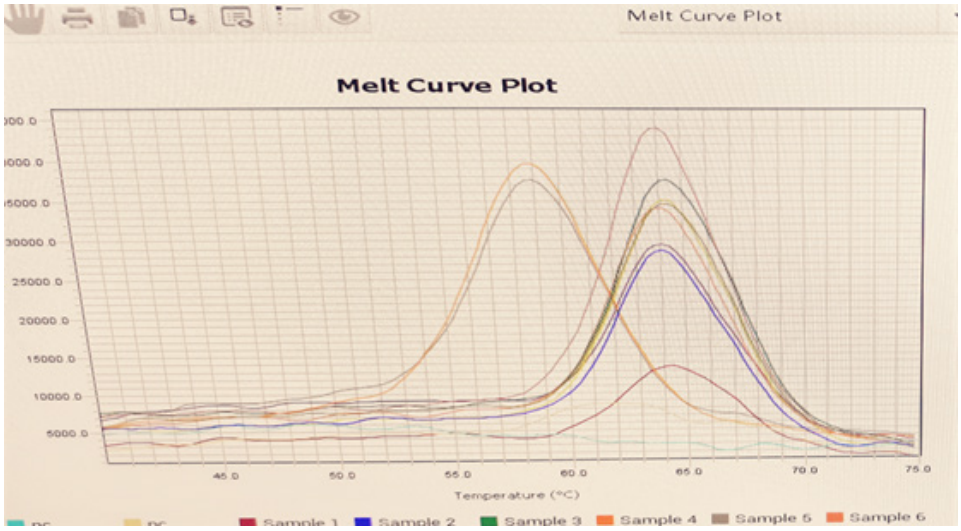
Графикон 2. Визуелен приказ на тестираните примероци и нивното место на потекло



Од месец април 2021 се прави селекција на примероци кај кои е утврдено отсуство на амплификација на S генот при користење на Thermofisher® TaqPath™ COVID-19 RT-PCR (TaqPath) и Genrui. Тестирани се вкупно 21.898, од кои 5.006, односно 22,86% се позитивни. Од овие позитивни примероци од различни региони во државата (графикон 3), по возрасни групи (графикон 4) и со Ct до 25, 320 се детектирани како алфа варијанта и 144 како делта варијанта (графикон 5) со S gene dropout (9,26%).

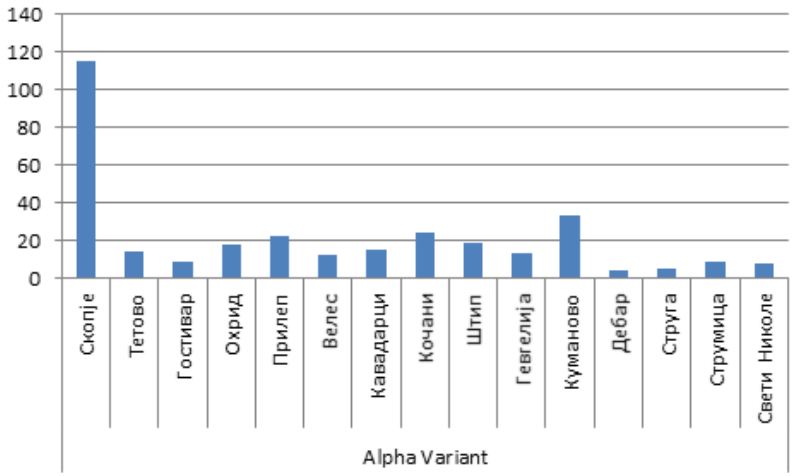
Истите изолати се анализирани со Bio-Speedy® *SARS-CoV-2* Variant Plus RT-qPCR за детекција на B.1.1.7 (алфа варијанта), Б.1.351 (бета варијанта) и P.1 (гама варијанта). Кај сите примероци е утврдено присуство на B.1.1.7 варијанта (алфа), преку детекција на мутацијата N501Y.

Кај 96 од позитивните 320 изолати, е направен дополнителен тест VirSNiP *SARS-CoV-2* Spike N501Y со приказ на точка на топење (melting curve) (слика 3). Кај сите овие примероци со овој тест е потврдено присуство на мутацијата N501Y, односно B.1.1.7 варијанта (алфа). Истиот тип е потврден со постапка на секвенционирање на селектирани 50 примероци.

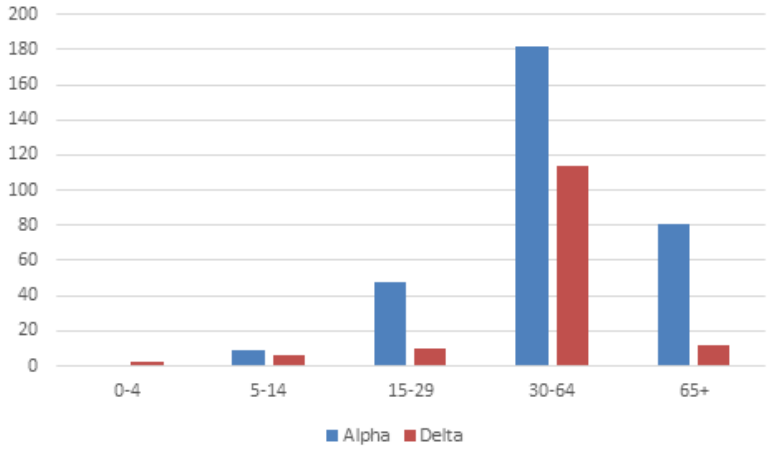


Слика 3. Резултат од SNP тест за детекција на варијанти со мутација N501Y

Графикон 3. Дистрибуција на примероци по градови за алфа варијанта

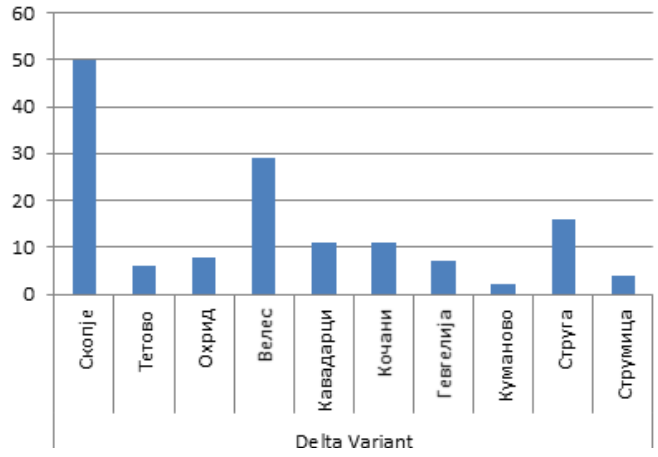


Графикон 4. Дистрибуција на примероци по возрасни групи за Алфа и Делта варијанта

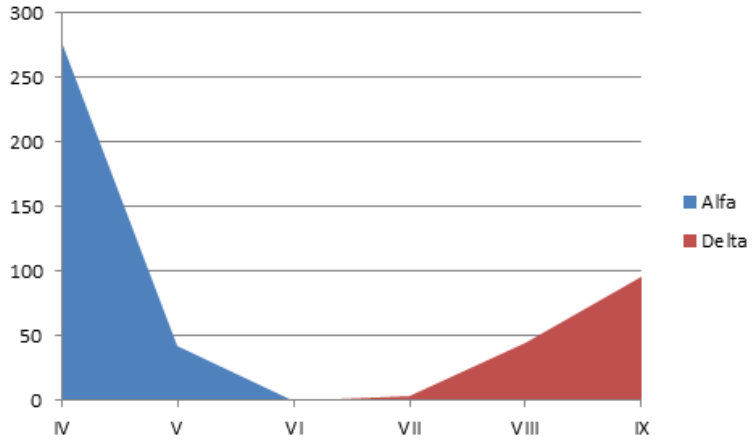


Во текот на месец јули на рутинските секвенционираните примероци детектирана е делта варијантата. Од анализираните 144 примероци на делта варијанти, 107 се позитивни (74%). Графикон 5 ја покажува географската дистрибуција на тестираните пациенти со делта варијантата.

Графикон 5. Дистрибуција на примероци по градови за делта варијанта



Графикон 6. Графички приказ на доминација на алфа и делта варијанта во период 04 – 09 месец



Со секвенционирање на позитивните промероци, бета варијантата е детектирана кај еден примерок, додека гама варијантата не е детектирана.

Дискусија

Во Лабораторијата за вирусологија при рутинската работа и за детекција на *SARS-CoV-2* се следат протоколите на СЗО за дијагностика и биосигурност за работа со *SARS-CoV-2* и добра лабораториска пракса (ДЛП).[26] За ракување со примероци за молекуларно тестирање потребно е да се обезбеди најмалку второ ниво на биобезбедност (BSL-2), додека за култивирање на вирусот потребно е минимум BSL-3.26 За примена на РТ-ПЦР тестот се применува BSL-2 односно КБР класа 2 и специфична лична заштитна опрема (ЛЗО).

Бидејќи КОВИД-19 е респираторно заболување примерок за лабораториска потврда на заболувањето се земаод горниот или долниот респираторен тракт. Респираторните примероци се земаат со суви дакронски или рајонски брисеви со пластични дршки/стапчиња во универзален вирусен транспортен медиум (ВТМ) за да се зачува виталноста на вирусот.4 Нашата препорака е од еден ист пациент да се земат и назо- и орофарингеален брис кои се стават во ист ВТМ заради повисоката сензитивност на комбинираниот брис.[27]

Примероците за детекција на вирусот треба да стигнат до лабораторијата што е можно поскоро по собирањето и во добра состојба. Правилното ракување со примероците за време на транспортот е од големо значење во добивањето на веродостоен резултат.[5]

Екстракцијата на нуклеинска киселина е првиот чекор од секој експеримент за амплификација, без оглед каков вид амплификација или друга молекуларна техника се користи за откривање на специфичен патоген. Процесот се изведува во кабинет за биобезбедност од класа 2 имајќи предвид дека со него се штитат примероците од контаминација, се штити здравствениот работник од заразување со потенцијално заразниот агенс и се штити надворешната средина од контаминација. При автоматската изолација на нуклеинска киселина се добива високо ниво на стандардизација, минимално можно влијание на операторот, а со тоа и на евентуална грешка при пипетирање или контаминација. Рачната и автоматска постапката вклучуваат отстранување на инхибитори и овозможуваат концентрација на изолирана РНК.

Секој примерок прво оди на тест за детекција на *SARS-CoV-2* со РТ-ПВР во реално време согласно водичот за детекција на СЗО.[27]

Вирусната едноверижна РНК која е целна секвенца прво треба да биде препишана во комплементарна ДНК со помош на ензимот реверзна транскриптаза. Во смесата од реагенси има и специфични прајмери и проби кои се комплементарни и анилираат со специфични целни региони од вирусниот геном. Добиената комплементарна ДНК (кДНК), ензимот Taq полимераза ја мултиплицира во голем број копии за кои специфично се врзуваат прајмерите и пробите. Етапите на ПВР реакција се следните: денатурација на нуклеинските киселини на 95оС; спојување на прајмерите (анилирање) на 60оС. Флуоресцентните проби се олигонуклеотидни секвенци обележани на 5' крајот со репортер молекула (најчесто 6-карбоксифлуоресцеин- ФАМ) и на 3'

крајот молекула пригушувач. Пробите се врзуваат на различна позиција од прајмерите и благодарение на полимеразната активност на Taq ензимот се откинува пригушувачот на флуоресценција од 3' крајот и флуорофорот емитува флуоресценција во одреден спектар. Real-time PCR апаратите ја детектираат оваа флуоресценција и таа е претставена како експоненцијална крива. Точката во која т.н "background noise" го поминува прагот се означува како Ct вредност на примерокот.

Секогаш се детектираат минимум 2 целни гени (во поединечни реакции - singleplex или повеќе гени во една иста рекација- multiplex).27 Освен примероците кои се тестираат, во секоја реакција задолжително се вклучени контроли и тоа: негативна (дејонизирана вода) за да се исклучат лажно позитивните резултати; позитивна контрола (синтетски добиена РНК или РНК добиена од вирусна култура на разраснат вирус или веќе познат примерок кој бил позитивен); и внатрешна контрола која се вклучува во секој примерок од моментот на екстракција на РНК, го следи целиот процес на примерокот и служи да се исклучи лажно негативен резултат.

Отсуство на амплификација на S генот (т.н. S drop-out) може да биде сигнал за присуство на 69-70дел мутација за понатамошна истрага, особено ако капацитетот за секвенционирање е ограничен. Мултицелните тестови за РТ-ПЦР кои користат региони на S-ген погодени од мутацијата 69-70дел, се побрзи и поевтини од секвенционирање на целиот вирус и можат да помогнат да се следат овие мутантни соеви.

За детекција на варијантите се следи документот на СЗО и ЕЦДЦ за методи на детекција и идентификација на *SARS-CoV-2* варијантите и СЗО водичот за следење на варијантите.[23,28]

S gene target failure или S gene target late detection (SGTF/SGTL, соодветно) профилите идентификувани со примена на анализата TaqPath и резултатите од триплекс Bio-Speedy® *SARS-CoV-2* Variant Plus RT-qPCR се соодветни за откривање на варијантите алфа, бета и гама. Анализата за Bio-Speedy Variant Plus која ги одредува сите три тековни VOCs истовремено, може да биде вредна алатка за ограничување на ширењето на вирусот преку поддршка за следење контакт и изолација.

За време на рутинската верификација на тестот TaqPath во нашата Лабораторија со користење на стандардни примероци од тестот на компетентност (EQA) добиени од култивиран SARS-CoV-2, не се забележани SGTF наспроти појавата на SGTF во нашите податоци. Ова дополнително го потврдува влијанието на делеции и мутации во гените врз ефикасноста на на реакцијата на RT-qPCR. Објавени докази покажуваат дека присуството на мутацијата Δ69/70 во вирусниот геном, предизвикувајќи го феноменот SGTF кај тестовите TaqPath RT-qPCR, корелира со присуството на VOC/B1.1.7 во клинички примероци како што е потврдено и со секвенционирање.

Co Single Nucleotide Polymorphism (SNP) тестот за детекција на N501Y на spike генот се одредува присуството на единечна мутација која доведува до промена на температурата на топење.[25] Тестот се одвива во два чекора. Првиот чекор е амплификација при која пробите кои се употребуваат се разликуваат само во еден нуклеотид и се поврзуваат за соодветниот тип присутен во примерокот од пациентот и се де-

тектира Е генот (Е генот во оваа реакција е контрола дека прајмерите и ензимите функционираат). Вториот чекор е детекција на кривата на топење (melting curve) на spike генот. Детекцијата на типовите зависи од точката на топење. „Див тип“ вирус има пониска температура на дисоцијација Tm (*SARS-CoV-2* wild type: AGTCGACTACGGTCGGCTT Tm = 59°C) додека присуството на варијантата од интерест има температура на топење на 64°C (N501Y *SARS-CoV-2* variant: AGTCGACTACGGGCGGCTT Tm = 64°C).(15) Како и во секоја реакција овде има позитивна контрола која се состои од смеса од 501N и Y.

Со брзото ширење на нова варијанта воведен е нов дополнителен скриниг тест за детекција на варијанта на загриженост Dna – Tehnology *SARS-CoV-2* DELTA RT PCR Genotyping Kit, со кој се детекираат специфични мутации L452R и T478K.21

Медицинскиот отпад се деконтаминира со негово автоклавирање пред понатамошна диспозиција што е значаен сегмент во лабораториската биобезбедност.[4]

Лична заштитна опрема (лабораториски мантил за една употреба или скафандер, респираторна заштита со респоратор маска за една употреба - N95, FFP2 или FFP3, ракавици за еднократна употреба, безбедносни очила или штит за лице и лабораториски обувки) во лабораторија е задолжителна. За поединични сегменти од работниот процес ЛЗО се менува т.е. при движењето од еден во друг процес не смее да се користи иста ЛЗО.

Заклучоци

Добро развиените лабораториски капацитети се во основата на еден добро развиен систем за следење на заразните заболувања, а со тоа и на брзиот одговор за контрола и спречување на понатамошно ширење на кое било заразно заболување со високо патоген агенс, вклучително и SARS CoV-2. Без брза и точна лабораториска дијагностика ниеден од чекорите не е возможен. Лабораторијата за вирусологија при ИЈЗ - Скопје е одредена како национална референтна лабораторија за детекција на Ковид-19 кај луѓето. Во својата работа Лабораторијата ги следи препораките и водичите на СЗО во однос на самата дијагностика како и стандардите за биобезбедност и контрола на квалитет.

Следењето на варијантите за загриженост (VOC) и варијантите од интерес (VOI), како и на евентуалната појава на нови мутации и варијанти е една од задачите на националната лабораторија во континуитет. Ова е од особена важност ако се има предвид дека новите варијанти може да манифестираат промена во трансмисибилноста на вирусот, неговата патогеност и исход на болеста и слично, што, пак, е тесно поврзано со преземањето соодветни јавноздравствени мерки, односно корекција на актуелните јавно здравствени мерки врз основа на новонастанатата состојба.

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PUBLIC HEALTH

UNDERSTANDING THE HEALTH CONTEXT FOR IMPLEMENTATION OF A NEW DIGITAL PSYCHOSOCIAL INTERVENTION FOR IMPROVEMENT OF THE MENTAL HEALTH IN NORTH MACEDONIA

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Key words: local context, psychosocial intervention, DIALOG+, psychotic disorders, mental health

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Abstract

The aim of this study was to identify the contextual attributes in North Macedonia and their characteristics relevant to the implementation of a new digital intervention to improve mental health, called DIALOG+. This research is the first of its kind in North Macedonia due to the analysis of contextual attributes that may affect the effectiveness of the intervention and its acceptability in various settings of mental health care. Some of the data processed in this paper were provided and analyzed by the National Mental Health Strategy 2018-2025 and other relevant accompanying documents from the World Health Organization and action plans, as well as through interviews with stakeholders (patients, carers, clinicians and policy makers) for their opinion before introducing the DIALOG + intervention and the report on the assessment of the situation in the centers where the implementation of the intervention should have started. The collected data were then mapped to a framework developed by the Ottawa Implementation Group, which included 14 contextual attributes. The results are summarized in 2 subgroups, and are presented as facilitators and barriers to implementation, specific to the mental health system in North Macedonia. The characteristics of DIALOG + (widely applicable psychosocial intervention) are in accordance with modern assumptions for psychosocial rehabilitation of patients with psychosis. Hence, we can conclude that it is a useful tool for professionals in monitoring and achieving the true vision and mission of these institutions. It will help patients reintegrate into society, become more independent and use their full potential in the pursuit of healthy and functional living.

ЈАВНО ЗДРАВЈЕ

РАЗБИРАЊЕ НА ЗДРАВСТВЕНИОТ КОНТЕКСТ ЗА ИМПЛЕМЕНТАЦИЈА НА НОВА ДИГИТАЛНА ПСИХОСОЦИЈАЛНА ИНТЕРВЕНЦИЈА ЗА ПОДОБРУВАЊЕ НА МЕНТАЛНОТО ЗДРАВЈЕ ВО СЕВЕРНА МАКЕДОНИЈА

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Клучни зборови: локален контекст, психосоцијална интервенција, DIALOG+, психотични растројства, ментално здравје

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Извадок

Целта на оваа студија беше да ги идентификува контекстуалните атрибути во Северна Македонија и нивните карактеристики релевантни за спроведување на нова дигитална интервенција за подобрување на менталното здравје, наречена DIALOG+. Ова истражување е прво од ваков вид во Северна Македонија поради анализата на контекстуалните атрибути што може да влијаат на ефективноста на интервенцијата и на нејзината прифатливост во различни поставки на здравствената заштита на менталното здравје. Дел од податоците обработени во овој труд се обезбедени и анализирани од Националната стратегија за ментално здравје 2018-2025 и други соодветни придружни документи од Светската здравствена организација и акциски планови, како и преку интервјуа со засегнатите страни (пациенти, негуватели, клиничари и креатори на политики) за нивното мислење пред воведување на интервенцијата DIALOG+ и извештајот за проценка на состојбата во центрите каде требаше да се започне со имплементирање на интервенцијата. Потоа, собраните податоци беа мапирани на рамката развиена од Групата за имплементација на Отава, која вклучува 14 контекстуални атрибути. Резултатите беа сумирани во 2 подгрупи, и се прикажани како фацилитатори и бариери за спроведување, специфични за ментално-здравствениот систем во Северна Македонија. Карактеристиките на DIALOG+ (широко применлива психосоцијална интервенција) се во согласност со современите претпоставки за психосоцијална рехабилитација на пациенти со психоза. Оттука, може да заклучиме дека претставува корисна алатка за професионалците во следење и остварување на вистинската визија и мисија на овие установи. Тоа ќе им помогне на пациентите да се реинтегрираат во општеството, да станат понезависни и да ги искористат своите целосни капацитети во потрага по здравствено и функционално живеење.

Introduction

People with severe mental illness within psychotic disorders, such as schizophrenia, schizoaffective disorder, and bipolar disorder, can have a wide range of symptoms. These disorders can include hearing voices, delusions, suspicion, withdrawal from family and friends, mood fluctuations[1]. In North Macedonia, but also in other countries, stigma, discrimination and violation of human rights of people with psychotic disorders are very common. These psychotic spectrum disorders usually last for decades and pose a major health, social and economic burden to patients, families, carers and society at large. Otherwise, life expectancy is 15-20 years shorter than that of the general population due to insufficiently diagnosed physical illnesses, poor access to health care and more frequent suicides[1].

In our country, most of the patients with psychotic disorders are mainly treated in psychiatric hospitals where the treatment is largely focused on psychopharmacotherapy and antipsychotic drugs, and the psychosocial needs of the patients are often secondary. The approach in the Community Mental Health Centers, which are seven in total and were established with the last reform of the mental health system which began in 2000, in cooperation with the World Health Organization (WHO), is completely different. In these centers, the psychosocial treatment is included in the individual treatment plans of each patient, as a complementary part, together with the basic psychopharmacological treatment.

This reform in our country is on a positive path, approaching the organized health systems in high-income countries that provide a combination of care, including medication and psychosocial interventions, which helps people affected by psychosis to lead a productive life and integrate into the society. However, low- and middle-income countries have neither sufficient funding nor sufficient staff to fully reform the mental health system and provide such specialized services to all patients with severe mental disorders as those mentioned in systems that are predominantly oriented to providing services through community mental health services[2]. One way to accelerate health care reform and improvement for this group of patients would be to implement effective, low-cost psychosocial interventions, which make existing routine clinical examinations more therapeutic.

When introducing such new specialized treatments in the community, contextual factors must be taken into account when assessing whether an intervention is effective or not and whether it leads to improvement in clinical practice[3]. Context is defined as a factor that is separate from the actual intervention itself (both from the patients receiving the intervention and the clinicians delivering it), but which may still contribute to the success of the intervention[4,5]. Adapting interventions to local contexts is an essential part of pragmatic research; unfortunately, implementation science cannot explicitly consider how local contextual factors affect the success of implementation[6]. This leads to the implementation of interventions being successful in one context but failing in another[4]. To increase the likelihood of successful implementation, researchers need to

assess and explicitly address contextual barriers and/or promote facilitators and reduce barriers to implementation[7].

Description of the new digital intervention DIALOG+ for improving mental health

The IMPULSE project (Implementation of an effective intervention for patients with psychotic disorders in low- and middle-income countries in Southeast Europe) aims to apply and evaluate the effectiveness of a new digital psychosocial intervention in patients with psychosis in five countries in Southeast Europe (North Macedonia, Serbia, Montenegro, Bosnia and Herzegovina and Kosovo). The intervention, called DIALOG+, is designed to increase the therapeutic efficacy of routine clinical appointments to improve the mental health of people with psychotic spectrum disorders and thus improve the quality of life for patients. The basic elements of DIALOG+ are structured interviews using a tablet computer, which assesses patients' satisfaction in 11 areas of their lives (mental and physical health, work, leisure activities, residence, partner/family, friends, safety, medication, practical help and satisfaction from the sessions). Then, with the help of the clinician, the patient selects from 1 to 3 areas that will be further examined/resolved during the control examination, through the approach of solution-based therapy in 4 steps (understanding the problem, looking forward, research and agreement). At the end of the session, an agreement is made on the activities that need to be completed between the sessions[8]. Therefore, this new digital psychosocial intervention is a solution-focused therapy and patient-centered communication, characterized by positive reinforcement. It can be performed by psychiatrists, psychologists and mental health nurses who need to be educated on how to perform the intervention. The interaction between the clinician and the patient during the DIALOG+ session is characterized by positive reinforcement, patient-oriented communication and great patient involvement. More details about the IMPULSE protocol were previously published[9].

The aim of this study is to identify the contextual attributes in North Macedonia and their characteristics relevant to the implementation of a new digital psychosocial intervention to improve mental health, called DIALOG+. This research is the first of its kind in North Macedonia due to the analysis of contextual attributes that may affect the effectiveness of the intervention and its acceptability in various settings of mental health care.

Material and methods

Some of the data processed in this paper are provided and analyzed by the National Mental Health Strategy 2018-2025[10] and other relevant accompanying documents from the World Health Organization and action plans, as well as through interviews with stakeholders (patients, carers, clinicians and policy makers) for their opinion before the introduction of the DIALOG+ intervention and the report on the assessment of the situation in the centers where the implementation of the intervention should have started. The collected data were then mapped to the framework developed by the Ottawa Imple-

mentation Group, which included 14 contextual attributes.[11] The results are summarized in 2 subgroups, as facilitators and barriers to implementation, specific to the mental health system in North Macedonia.

The paper of Squires[11] describes the contextual attributes and their characteristics according to which we analyzed and described the conditions of the context, i.e. the barriers and facilitators for the application of the new psychosocial intervention DIALOG+ in North Macedonia. In total, this paper describes 62 unique features of context. They are grouped into 14 broader attributes. The number of features in each of them varies and that number is not the same. To better understand these attributes and their characteristics, we will first give a brief description of each of them, and then present our results obtained from the interviews and the report from the visits to the places where the DIALOG+ intervention should be applied.

1. **Access to resources** - This does not necessarily mean the proximity of such resources, but only their accessibility or availability in the broadest sense (e.g. physical space). The number of features in this attribute is 14: time and space as a resource, guides and instructions, documentation, formal communication, training and education, staff, technology, expert support, online resources, programs and quality. Time as a resource is considered in economic terms, for e.g., how long it takes to complete the tasks, how the staff redistributes the time in the work schedule. Guides and instructions are then included to assist physicians in making appropriate health care decisions in patients' specific clinical circumstances. Formal documentation includes presentations, newsletters, formal meetings, etc.
2. **Structure of work** – This attribute includes 11 characteristics of the structure of the workplace, such as: time frame, continuity and standardization of care, teamwork, work overload, order of work tasks, reminders, delegation of tasks, schedule and shift work- . So, this attribute comprises factors such as delegating tasks between supervisors and subordinates; schedule of shifts and duties on call; sequence of work tasks and procedures; and workload management.
3. **Patients characteristics** - Attributes to persons under medical care or treatment refer to the characteristics of patients being analyzed as a group rather than as individuals. This includes 2 attributes: demographics and expectations, and patient preferences.
4. **Professional role** – This attribute describes 7 characteristics / set of expectations, both formal and informal, related to the given clinical profession: clinical skills, training for professional role, conflicts, responsibility, work autonomy, professional development and code of ethics.
5. **Culture** - The inherited ideas, beliefs, values and attitudes of a group are grouped into 2 characteristics of organizational culture and culture in general.

6. **Object characteristics** - These characteristics are 7 in total (object type, geography, volume, atmosphere, general characteristics of the object, size), i.e., include the type of facility (hospital, day care center, outpatient clinic), the number of patients cared for at that location, the geographical location, and the presence or absence of medical personnel.
7. **System features** - 3 features (resource spending, record keeping and logistics and coordination) relevant to the health system operation and clinical practice.
8. **Characteristics of health professionals** - This code refers to the characteristics of individuals who are considered as a group rather than as individuals; thus, all subcodes considered for inclusion here should be generalized to the health professional population (an attribute that can potentially be measured and summed up). They are grouped in 2 characteristics: experience and group composition.
9. **Finance** - Understandably, finance means cash income and expenses (costs) related to clinical work or institutional standards. These include 3 attributes: financial incentives, financing system and finance (general).
10. **Collaboration** - This code refers to collaborative work (including other organizations) and covers only 1 feature.
11. **Leadership** - This code covers 3 characteristics, namely: role modeling, mentoring and leadership, primarily in the introduction and application of some new techniques and methods.
12. Evaluation - Evaluation involves the systematic collection of information about the activities, features, and results of programs, services, policies, or processes in order to evaluate program/process, improve effectiveness, and/or inform future and development decisions. It includes 4 features: general evaluation, organizational evaluation, audit and patient evaluation.
13. **Regulatory and Legislative Standards** - The 2 characteristics of law and standard of practice or care are usually beyond the control of healthcare organizations.
14. **Social influences** - This code with 1 characteristic of social influences is a general level of social knowledge and attitude towards a certain clinical behavior or procedure, such as the case with the stigma of mental illness.

Results

Analysis of data from available documents (state of mental health in North Macedonia)

In North Macedonia, the Law on Mental Health was adopted on October 13, 2005[12]. Article 7 in the second chapter clearly states that persons with mental disorders have the right to be protected from any form of harassment, humiliation and discrimination. Article 9 specifies that every person with a mental disorder has the right to undergo an optimal rehabilitation/program that will improve his or her mental health status.

According to the National Mental Health Strategy 2018-2025[10], prepared by the Ministry of Health, the current mental health system is characterized by insufficient psychosocial outpatient services that are applied only in community mental health centers, few alternatives to hospital treatment, lack of programs for promotion, prevention and rehabilitation, lack of family involvement and social support, and lack of support and opportunities for people with mental illness to live and join the community. An organized mental health system indicates slow development and significant mental health challenges.

The health care of people with mental health problems is performed at all three levels - in the primary, secondary and tertiary health care. Mental health care in primary health care is the responsibility of selected physicians and they serve as "gatekeepers"; they detect the problem and refer patients to higher levels of health care. The secondary level includes the psychiatric counseling-specialist outpatient services that operate within the Medical Centers throughout the country, as well as the Institutes for Children and Youth in Skopje and Bitola. Neuropsychiatric wards at 13 medical centers (within general and clinical hospitals) throughout the country provide secondary patient care (wards provide hospitalization to both neurological and psychiatric patients). At the secondary level of health care there are three specialized health institutions (PHI Psychiatric Hospital Skopje, PHI Psychiatric Hospital Demir Hisar and PHI Psychiatric Hospital "Negorci" Gevgelija) through which the regionalization and availability of health services is obtained. The Psychiatric Hospital in Skopje was established in 1954. Its capacity includes 330 beds. Three Community Mental Health Centers are organizationally linked to this psychiatric hospital. Demir Hisar Psychiatric Hospital was established in 1956 and has a capacity of 375 beds. The Center for Community Mental Health in Prilep is organizationally connected with this psychiatric institution. "Negorci" Psychiatric Hospital was established in 1972 and has a capacity of 257 beds. Within this psychiatric hospital there is one Center for Mental Health Care.

In addition, there is only one psychiatric institution that covers the activities in tertiary mental health care, and that is the University Clinic for Psychiatry in Skopje that provides hospital and outpatient services with about 16,000 outpatient visits per year. As part of the University Clinic for Psychiatry in Skopje, there is a day hospital - Center for extended treatment in the community of patients suffering from severe mental disorders, which provides complete psychosocial and extended psychopharmacological treatment for its users. In addition to health care, the Clinic performs educational and scientific research activity, i.e., it is a base for the Department of Psychiatry within the Faculty of Medicine in Skopje at Ss. Cyril and Methodius University in Skopje. The capacity of the Clinic in Skopje is 55 beds. The outpatient services in the health centers provide services mainly from the medical-psychiatric aspect of the treatment, without realizing any effects on the socio-rehabilitation plan.

As part of its support for the Ministry of Health's mental health reforms, the World Health Organization

(WHO) Mental Health Project has opened 5 Community Mental Health Centers (CMHs) in Skopje - two, and one in Gevgelija, Prilep and Tetovo, between 2000 and 2004. The Ministry of Health, financially supported by the Regional Project of the Stability Pact with the WHO, established the sixth Community Mental Health Center in Strumica at the beginning of 2004. Within the University Clinic for Psychiatry, a Day Hospital for people with psychosis has been established, which functions as a Community Mental Health Center, which makes it 7 centers.

According to a document from 2011[13], there are 9.98 psychiatrists, 1.47 psychologists, 0.83 social workers and 26.92 nurses per 100,000 inhabitants in North Macedonia. According to this, there are approximately 35 to 40 mental health professionals per 100,000 inhabitants. This assessment should support the need to expand human resources in relation to psychiatric staff. Within the existing Community Mental Health Center only 20-50% of patients receive one or more types of psychosocial intervention compared to 100% of the received treatment with psychotropic drugs.

Users' diagnoses also vary by facility type: neurotic disorders are the most common diagnosis in outpatient facilities and general hospital units, while schizophrenia, schizotypal and delusional disorders are the most common among patients in psychiatric hospitals. The longest stay is in psychiatric hospitals (57 days). Thirteen days is the average length of stay in general hospital units. Psychotropic drugs are available year-round in mental hospitals as well as in psychiatric hospital units. The same drugs are available in 91% of outpatient facilities.

Given that the best effect is achieved when drug therapy is combined with other forms of treatment, such as individual and group psychotherapy, occupational therapy, rehabilitation and psychosocial support of the individual and/or the whole family as well as other forms, it is necessary to develop and foster a combined approach to mental health. In North Macedonia, in addition to psychopharmacological therapy, the following psychotherapeutic interventions for treatment of schizophrenia are recommended:

a) psychoanalytic psychotherapy;

b) cognitive-behavioral therapy (CBT);

c) psychoeducation;

d) rehabilitation (social skills training).

The National Health Insurance Fund includes several psychosocial/psychotherapeutic interventions in the list of mental health care services that are delivered free of charge to all state institutions. In theory, and as stated in the national guidelines, they are offered as regular services, and their implementation should be performed as an outpatient service. However, there is a large gap in practice, for two reasons: either there are few certified professionals or some types of psychotherapy are not covered by the fund and are therefore not available to all patients.

The process of opening the Community Mental Health Centers on the whole territory is relatively slow and there is still a lack of programs and activities for social rehabilitation and

reintegration of people with mental illness. DIALOG+ intervention is one of the measures to improve mental health services. Based on the assessment of the factual situation with mental health, the review of which is given above, we will try in this paper to present the facts according to which psychosocial support would be improved, especially in patients with psychosis and bipolar disorder.

Analysis of interview data

Secondary data analysis was performed using data collected prior to the application of DIALOG+. The findings from this data were coded on the basis of context attributes developed by Squires[11].

To assess the understanding of the context, we conducted several interviews to find out the opinion of the participants in each of the groups. The new digital intervention was first presented to all groups, followed by focus group interviews. A transcript was made of the recorded data which was then processed. The groups were as follows:

- group of patients - 15 (8 male and 7 female),
- group of clinicians - 12 (4 male and 8 female) (7 psychiatrists, 1 psychologist, 2 nurses, 1 social worker and 1 special educator),
- group of carers - 6 (6 females),
- group of policy makers - 6 (6 females).

During the interviews, the intervention was explained to the respondents, and then they were asked about the benefits, facilitators or barriers to its application. The results for each of the groups are given below.

The obtained data are explained in detail, but also graphically shown in Table 1 for easier monitoring of the results.

Group of patients

Patients said that the use **of technology** (in the form of computer tablets) during the examination would be more optimal, more pleasant and they would have the information in front of them while talking. According to them, if the family would be involved to some extent, it would be good for the implementation of the intervention itself, but also for the activities between the sessions. **Family members** would be a kind of facilitator of change in the patients and therefore it would be best to do psychoeducation of all family members of patients with mental illness so that they would know how to recognize the deterioration of the condition and accordingly seek help in time. For that purpose, the patients themselves think that they should have **guides and directions** that they would receive from the family doctors for this intervention an3d in that way they would be informed even before they come for the examination and they would be properly prepared for that.

They also think **more frequent sessions, greater availability of doctors and greater media representation as facilitators would help in better implementation of the intervention**. Training and education of medical staff would also be of great benefit to the implementation of the intervention.

They regard **the culture of living** and the stigma surrounding mental ill-

ness, as well as religious affiliation as barriers in the implementation of the intervention. Then, they think that the **time for conversation** should be longer than now, if digital intervention is applied. It means that the time period given now in "My appointment" for one examination would not be enough in case of application of DIALOG+; therefore the time period is considered as a barrier in the implementation of the intervention.

Regarding the activities and tasks that are given to them between two sessions, they believe that our country does not offer enough activities. For example, there are no support groups, no jobs for this type of patients, etc.

Group of clinicians

Patients also think **that there is a shortage of medical staff**, so that would be another major barrier to implementing the intervention. Some of them also see the professional training of the staff as a barrier, because they think that only psychiatrists would have the appropriate skills and are reserved for nurses or other staff. Also, some patients are afraid that the doctor-patient relationship will be lost if too much time and attention is paid to technology.

Clinicians assessed technology, computer program objectification, questionnaire structuring of the session, measurability of assessment, and continuity of assessment as one of the many advantages of applying this intervention. For them, the preparation and education of professionals is crucial, as well as the involvement of nurses who can apply the intervention while patients wait in the waiting room. According to them, it is an easy tool to learn and to work with especially younger colleagues. The involvement of family members is also important. The choice of the patient is important (demography), etc. It's the patient's choice. A barrier would be the lack of staff because the intervention is applied one by one. Due to that, there would be a lack of time and space. Clinicians also see a financial problem - as the examination would cost more, and those from other cities would have to pay more for the trip. According to them, there is a need for reorganization of the psychiatric service and greater involvement of social services, psychoeducation of the family and its involvement, as well as a multidisciplinary approach.

Group of carers

They think that they need psychoeducation. **Then, financial help is needed, and maybe a patronage service that will visit them at home. The culture of behavior** is also important to them. The lack of small groups, as well as patients, share the opinion that the state needs to support small groups to support these patients, either for socializing or for work. Involvement of the intervention in the first stages of the disease, and not in the more advanced stage, would lead to a faster improvement of the condition.

Group of policy makers

According to them, the benefit of implementation would be that it guarantees **the same approach to all clinicians.** Digital documentation would be a greater value and advantage. It is

important to inform both clinicians and patients of the existence of such an intervention. They suggest having guides for "My appointment" entry and approaching world standards of psychiatry. To make changes and during the studies to introduce the students to the new way of examination and the doctor's approach to the patient. According to them, the useful thing is that **the software is free and available**. In that way, there would be a need to **open daycare centers and homes for support** or residential homes (which is one of the future tasks of the mental health strategy). Barriers to implementation would be the limited activities that the doctor can help with. **Reliability of information** received from patients. (Nurses have said the same thing and suggested another scale for a more objective simultaneous assessment by them and by the clinicians).

- No multisectoral connection.
- Resistance to innovations in practice by clinicians.
- The time required for the examination.

Table 1. Attributes mentioned on the interviews

Attribute and Feature				
Subgroups	clinicians	patients	caregivers	Policy makers
I. Resource Access				
1. Time as a resource				
2. Guidelines				
3. Documentation				
4. Proximity				
5. Resource quality				
6. Formal communication				
7. Organizational training and education				
8. Staff				
9. Space as a resource				
10. Technology				
11. Expert support				
12. Programs				
13. Online resources				
14. Team educator				
II. Work structure				
1. Timeframe				
2. Continuity of care				
3. Standardization of care				
4. Team work				
5. Reminders				
6. Work load				
7. Delegation of tasks				
8. Order of work tasks				

9. Work tempo				
10. Scheduling and shift work				
11. Patient wait times				
III. Patient characteristics				
1. Patient demographics				
2. Patient expectations and preferences				
IV. Professional role				
1. Clinical skill set				
2. Professional role training				
3. Job autonomy				
4. Conflict				
5. Professional development				
6. Accountability				
7. Code of ethics				
V. Culture				
1. Organizational culture				
2. Culture (general)				
VI. Facility characteristics				
1. Type of facility				
2. Geography				
3. Size				
4. Volume				
5. Atmosphere				
6. Facility characteristics (general)				
7. Religious affiliation				
VII. System features				
1. Resource waste				
2.Logistics and coordination				
3. Record-keeping				
VIII. Healthcare Professional Characteristics				
1. Experience				
2. Group composition				
IX. Financial costs				
1. Financial incentives				
2. Funding system				
3. Financial (general)				
X. Leadership				
1. Role modeling				
2. Mentorship				
3. Champion				
XI. Collaboration				

1. Social interactions				
XII. Evaluation				
1. Evaluation (general)				
2. Audit				
3. Organizational evaluation				
4. Patient evaluation				
XIII. Regulatory or Legislative standards				
1. Legal				
2. Standard of practice or care				
XIV. Societal influences				
1. Societal influences (general)				

On-site condition assessment analysis

In analyzing the data obtained from the on-site assessment carried out during the visit by a responsible person in charge of Queen Mary University of London, we obtained the following attributes and their corresponding characteristics:

1. Access to resources
   - Number of clinical staff in the service
   - Internet (under technology)
   - Where will a study meeting be held between patients and clinicians?
   - Identified dedicated meeting space
2. Working structure
   - Type of service
   - Do patients in the service see the same clinicians at the patients meeting?
   - Duration of routine meetings (average)
   - Type of therapy
3. Patient characteristics
   - Number of patients with psychosis observed in the previous year
   - On average, how often do patients with psychosis see each other at routine appointments
4. Features of the building
   - Type of service
     - Number of patients recorded in the previous year
5. System features
   - Preservation of medical records
6. Evaluation
   - Organizational readiness

Discussion

The idea of this paper was to analyze the attributes of the context in North Macedonia regarding the implementation of a new digital instrument/ mental health intervention that can be used in everyday practice and to change the doctor-patient communication. The difference in the application of this intervention is that the quality of life of the patient is developed and seen.

Patients have the right to be actively involved in the design of their treat-

ment plan, along with its implementation. They also have the right to participate in the recovery and resocialization planning process, while respecting their needs and abilities. The health system of North Macedonia is obliged to follow these principles.

DIALOG+ directly addresses these requirements by offering client-centered treatment and active patient involvement through a "four-step approach". Because it is a time-saving intervention, DIALOG+ has a great potential to help overcome problems (e.g., lack of time, work overload, etc.) resulting from the low ratio of mental health professionals/residents.

All countries have community mental health centers, but they generally do not operate independently of hospitals. In addition, the hospital-based approach is still dominant, especially given the existence of many hospitals specializing in the treatment of psychiatric disorders. The characteristics of DIALOG+ (widely applicable psychosocial intervention) are in line with modern assumptions about the psychosocial rehabilitation of patients with psychosis. Hence, it can be a useful tool for professionals in monitoring and realizing the true vision and mission of these institutions. It will help patients reintegrate into society, become more independent and use their full potential in the pursuit of healthy and functional living.

First, it empowers patients in the community in terms of their satisfaction with life and social functioning. Second, it promotes and encourages the involvement of carers and other community members in the process of psychosocial reintegration of these patients.

In a study conducted in the United Kingdom, Spain, the Netherlands, Sweden, and Switzerland[14] DIALOG+ proved to be an effective psychosocial intervention. If DIALOG+ proves to be an effective intervention (i.e., if it proves beneficial for patients in low- and middle-income communities), it is likely to be recognized and approved by national health insurance funds in low- and middle-income countries.

Contextual implementation facilitators that emerged from our analysis are the following:

- the use of technology and data storage on tablets
- objectification through a computer program
- structuring the session through the questionnaire
- the measurability of the assessment
- continuity of assessment
- involving family members
- preparation of guides and guidelines for patients, but also for clinicians
- more frequent sessions, greater availability of doctors and greater media coverage
- training and education of medical staff
- involvement of other clinicians in the intervention (for e.g., nurses).

Contextual implementation barriers that will need to be bridged are the following:

- culture of living and stigma

- longer talking sessions
- lack of sufficient activities to be offered to patients
- lack of medical staff,
- professional training of staff
- loss of doctor-patient relationship if too much time is devoted to technology
- lack of staff
- lack of time and lack of space
- financial problem
- reorganization of the psychiatric service
- greater involvement of social services.

The basic skills of someone who would work with DIALOG+ should be patience and trust, confidentiality. There is a structure to the interview, and if we stick to the structure, then we will really take the time to ask questions to people who have problems and who have come to discuss their problems. In particular, it does not matter if the ranking will be 2 or 4 at the moment and then it will be 3. It does not matter at all, but it is important to conduct a conversation and find a solution that will be considered. Therefore, this therapy is aimed at finding a solution. The clinician will suggest an activity; the patient will have to suggest an activity. We, of course, will not be able to solve all the problems, but if we stick to this structure, we will be able to have more domains that people can talk about.

The most important thing is that clinicians put all life segments in the direction of diagnosing, treating and monitoring the whole process. DIALOG+ will monitor all these 11 segments of life that are related and if a smaller part is solved, the remaining cubes will be like a domino effect. Therefore, this domino effect in most cases would have a positive outcome for both patients and clinicians who will learn a more comprehensive approach. Therapists will be upgraded in their domain, and patients will gain that trust and respect in order to get the most out of this. This intervention ensures that the 11 domains of life and treatment are constantly addressed and that patients' attitudes and priorities are always taken into account[15]. This is likely to increase awareness of patients' attitudes and their changes over time, resulting in care that reduces unmet needs and increases patients' quality of life and satisfaction with treatment[16]. Some authors expect and suggest that patients' quality of life may improve even when symptoms do not show significant changes[17,18].

If applied at the secondary level, an information campaign will be required. The directors, i.e. the management of the health institution, will have to lobby for the workers and their employees to use that tool more often. Training of other medical professionals, logistical support (tablet service) will also be required. Patients would prefer this intervention take place in the outpatient services of the community, than in the hospital conditions and because of the stigma not to be seen, but also because of the faster and closer availability of Mental Health Centre.

Conclusions

DIALOG+ training should be included in the continuous professional development of clinicians, to have online tutorials, to organize additional activities with patients who use DIALOG+, to distribute a brochure to introduce the tool to patients (such a brochure already exists), to involve family members in the intervention, support from the association of psychiatrists and support from the Ministry of Health.

Here are some of our recommendations for better implementation not only of this new digital psychosocial intervention, but also for the implementation of some new interventions to improve mental health in the future:

- Application at all levels and electronically documented patient record.
- As one of the basic aspects of DIALOG +, it is a step forward in terms of encouraging the use of technology in health care in our country.
- Access to information in order for clinicians to know how to use it and access to the application and eventually enable some systems to have easier access.
- Self-evaluation for patients.
- Upgrading a system that may already be obsolete, and already with the help of new technologies allows you to save resources and time.
- Appropriate psychoeducation and technical support for practical application of the intervention.
- Systematized scientific research work.
- Financial assistance is necessary because the implementation of services depends on providing tablets, phones and computers dedicated to this type of intervention.
- The long-term effects would be to reduce symptoms, reduce relapse and improve the quality of life of our patients.
- Due to the nature of the intervention, which requires technical knowledge and operation of applications on tablets and smartphones, we expect younger doctors, psychologists and nurses to be the first ones to accept the service in their daily practice.
- The selection of the patient profile is aimed at the younger population who is technically and digitally more prepared to accept this type of intervention that includes working on applications on a tablet or smartphone.
- These contents should be part of the continuous medical education and should be appreciated and evaluated and in the process of renewing the licenses there should be a mandatory number of hours in which the technique would be mastered.
- Its usage to be covered by the health insurance fund.

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CLINICAL SCIENCE

METABOLIC DISTURBANCES DURING TREATMENT WITH SECOND GENERATION ANTIPSYCHOTICS

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Abstract

Second generation antipsychotics (SGA) cause side effects through weight gain, dyslipidemias (cholesterolemia, hypertriglyceridemia) as well as affected glucose homeostasis in terms of hyperglycemia, insulin resistance and the incidence of type 2 diabetes mellitus. The aim of this study was to investigate metabolic changes in patients treated with SGA. Materials and methods: This was a prospective study of 50 patients treated with SGA (olanzapine, clozapine, risperidone, quetiapine, aripiprazole) at the PHI University Clinic of Psychiatry who met the relevant ICD-10 criteria. The following parameters were monitored: history and clinical examination, blood pressure and pulse, height, weight, body mass index (BMI), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression Scale (CGI-S), dose of prescribed SGA,as well as: fasting glycemia, lipid status, HDL, LDL, glycosylated hemoglobin (HgA1C). The parameters were determined at the beginning and after three months of treatment. Results: The subjects in terms of the criteria of metabolic syndrome were: 64% with a larger waist circumference, 53.2% with an increase in systolic and/or diastolic blood pressure, 31.3% with a BMI>30, and 39% with an increase in glycaemia and reduced HDL values at 23.4%. Also,18% of the respondents met three or more criteria. Statistical analysis of the differences in the analyzed parameters showed statistically significant differences for the CGI-S score (p = 0.00007) and for the diastolic pressure (p = 0.038). Correlation of equivalent doses of SGA with BMI (r = -0.637) was obtained. Discussion: The study confirmed presence of metabolic disorders in patients treated with SGA. Although there was no significant difference of metabolic syndrome parameters in relation to the general population, a correlation with BMI has been established. Conclusion: This study showed that patients treated with second-generation antipsychotics should be monitored during their treatment for the parameters of the metabolic syndrome, particularly BMI.

КЛИНИЧКО ИСТРАЖУВАЊЕ

МЕТАБОЛНИ НАРУШУВАЊА ПРИ ПРИМЕНА НА ВТОРА ГЕНЕРАЦИЈА НА АНТИПСИХОТИЦИ

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Клучни зборови: метаболен синдром, втора генерација антипсихотици, психијатриски растројства

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Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Втората генерација на антипсихотици (second generation antipsychotics–SGA) предизвикуваат несакани ефекти преку пораст на телесна тежина, дислипидемии (холестеролемија, хипертриглицеридемија) како и засегната хомеостаза на гликозата во смисол на хипергликемија, резистентност на инсулин и појава на диабетес мелитус тип 2. Цел на ова истражување е да се испитаат метаболните промени кај пациентите третирани со SGA. Материјали и методи: Ова беше проспективна студија на 50 пациенти третирани со SGA (olanzapine, clozapine, risperidone, quetiapine, aripiprazole) на ЈЗУ Универзитетска клиника за психијатрија кои ги исполнуваа соодветните МКБ-10 критериуми. Беа следени следните параметри: анамнеза и преглед, ТА и пулс, висина, тежина, индекс на телесна маса (bodymassindex-BMI), Кратка скала за психијатриска проценка(BPRS), скала за глобален клинички впечаток (CGI), дозата на ординираниот SGA, како и: гликемија на гладно, липиден статус, HDL, LDL, гликолизиран хемоглобин (HgA1C). Параметрите беа одредувани на почеток и после три месечен третман. Резултати: Испитаниците во однос на критериумите на метаболен синдром беа: 64% со поголем обем на струк, 53,2% со пораст на систолен и/или дијастолен крвен притисок, 31,3% со BMI>30, а 39% со пораст на гликемија и намалени вредности на HDLкај 23,4%. Со исполнети три и повеќе критериуми беа 18% од испитаниците. Статистичката анализа на разликите во анализираните параметри покажа статистички сигнификантни разлики за CGI-S скорот (p=0.00007) и за дијастолниот притисок (p=0.038). Добиена е корелација на еквивалентните дози на SGA со BMI (r= -0,637). Дискусија: Истражувањето ја потврди присутноста на метаболни нарушувања кај пациентите третирани со SGA. Иако на самиот почеток на третманот не постои битна разлика во однос на присуството на метаболниот синдром во однос на општата популација, сепак утврдена е корелација со BMI. Заклучок: Ова истражување покажа дека пациентите кои се третирани со втора генерација на антипсихотици треба да бидат мониторирани во текот на нивниот третман во однос на параметрите кои го сочинуваат метаболниот синдром, особено BMI.

Introduction

Second generation antipsychotics (SGA) reduce the risk of extrapyramidal symptoms, but cause side effects through weight gain, dyslipidemias (cholesterolemia, hypertriglyceridemia) as well as affected glucose homeostasis in terms of hyperglycemia, insulin resistance and the onset/occurrence of type 2 diabetes mellitus[1].

According to some authors, as many as 50% of SGA patients meet the criteria for metabolic syndrome, which increases the risk of cardiovascular disease. This metabolic syndrome is often not diagnosed in psychiatric patients, because according to some authors only 2.4% of patients were evaluated, and 34.5% of them met the criteria for this condition[2]. According to the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness), specific gender differences have been identified in terms of metabolic risk in women[3]. It is considered that in schizophrenia, especially in the female population, the obesity would have higher values, while in bipolar affective disorder (BD) it would have a 50% increase in incidence. Numerous epidemiological studies indicate that people with affective disorders and schizophrenia have an increased relative risk of mortality that is 1.5 to 3.3 times higher than the general population, which can be attributed to cardiovascular disease or cerebrovascular incidents. It is considered that this may be due to poor diet or reduced physical activity, smoking or various forms of alcoholism and other addictions, but also other high-risk behaviors for the health (various infections, etc.). The treatment itself carries a special risk, i.e. the medications that are used[4].

Bipolar affective disorder and schizophrenia are endogenous mental disorders with common clinical features such as psychotic or affective symptoms, sometimes cognitive symptoms, but also common genetic risk for obesity, DM and CVD, which are thought to have a 15-20year shorter lifespan compared to the generalized population. In addition, antipsychotics are used in therapy, which in addition to the expected therapeutic effect, carry certain risks in terms of side effects, especially the second generation of antipsychotics that affect general health in terms of the occurrence of metabolic changes[5].

In the treatment of various psychiatric disorders and conditions, especially psychotic disorders, different antipsychotics are used, which can significantly differ in their effectiveness and profiles of side effects. The differences in efficacy, but also the occurrence of side effects depend on the mechanism of action on different neurotransmitter systems and receptors[6]. A difference in the effect on metabolic function in patients treated with SGA is shown in a meta-analysis published in 2020[7].

The use of antipsychotics worldwide has grown exponentially in the last 15 years. In the United States for the period 1997-2007 the number of users increased from 2.2 to 3.9 million people, and in the pediatric population by 60% in the period 2002-2007[8]. This is considered to be due to an improved profile with reduced extrapyramidal symptoms, the use as adjunctive therapy in affective disorders, and the improved patient acceptance. The meta-analysis confirmed the prevalence of metabolic syndrome in both acute and chronic forms of schizophrenia, independent of antipsychotics, and that percentage was about 32%. On the other hand, cross-sectional studies have shown that the prevalence of meta-

bolic syndrome (MetS) in patients treated with AP was 45-50% with a correspondingly high risk of CVD8. SGA is increasingly used outside the indication area, in terms of treatment of psychotic depressions, at inadequate personality structures, as well as other conditions that are refractory to therapy (eating disorder, obsessive-compulsive syndrome, etc.)[9].

Metabolic syndrome can be diagnosed if three of five criteria focused on specific cardiovascular risk factors are met: abdominal obesity, low HDL values, elevated triglycerides, hypertension, and affected fasting plasma glucose. This definition is accepted by the International Diabetes Federation[10] and also by the American Society of Cardiology[11]. The prevalence of meeting three, four, or five components of metabolic syndrome is often examined and in relation to the most prevalent combinations: triglyceride elevations, blood pressure and glycaemia, which in the Korean study case are described as more often in men (30, 8%) in relation to women where they were present in 14.5% of the respondents[12].

According to the criteria that take into consideration the differences in populations according to the European criteria of IDF (Europid), i.e. the Mediterranean type to which we belong, the following values have been determined for the metabolic syndrome criteria: waist circumference for men ≥ 94 cm for men and ≥ 80 cm for women; triglycerides ≥ 1.7 mmol/L; HDL cholesterol for men <1.03 mmol/L and for women <1.29mmol/L; elevated systolic pressure ≥ 130mmHg and elevated diastolic pressure ≥85 mmHg, as well as elevated glycemic values ≥5.6 mmol/L.[13] In addition, it is necessary to describe the categories according to the body mass index, such as malnutrition with BMI ≤ 18.5; normal body weight with BMI of 18.5-24.9; overweight if BMI = 25-29.9 and obese with BMI ≥ 30.

The aim of this study is to examine metabolic changes in patients treated with SGA regardless of diagnosis.

Material and methods

This was a prospective study of 50 patients treated at the PHI University Clinic of Psychiatry and followed up after 3 months of treatment. Patients treated with inpatient or outpatient treatment with SGA (risperidone, olanzapine, clozapine, quetiapine, aripiprazole) were included. Patients met the ICD-10 criteria for: schizophrenia disorders, schizoaffective disorders, acute psychotic disorders, persistent delusional disorders (F20-F29), affective disorders (F30-F34) as well as other diagnoses such as inadequate personality structure (F60), compulsive disorder (F 42), inorganic insomnia (F51), and other disorders.

Inclusion criteria: Patients aged 18-65 who meet the criteria for the above disorders and who have given consent.

Exclusion criteria: no consent given, diagnosed with type 2 diabetes mellitus (DM) before SGA, pregnancy and lactation.

Using a clinical interview, demographic data were obtained (gender/sex, age, employed/unemployed, marital status, smoker, etc.), current and past illnesses, family history of diabetes mellitus, and then a psychiatric examination was performed and evaluation using clinical scales: Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression - Severity (CGI-S). According to the recommendations of the European Psychiatric Association from

2009, the somatic condition was taken into consideration through vital signs: blood pressure (BP) and pulse, height, weight and measurement of waist and hip circumference from which BMI will be obtained. Laboratory tests that were monitored were: fasting glycaemia, lipid status, HDL (high density lipoprotein), LDL (low density lipoprotein), TG (triglycerides), glycosylated hemoglobin (HgA1C) which were determined before the beginning of the therapy and after three months. Each patient received information on the risk of developing metabolic syndrome and a recommendation for a hygienic-diet regimen according to the WHO.

The statistical analysis of the data obtained from the research was done in the statistical program SPSS 23.0. Shapiro Wilk's test was used to test the normality of the data distribution. The categorical (attributive) variables are represented by absolute and relative numbers. The numerical (quantitative) variables are represented by average, standard deviation, minimum and maximum values, median value and interquartile rank. Student t-test for dependent samples and Wilcoxon matcher pairs test were used to compare the analyzed variables before the start of therapy and 3 months later, while Chi-square test, Student t-test were used to compare the variables in relation to gender, independent samples and Mann-Whitney test. Equivalent dose correlation with certain variables was analyzed using Pearson's linear correlation coefficient and Spearman's rank correlation coefficient. Statistical significance was defined at the level of $p < 0.05$.

Results

The survey included 50 respondents who met the inclusion criteria. From the beginning, due to the current symptomatology and the need for correction of the treatment or due to the somatic condition, 5 respondents were excluded (one patient was transferred to another treatment facility, one patient had high glycemic values, one patient was placed in a depot preparation which is not included in the study, one patient was diagnosed with psychoorganic syndrome, and one patient developed a complication of a metabolic nature that has been described as a case study[14]. Out of the remaining 45 patients, at the first control after 3 months, only 15 patients were followed up who received appropriate parameters for analysis and comparison. An overview of this data is given in Figure 1.

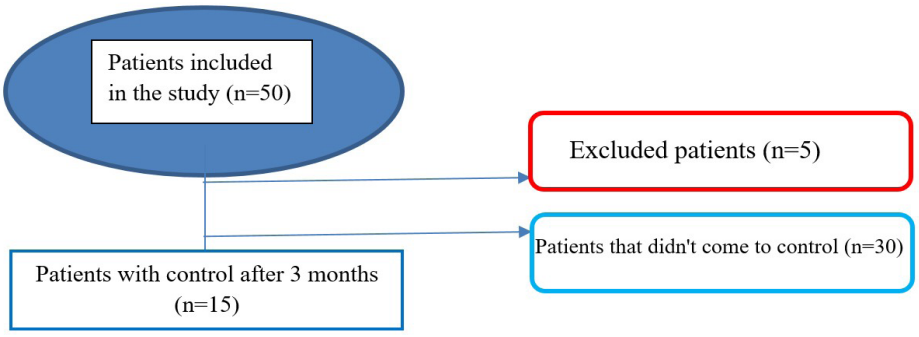

Figure 1. Diagram of patients involved

From the obtained parameters we present the demographic indicators in Table 1. The research included 50 respondents, aged 18 to 63 years, with average age 37.4 ± 12.5 years. The gender structure of the respondents consists of 48% (24) male patients and 52% (26) female patients.

Table 1. Overview of the respondents according to demographic characteristics

Parameter	N (percent %)
Gender/Sex	
Men	24 (48)
Women	26 (52)
Age	
mean ± SD	37.44 ± 12.5
min – max	18 – 63
Marital Status	
- married	16 (32)
- devorced	6 (12)
- single	27 (54)
- no data	1 (2)
Employment Status	
- unemployed	29 (58)
- employed	19 (38)
- pensioner	2 (4)
Smoker	
- yes	23 (46)
- no	27 (54)
Previously treated	
- yes	22 (44)
- no	28 (56)
Family anamnesis for DM	
- yes	8 (16)
- no	42 (84)

Table 2 shows patients according to diagnoses, and the presentation includes acute psychoses (F23), chronic psychoses (F20, F21, F22, F25), affective disorders (F30, F31, F32, F33, F34) and other disorders (F41), F42, F45, F51).

Table 2. Overview of patients according to diagnoses

Diagnosis	N (%)
Acute Psychosis (AP)	18 (36)
Chronic Psychosis (CP)	17 (34)
Affective disorders (AD)	11 (22)
Other Disorders (OD)	4 (8)

Table 3 shows distribution of respondents in relation to the type of the prescribed therapy.

Table 3. Overview of used second generation antipsychotics

Diagnosis	Start N (%)	mean ± SD	Second visit N (%)	mean ± SD
Aripiprazole	11 (22)	22,50±36,20	6 (12)	16,67±6,83
Clozapine	2 (4)		1 (2)	
Quetiapine	4 (8)	75,00±35,36	3 (6)	56,25±12,5
Risperidone	17 (34)	3,19±1,33	4 (8)	4,25±0,96
Olanzapine	16 (32)	9,71±5,15	2 (4)	

Table 4 shows the data on how many criteria of the metabolic syndrome were present at the beginning of the study. On this table it can be seen that out of the total number of respondents, 64% are those who have a larger waist circumference according to the criteria for the population of the Mediterranean or according to EUROID, of which 14 male and 18 female respondents.

Table 4. Present criteria of metabolic syndrome in the respondents

Criteria	N	%
Waist Circumference Men ≥ 94cm Women ≥ 90cm	50 14 18	100 28 36
Blood Pressure(BP) Systolic>130mmHg Diastolic>85mmHg	47 7 18	100 14,9 38,3
BMI 25-29,9 ≥ 30	48 13 15	100 27,1 31,3
Glycaemia Fasting ≥ 5,6 mmol/L	46 18	100 39,1
HDL Men<1,03mmol/L Women<1,29mmol/L	30 2 5	100 6,7 16,7
Fulfilled Criteria ≤ 1 2 3 4	50 30 11 8 1	100 60 22 16 2

In the criterion of increase in blood pressure, at 53.2% of the respondents it is with higher values, and the percentage is higher in diastolic pressure. Regarding the body mass index (BMI) of the total number of respondents with values higher than 30 (obese) were 29.2% of the respondents, but

also the percentage of persons with TT above average (overweight) were 27,1% of respondents. Fasting blood glucose was above the recommended average at 18 people or 39.1% had an increase. The parameter with lower HDL values was present in 23.4% of the respondents, a slightly higher percentage in women. In relation to the criteria present for metabolic syndrome, it can be seen in Table 4 that even on the first visit, 18% had 3 and more fulfilled metabolic syndrome diagnosis criteria, which should be prevented from further progression.

In order to determine the differences in the analyzed parameters of the metabolic syndrome that were available for comparison after 3 months of treatment, only the results of population of 15 respondents who had complete data were taken for mutual comparison. The results of the statistical analysis for the tested differences in the analyzed parameters between the two time points, before the start of therapy and after 3 months of therapy are shown in Table 5. No statistically significant difference was found in the values of BMI (p = 0.13), glycaemia (p = 0.75), total cholesterol (p = 0.64), triglycerides (p = 0.67), HDL (p = 0.15), LDL (p = 0.75), HgA1C (p = 0, 18), BPRS score (p = 0.63), and systolic pressure (p = 0.27), whereas after 3 months of therapy a significant difference was found in the values of CGI-S score (p = 0.00007) and diastolic pressure (p = 0.038). After 3 months of therapy, a significant reduction in CGI-S score (4.67 ± 0.65 vs. 3.75 ± 0.62) and diastolic pressure (91.9 ± 14.9 vs. 79.7 ± 6,4) was registered.

Table 5. Overview of the tested differences before and after 3 months of treatment

Parameters	First visit mean ± SD	Second visit mean ± SD	p-value
BMI	30.5 ± 8.8	31.8 ± 8.5	t=1.6 p=0.13
Glycaemia	5.48 ± 0.9	5.57 ± 0.4	t=0.3 p=0.75
Total cholesterol	5.0 ± 0.9	4.9 ± 0.8	t=0.5 p=0.64
Triglycerides (TG)	1.32 ± 0.4	1.38 ± 0.6	t=0.4 p=0.67
HDL	2.07 ± 0.6	1.68 ± 0.3	t=1.7 p=0.15
LDL	2.57 ± 0.9	2.38 ± 0.9	t=0.3 p=0.75
HgA1C	5.8 ± 0.5	4.9 ± 2.4	t=0.9 p=0.37
BP- systolic	121.3 ± 19.2	116.7 ± 10.0	t=1.2 p=0.27
BP - diastolic	91.9 ± 14.9	79.7 ± 6.4	t=2.5 *p=0.038
BPRS	34.4 ± 12.2	38.9 ± 32.5	Z=1 p=0.3
CGI-S	4.7 ± 0.6	3.7 ± 0.6	t=6.2 ***p=0.00007

t (Student t-test for dependent samples) *p<0.05;***p<0.0001

Z (Wilcoxon matched pairs test)

The study also analyzed the correlation between the equivalent dose of SGA with BMI, glycaemia, total cholesterol, TG, HDL, LDL, blood pressure and HgA1C. The correlation between the equivalent dose of SGA and BMI (p = 0.014) was confirmed as significant, which according to the value of Pearson's correlation coefficient is negative, i.e. indirect and of moderate intensity (r = -0.637). It shows that with increasing the equivalent dose of the SGA, the

body mass index decreases, and vice versa. The obtained correlation of BMI with the applied equivalent dose of SGA is graphically shown in Figure 2.

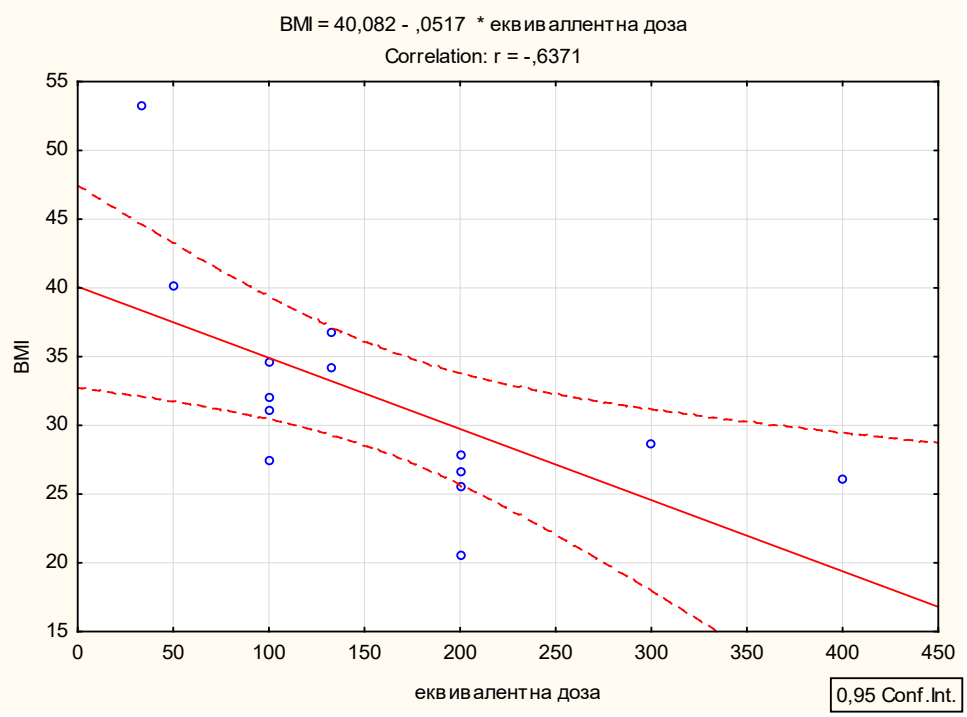

Figure 2. Correlation of BMI with the equivalent dose of administered SGA

Discussion

This is a first study in our country that monitors and controls the parameters that are key to diagnosing metabolic syndrome in patients treated with SGA. The results confirmed the presence of metabolic disorders in patients that can lead to increased cardiovascular risk and the occurrence of type 2 diabetes mellitus. The results of the study showed that at the beginning 64% of respondents had an increased waist circumference, and 53.2% were with elevated blood pressure values. In terms of BMI, 31.3% of respondents were with a score higher than 30, but also 27.1% of respondents were overweight. Examination of the laboratory parameters of glycaemia showed elevated values in 39.1% of the subjects, and decreased values of HDL in 23.4%. Thereby, 18% of the respondents met 3 or more criteria for MetS.

These data are in line with data from the IDF, which estimates that metabolic syndrome occurs due to a sedentary lifestyle in the modern world, and it is estimated that about 25% of the world's population has metabolic syndrome[15]. Therefore, predictors of metabolic syndrome through anthropometric measurements and bioelectrical measurements (Bio-Electrical Impedance Analysis i.e. BIA-test values) belonging to the latest technologies are introduced. Numerous other studies have confirmed a prevalence of MetS of 23–29% depending on gender16 or 20–30% in the general population, and which increases with age with respect to gender[17-19].

Regarding the examined differences in the parameters of MetS[20-24] after three months of treatment, a highly significant difference was found in the values of the CGI-S score (registered significant decrease thereof), as

well as a statistically significant difference in diastolic pressure which showed a significant reduction in initial values. Both parameters indicate a significantly improved state, one (CGI-S score) by directly measuring the condition, and the other indirectly by calming the mental state leading to a reduction in anxiety and a consequent reduction in diastolic blood pressure[7,25]. Unlike other studies which, after 6 months[26,27] of monitoring MetS parameters, found weight gain and increase in total cholesterol and triglyceride levels, whereas our study found no changes, perhaps because the monitoring was only three month long.

Because SGAs vary widely in their effect on MetS parameters[6,7,28-31] and to avoid dose influence, conversion to chlorpromazine equivalent doses was performed[32-34]. The obtained correlation between the equivalent doses of SGA and MetS which is negative, i.e. indirect and of moderate intensity, shows that with increasing the equivalent dose of SGA, the body mass index decreases and vice versa. This is significant because there is no direct positive correlation between the doses used and the increase in TT and the occurrence of MetS.

In order to get a more complete picture of the impact of SGA on the occurrence of MetS, it is necessary to process data from patients who have not been previously treated with such drugs (drug-naive). In addition, another limitation of this research is the insufficient number of respondents for the reliability of the obtained data. It should be emphasized that the research was conducted during the period of the declared pandemic with Covid-19, which prevented the monitoring of patients and complete processing of respondents, because laboratory tests were reduced to a minimum and of what is necessary. Apart from these changes in the overall organization of the health system, the current situation had an impact on the mental health of both the general population and the respondents. On the other hand, the fact from numerous studies that persons with psychiatric disorders do not adhere to research protocols and do not report to scheduled appointments should be emphasized[24].

Conclusions

It is very important that patients respond well (60-80%) to antipsychotic treatment in the first episode of psychosis, but the side effects should be considered from the very beginning. Although second-generation antipsychotics are better tolerated, they also carry the risk of side effects in terms of occurrence of metabolic syndrome features, and should be monitored regularly for these parameters.

Psychiatrists, as well as family physicians who are in frequent contact with their patients, in addition to the therapeutic response to the applied SGA, need to monitor these parameters of the metabolic syndrome regularly, especially BMI, in order to early recognize and diagnose the initial changes. Since there is an individualized response to a particular SGA that the patient is receiving, it is necessary, when the early detection of an increase in one of the parameters of the metabolic syndrome, to change the antipsychotic with another that carries a lower risk of developing metabolic disorders. In the meta-analysis that includes 18 antipsychotics, a recommendation is given which drug has the least effect and an individualized approach to treatment is recommended.

In such conditions, there is a need for an interdisciplinary approach and close cooperation, i.e. teamwork with a specialist in the field of endocrinology who would have a role in managing the risk of type 2 diabetes mellitus and the risk of cardiovascular disease.

Although not scientifically proven, there is hope that understanding the diagnosis of metabolic syndrome will motivate people and their GPs to take appropriate steps to reduce the risk of CVD and DM2, especially in the practice of lifestyle modification. The risk of metabolic disorders can be reduced by appropriate psychoeducation of patients in terms ofa hygienic-diet regime and proper nutrition, as well as advice on increased psycho-physical activity. However, if necessary, appropriate pharmacological interventions should be applied depending on the parameters involved.

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CLINICAL SCIENCE

PRESENCE OF ANTI-TF4/HEPARIN ANTIBODIES IN PATIENTS PREOPERATIVELY TREATED WITH ENOXAPARINE AFTER ORTHOPEDIC SURGERY

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Abstract

Heparin-induced thrombocytopenia (HIT) is a condition caused by antibodies against the platelet factor 4 (PF4)/heparin complex. This significantly increases the risk of bleeding and thrombosis in patients, which is essential in the postoperative period. In this study we examined the rate of seroconversion of anti-PF4/heparin antibodies in patients with rheumatoid arthritis (RA) and osteoarthritis (OA) after total knee or hip arthroplasty. The aims of the study were to assess the risk of HIT by evaluation of induction of anti-PF4/heparin antibodies in patients with RA and OA after total knee or hip arthroplasty, treated prophylactically with enoxaparine. Material and methods: We followed 36 patients aged 18 to 80 years, after total knee or hip arthroplasty, treated prophylactically with enoxaparine. Patients were divided in two groups: patients with RA and patients with OA. They were examined for occurrence of HIT. Blood was sampled twice, from a peripheral vein, for immunologic tests. The first time it was done before enoxaparine application and the second time postoperatively 10 days after surgery. We noted demographic data, anti-PF4/heparin antibodies, erythrocyte sedimentation rate (ESR), CRP, RF, antiCCP and anti-nuclear antibodies Hep2 (ANA). Results: There was no significant difference in the values of anti-PF4/heparin antibodies in patients with RA and OA preoperatively. The presence of anti-PF4/heparin antibodies was significantly lower in RA patients compared to OA (7.14% versus 27.27%, p=0.034). There was no significant association between levels of anti-PF4/heparin antibodies and ESR, CRP, RF, CCP, ANA. Conclusion: The results obtained showed a lower level of anti-PF4/heparin antibodies in patients with RA than in patients with OA. This shows that there may be a difference in the generation of this antibody in patients with RA compared to patients with OA, prophylactically treated with enoxaparine after total knee or hip arthroplasty.

КЛИНИЧКИ ИСТРАЖУВАЊА

ПРИСУСТВО НА АНТИ-ТФ4/ХЕПАРИН АНТИТЕЛА КАЈ ПАЦИЕНТИ ПРОФИЛАКТИЧКИ ТРЕТИРАНИ СО ЕНОКСАПАРИН ПО ОРТОПЕДСКИ ОПЕРАТИВЕН ЗАФАТ

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Клучни зборови: хепарин-индуцирана тромбоцитопенија, анти-ПФ4/хепарин антитела, имплантација на протеза на колк или колено, еноксапарин, постоперативен ризик

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Извадок

Хепарин-индуцираната тромбоцитопенија (ХИТ) е предизвикана од антитела кон тромбоцитниот фактор 4 (ТФ4)/хепарин комплексот. Таа значително го зголемува ризикот од крвавење и тромбоза кај пациентите, што е особено есенцијално во постоперативниот период. Во оваа студија ја проценуваме стапката на сероконверзија на анти-ТФ4/хепарин антителата кај пациенти со ревматоиден артритис и остеоартритис по имплантација на протеза на колк или колено лекувани профилактички со еноксапарин. Целта на истражувањето беш да се процени ризикот од хепарин-индуцирана тромбоцитопенија преку евалуација на индукцијата на анти-ТФ4/хепарин антителата кај пациенти со ревматоиден артритис и остеоартритис по имплантација на протеза на колена или колк, лекувани профилактички со еноксапарин. Материјал и методи: Беа испитани 36 пациенти, на возраст од 18 до 80 години, по имплантација на протеза на колк или колено, лекувани профилактички со еноксапарин. Пациентите беа поделени во две еднакви групи, односно пациенти со ревматоиден артритис (РА) и пациенти со остеоартритис (ОА). Пациентите беа следени за време на хоспитализацијата на Клиниката за ортопедски болести за појава на ХИТ. Во два наврата беше земена венска крв, од периферна вена, за имунолошки иследувања. Прв пат тоа беше направено пред почеток на лекување со еноксапарин, а втор пат постоперативно, 10 дена по оперативниот зафат. Беа нотирани демографски податоци, анти-ТФ4/хепарин антитела, седиментација на еритроцити (ESR), CRP, RF, CCP, ANA, појава на ХИТ. Резултати: Немаше сигнификантна разлика во вредностите на анти-ТФ4/хепарин кај пациентите со ОА и РА предоперативно. Стапката на анти-ТФ4/хепарин антитела кај пациентите со РА беше сигнификантно пониска од онаа кај пациентите со ОА (7,14% наспроти 27,27%, p=0,034). Немаше сигнификантна поврзаност на вредностите на анти-ТФ/4 антителото со вредностите на ESR, CRP, RF, CCP или ANA. Заклучок: Резултатите укажаа на намалена инциденција на анти-ТФ4/хепарин антитела кај пациентите со РА во споредба со оние со ОА. Ова укажува дека постои разлика во анти-ТФ4/хепарин имуниот одговор кај пациенти со РА наспроти оние со ОА, профилактички лекувани со еноксапарин, по ортопедски оперативен зафат за имплантација на протеза на колк или колено.

Introduction

Heparin-induced thrombocytopenia (HIT) is an immunologic condition which can develop in patients treated with heparin ([1]), through the generation of antibodies which recognize the complex between platelet factor-4 (PF4) and heparin[2]. PF4 is released rapidly after platelet activation and binds to heparin, forming PF4-heparin complexes[3]. These molecules elicit an immune response, thus the creation of anti-PF4/heparin antibodies[4]. Recent data suggests that these antibodies bind to the PF4/heparin complexes and activate platelets thus accelerating the process of coagulation[5]. There is data showing the presence of anti-PF4/heparin antibodies in patients who have not received heparin[6]. PF4 could also be an antigen target for autoimmune diseases[7]. Anti-PF4/heparin antibodies could be induced in patients after major surgery without exposure to heparin[8]. HIT is even discovered after the postoperative prophylactic use of fondaparinux, an inhibitor of factor Xa[9]. Studies have reported the existence of "spontaneous" HIT, potentially caused by inflammation or infection[10]. Crauel et al. showed an association between bacterial infections and occurrence of anti-PF4/heparin antibodies[11]. These were present in about 20% of patients after total knee arthroplasty[12]. Besides the routine prophylactic use of heparin products in these patients, the prothesis itself is a major challenge for the immune system because of the mechanical damage to bone and connective tissue during the surgery[13].

Compared to different surgical procedures, arthroplasty results in a high postoperative incidence of anti-PF4/heparin antibodies. The procedure itself can induce their creation in patients with RA (which is an autoimmune disease by itself) or in patients with OA. The presence of anti-PF4/heparin antibodies and its risks in patients with RA, treated prophylactically with enoxaparine after total knee or hip arthroplasty has not been well examined.

We investigated the induction of anti-PF4/heparin antibodies in patients with RA and OA treated prophylactically with enoxaparine after total knee or hip arthroplasty and its potential association with erythrocyte sedimentation rate in the first hour (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-CCP (anti-cyclic citrullinated peptide), antinuclear antibodies by Hep2 (ANA).

The aims of this study were to examine the induction of anti-PF4/heparin antibodies in patients with RA and OA after total knee or hip arthroplasty, prophylactically treated with enoxaparine. We also examined whether there was any association in the induction of these antibodies and ESR, CRP, RF, anti-CCP, ANA. This was done with the goal to recommend an optimal model for postoperative management of these patients.

Material and methods

We investigated the induction of anti-PF4/heparin antibodies in patients with RA and OA, prophylactically treated with enoxaparine after total hip or knee arthroplasty and its association with ESR, CRP, RF, anti-CCP, ANA. The study was conducted at PHI University Clinic for TOARILUC where recruitment and follow-up of

patients was done. Laboratory tests were conducted at the immunology laboratory of the University Clinic for Rheumatology.

The study included patients aged 18 to 80 years, previously diagnosed with RA or OA, hospitalized at TOARILUC Department of Orthopedic Surgery for total knee or hip arthroplasty, prophylactically treated with enoxaparine. All patients were informed about the goals and procedures involved in the study and signed an informed consent form before being included.

A total of 36 patients were divided into two groups, patients with OA and RA. The groups were comparable in regards to size, age and sex distribution.

Patients with an infection, thrombosis on admission to hospital, those treated with heparin in the last month before admission or patients with other autoimmune diseases such as systemic lupus, systemic sclerosis, sarcoidosis, Lyme borreliosis, etc. were not included in the study.

After a detailed anesthesiologic examination, detailed demographic data were collected. Blood was collected preoperatively from a peripheral vein for anti-PF4/heparin antibodies, ESR, CRP, RF, anti-CCP, ANA. Postoperatively blood was collected on the tenth day of enoxaparine prophylaxis for anti-PF4/heparin antibodies, ESR, CRP, RF, anti-CCP, ANA.

The blood was analyzed at the immunology laboratory of the University Clinic for Rheumatology in Skopje. RF and CRP test were done with a BioSystem A15 biochemical analyzer. The levels of anti-CCP antibodies was done with Elisis Duo (Human) ELISA analyzer, while for the anti-PF4/heparin antibodies a Mindray MR-96A ELISA analyzer was used. Antinuclear antibodies were tested by immunofluorescence by the same certified physician on an Olympus CX31 immunofluorescence microscope.

During the hospitalization all patients received standard follow-up regarding blood tests and physical examination. Patients were assessed for the emergence of HIT, which was done using the 4T test.

Data were entered into an electronic database and analyzed by SPSS, v19.1 (SPSS, Chicago, IL, USA). Comparison was done with the Student's t-and Chi-square tests. We used a multivariant logistic regression to identify independent risk factors for the induction of anti-PF4/heparin antibodies. Correlation was assessed using the Pearson's analysis of correlation. P values <0.05 were considered statistically significant.

Results

Patient's average age was 70.1 +/- 9.23 in the RA group and 72.7 +/- 7.5 years in the OA group. In the RA group 2 (14.28%) were men and 12 (85.72%) women, while in the OA group 7 (31.82%) were men and 15 (68.18%) women. All patients with RA were previously diagnosed according to the EULAR 2010 criteria. Of these patients, 10 (71.43%) were anti-CCP positive, 9 (64.29%) were positive for RF IgG and 2 (14.29%) were ANA Hep2 positive. Twelve patients (85.71%) with RA were treated with disease-modifying antirheumatic drugs (DMARDs) according to the definition of EULAR (biologic, methotrexate, leflunomide, sulfasalazine or antimalarial).

Table 1. Postoperative occurrence of anti-PF4/heparin antibodies. Demographic, clinical, serologic and immunologic characteristics

	Rheumatoid arthritis Postoperative conversion			Osteoarthritis Postoperative conversion		
	Positive n=1	Negative n=13	P value	Positive n=6	Negative n=16	P value
Sex (male/female)	0/1	2/11	0.584	2/4	5/11	0.291
Age +/- SD	66.7 +/- 9.2	70.4 +/- 7.99	0.630	72.9 +/- 7.6	72.6 +/- 7.5	0.601
BMI (kg/m2) +/- SD	24.8 +/- 1.1	25.2 +/- 3.8	0.901	28.1 +/- 3.8	27.6 +/- 3.9	0.599
RF IgG (IU/ml)	18.8 +/- 25.9	60.1 +/- 70.9	0.137	5.6 +/- 11.2	7.8 +/- 13.4	0.145
CRP (mg/dl)	1.62 +/- 1.13	1.32 +/- 1.45	0.316	0.15 +/- 1.01	0.21 +/- 0.96	0.532
ESR (mm/1 час)	54.4 +/- 23.4	58.1 +/- 30.1	0.334	61.2 +/- 21.1	59.4 +/- 16.9	0.312
Anti-CCP (mg/dl)	0.6 +/- 0.1	250 +/- 543.2	0.022	0.0 +/- 55.6	0.0 +/- 0.0	0.667
ANA (Hep2)	0/1 (0%)	2/13 (15.38%)	0.879	1/6 (16.67%)	2/16 (12.5%)	0.918
Use of DMARD	1/1 (100%)	11/13 (84.61%)	0.856	0/6 (0%)	0/16 (0%)	NA
HIT	0/2 (0%)	0/13 (0%)	NA	0/6 (0%)	0/16 (0%)	NA

There were no anti-CCP positive patients in the OA group, while 2 (9.09%) were RF IgG positive and 3 (13.64%) were ANA Hep2 positive.

We compared the presence of anti-PF4/heparin antibodies in both groups. The rate of postoperative conversion was significantly lower in patients with RA compared to patients in OA group (7.14% versus 27.27%, p=0.034). There was no statistical significance in the association of anti-PF4/heparin antibody incidence and ESR, CRP, RF, anti-CCP or ANA.

There were no patients diagnosed with heparin-induced thrombocytopenia in the study period.

Discussion

In this study we examined the occurrence of anti-PF4/heparin antibodies in patients with RA and OA after surgery, prophylactically treated with enoxaparine. Previous studies have shown the presence of anti-PF4/heparin antibodies in patients with systemic erythematous lupus (SLE) and antiphospholipid syndrome[5,14]. To date there are very few studies examining the association of anti-PF4/heparin antibodies with other diseases and risk factors such as RA, OA and knee or hip arthroplasty. Izumi et al. presented data that the generation of anti-PF4/heparin antibodies was reduced in patients with RA, compared to patients with OA after total knee arthroplasty, prophylactically treated with edoxaban[15]. According to this study, 25.5% of patients with OA after total knee arthroplasty were positive for anti-PF4/heparin antibodies. This correlates well with our data, since we observed a lower postoperative seroconversion in the RA compared to the OA group (7.14% versus 27.27%, p=0.034).

Heparin-induced thrombocytopenia is caused by antibodies against the complex of platelet factor-4 and heparin 2. Heparin has high affinity to-

wards PF4 and after binding together they become a center of a powerful antigen stimulation, with the creation of anti-PF4/heparin antibodies (16). The presence of these antibodies is shown in patients after arthroplasty who have not been treated with heparin products[17]. It is considered to be an effect of the postoperative inflammatory process[18].

There are several theories regarding the lower incidence of anti-PF4/heparin antibodies in patients with RA. According to Ohayama et al.[19] the serum of patients with RA has many immune complexes containing PF4, so this molecule is much less available for the formation of anti-PF4/heparin antibodies. Other studies 15 present the opinion that treatment with DMARDs causes immunomodulation and immunosuppression which may be the reason for the lower generation of anti-PF4/heparin antibodies. Brauweiler et al. demonstrated the presence of B-cell anergy in patients with autoimmune inflammatory diseases because of which the generation of anti-PF4/heparin antibodies was inhibited[20].

Our data did not show an association between the use of DMARDs and the induction of anti-PF4/heparin antibodies. Previous studies have presented data that 52% of patients with RA who were anti-CCP positive had immune complexes containing PF4[21,22]. It is possible that patients, especially those with high levels of anti-CCP and RF are preimmunized towards PF4 which inhibits the production of anti-PF4/heparin antibodies[22].

This study t showed no statistical significance between the presence of anti-PF4/heparin antibodies and inflammatory markers such as ESR and CRP, immunologic factors such as RF, anti-CCP, ANA or clinical elements BMI, or the use of DMARDs.

Conclusion

The rate of postoperative seroconversion is significantly higher in patients with OA compared to the RA group. This suggests that OA patients require more attention from clinicians especially regarding potential HIT, after total hip or knee arthroplasty, prophylactically treated with heparin products such as enoxaparine.

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CLINICAL SCIENCE

DEVELOPMENTAL DISORDERS OF THE HIP TREATED AT THE CLINIC FOR ORTHOPAEDIC DISEASES – IN A PERIOD OF 10 YEARS (2009-2018)

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Abstract

Developmental hip dysplasia includes a wide range of conditions such as subluxation, dislocation, hip instability, and teratological hip. The diagnosis was confirmed by clinical examination, ultrasound examination and anterior-posterior view radiograph (AP). Treatment varied depending on the patient's age and the degree of dysplasia: Pavlik harness, closed reduction, open reduction and corrective osteotomies. In this study 242 patients were included, of whom 198 were female patients and 44 male. All of the patients were treated with conservative treatment-closed reducation and spica casting. Left-sided dislocations were more common than right sided dislocations with predominance in the female patients. The main treatment in follow-up patients was closed reduction with or without adductor muscle tenotomy (m. add. longus). In cases with unsuccessful attempt of closed reduction, open reduction was performed with or without adductor muscle tenotomy. Depending on the residual dysplasia, patients were additionally treated with pelvic osteotomies (Salter ,s inominate osteotomy), varus derotation osteotomy, valgus osteotomy, proximal femoral resection, and trochanter major transposition. 167 patients were treated with closed reduction and 3 with open reduction. The remaining patients were treated with closed reduction and additional surgery or with open reduction and additional surgery. Out of all treated patients, only 10 patients had recurrent dislocation of the hip, 7 female and 3 male patients. Closed reduction was performed again on two patients, and open reduction of the hip was performed on one patient. The average age of patients was 21.5 months. By presenting the cases in a period of 10 years, it was conclud that most cases were diagnosed later. Also, the standard closed reduction treatment was successful even after the first year in said patients. Depending on the residual dysplasia of the hip, in order to achieve better congruence of the joint, additional surgeries were performed.

КЛИНИЧКИ ИСТРАЖУВАЊА

РАЗВОЈНИ НАРУШУВАЊА НА КОЛКОТ КОИ СЕ ТРЕТИРАНИ НА КЛИНИКАТА ЗА ОРТОПЕДСКИ БОЛЕСТИ - ВО ПЕРИОД ОД 10 ГОДИНИ (2009-2018)

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Цитирање: Комненовиќ М, Божиновски З, Трајановски А, Савески А, Дамјановиќ Д, Атановски И. Развојни нарушувања на колкот кои се третирани на клиниката за ортопедски болести-во период од 10 години (2009-2018). Арх Ј Здравје 2022;14(1)91:97.

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Клучни зборови: развојни нарушувања, колк, некрвава репозиција, оперативен третман.

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Извадок

Во развојните нарушувања на колкот влегуваат широк спектар на состојби како субluксација, дислокација, нестабилност на колк и тератолошки колк. Дијагнозата се потврдува со клинички преглед, ехосонографски преглед и антеро-постериорна радиографија (АП). Третманот во зависност од возраста на пациентот и степенот на дисплазија може да биде со Павликови ременчиња и некрвава репозиција се до крвава репозиција и корективни остеотомии. Цел на овој труд е да се прикаже третманот на развојните нарушувања на колкот на Клиниката за Ортопедски болести во Скопје. Материјал и методи: Во оваа студија се вклучени вкупно 242 пациенти од кои 198 се женски пациенти и 44 машки пациенти. Кај сите пациенти основен третман е некрвава репозиција. Левостраните луксации се поброjни со предоминација кон женскиот пол. Основен третман кај следените пациенти е некрвава репозиција со или без тенотомија на аддукторната мускулатура (m. add. longus). Кај пациенти со неуспешен обид за некрвава репозиција направена е крвава репозиција со или без тенотомија на аддукторната мускулатура. Во зависност од резидуалната дисплазија на зглобот пациентите се третирани дополнително и со карлични остеотомии (иноминантна остеотомија по Салтер), варус деротативна остеотомија, валгус остеотомија, ресекција на проксимален фемур и транспозиција на големиот трохантер. Резултати: луксациите се со предоминација кај женскиот пол и позастапени се левостраните луксации во однос на десностраните луксации и кај сите основен почетен третман е некрвава репозиција на колкот. 167 пациенти се третирани само со некрвава репозиција на колкот, а 3 со крвава репозиција на колкот. Останатите пациенти се третирани со некрвава репозиција и дополнителен оперативен зафат или пак крвава репозиција и дополнителен оперативен зафат. Од сите третирани пациенти, само кај 10 пациенти имало релуксација на колкот и тоа кај 7 пациенти од женски пол, 3 кај пациенти од машкиот пол. Кај две од нив повторно е направена некрвава репозиција, а кај една крвава репозиција на колкот. Средна возраст на третман кај пациентите е 21,5 месеци. Повеќето од случаите се дијагностицираат подоцна, стандардниот третман некрвава репозиција е успешен и после навршена прва година кај пациентите. Во зависност од резидуалната дисплазија на колкот, со цел да се постигне подобра конгруентност на зглобот се прават дополнителни оперативни зафати.

Introduction

Developmental dysplasia of the hip can be defined as abnormal hip development which includes bone structures such as acetabulum and proximal femur, labrum, capsule and other soft tissue. This includes a wide range of conditions such as subluxation, dislocation, hip instability, and teratological hip.[1] The causes of developmental dysplasia of the hip are unknown. Aproximately one of 1000 children is born with a dislocated hip, while 10 out of 1000 children are born with a subluxated hip.[2] Dysplasia occurs in one out of 100 children; developmental dysplasia of the hip is more common in females (6:1), in 60% of the patients the left hip is affected.[2] Bilateral dislocation is found in only 20% of the cases.[2] Risk factors for developmental dysplasia of the hip are as follows: firstborn child, female sex, breech presentation, positive family history, oligohydramnios. The diagnosis is set with clinical examination, ultrasound examination and anterior-posterior view radiograph (AP). Clinical tests that are used during the examination are the Ortolani maneuver, the Barlow –maneuver and the Galeazzi sign. With the Ortolani maneuver we reposition the dislocated hip into the acetabulum. In infants who are more than 3 months old, the limited hip abduction (asymmetry in both hips abduction) is a sure sign of developmental dysplasia of the hip.

The study of Kotlarsky P et al., demonstrated that limited hip abduction after eight weeks of age is strongly associated with developmental dysplasia of the hip.[3] Additional characteristics are asymmetrical gluteal fold and lower limb-length discrepancy, standing or walking with external rotation of the leg in already walking patients.[1] Tpendelenburg sign can be seen in patients with dislocation who are already walking, while "waddling gate" can be seen in patients with bilateral dislocation, i.e., the child limps with both legs. In addition to the clinical examination, the ultrasound examination is also mandatory. According to the Graf method, the ultrasound finding includes static evaluation of the hip joint. The study of Dessi A. et al., indicates that ultrasound screening should be performed to all newborn babies aged 4–6 weeks, even when clinical signs or risk factors for developmental dysplasia of the hip are lacking.[4]

In cases when developmental dysplasia of the hip is diagnosed with ultrasound examination or it is diagnosed after 6-9 months of age, anterior-posterior view radiograph (AP) of the pelvis is done with central position of both knees. Another additional diagnostic is: arthrography, computed tomography and MRI scan. Computed tomography (CT) is performed more often in the assessment of the efficiency of the reposition after closed or open reduction of the hip. The efficiency of the closed reduction with standard anterior-posterior view radiograph (AP) cannot be assessed through the plaster cast immobilization. Computed tomography (CT) enables us to see the hips on the axial plane and thus confirm the reposition. By using low-dose radiation techniques, such as 1 mSv, we can obtain adequate radiation dosage for the hip radiography.[5]

The treatment of the developmental dysplasia of the hip depends in the age of the patient. According to Pavlik, the most suitable time for treatment with Pavlik harness are the first 8-9 weeks, while the acetabulum is still not filled with soft tissue structures. The repositioning and recentering of the femoral head in infants are much easier.6 If the treatment is unsuccessful or the patient is older than 6 months, closed reduction is performed with or without prior traction. If necessary, subcutaneous tenotomy is also performed on the m. add. longus. When the patient is above 2 years of age, i.e., the dislocation is diagnosed after the patient started walking, closed reduction is performed, and depending on whether there is subsequent dysplasia of the hip, surgical procedures follow.

If the closed reduction is unsuccessful, open reduction of the hip is performed. Depending on the condition of the dislocated hip and the subsequent dysplasia, several surgical treatments are sometimes needed in order to obtain a congruent joint.[1] There are many complications that can arise from the treatment of developmental dysplasia. One of the most serious complications is avascular necrosis (AVN) of the femoral head in children who are inadequately treated with maximal hip abduction. AVN is most often caused iatrogenically.[3]

The main iatrogenic causes of AVN are disorders of the circulation of the head, necrosis of the head due to pressure thereon, traction, the force with which the reposition is performed, the position of the immobilization after the "frog leg position" reposition, the ossification of the nucleus and the position of the femoral head, as well as the use of the Hilgenreiner brace.[7]

The aim of this paper is to present the treatment of developmental disorders of the hip at the Clinic for Orthopedic Diseases in Skopje.

Materials and methods

In the period 2009-2018, a total of 242 patients were included and treated in our study, whereas 44 male and 198 female patients were noted. The patients were treated at the Clinic for Orthopedic Diseases in Skopje.

Results

The average age of the treated patients was 21.5 months. The youngest patient was 2 months old, and

Table 1. Distribution of developmental disorders in patients by the conditions and gender.

Diagnosis	Female	Male	Total
Dislocations	183	41	224
Bilateral dislocations	67	8	75
Right-side dislocations	48	15	63
Left-side dislocations	60	18	78
Subluxations	9	/	9
Right-side subluxations	5	0	5

Left-side subluxations	6	2	8
Single-side subluxation with dislocation of the other hip	12	1	13
Dysplasia (without dislocation or subluxation)	5	/	5
Dysplasia with subluxation or dislocation	26	6	32
Bilateral dysplasia	12	2	14
Left-side Dysplasia	10	0	10
Right-side Dysplasia	11	3	14

the oldest patient was 153 months old (12 years and 9 months).

Developmental disorders of the hip are most common in Skopje – 70 patients, followed by Kumanovo – 30, Tetovo – 14, Veles – 12, Gostivar – 12, Strumica – 10, Stip – 6, Prilep - 4, Kriva Palanka – 4, Kavadarci – 4, Radovis – 3, Debar – 3, Gevgelija – 2, Struga – 2, Negotino – 1, Sveti Nikole – 1, Kratovo

Table 2. Distribution of developmental disorders in patients by the conditions and gender.

RNS without other intervention	RS without other intervention
167	3
RNS + tenotomy of add. muscles (RNS- Closed reduction)	31
RNS+ tenotomy of add. muscles +salter innominate osteotomy	1
RNS+ salter innominate osteotomy	2
RNS+pemberton osteotomy	1
RNS+ Pemberton osteotomy+derotative osteomy	1
RNS+derotative osteotomy	1
RNS+ tenotomy of add. muscles +derotative osteotomy	2
RNS+derotative osteotomy+Transposition of the greater trochanter distally	1
RNS+VRDO	1
RS+ tenotomy of add. Muscles (RS- Open reduction)	2
RS+ derotative osteotomy.	3
RS +tenotomy of add. muscles +derotative osteotomy	3
RS+ derotative osteotomy+Salter innominate osteotomy	1
RS+ tenotomy of add.muscles +Salter innominate osteotomy	1
RS+resectio femoris (shortening) +derotative osteotomy	5
RS+VRDO	1
Proximal Valgus osteotomy	1

VRDO (Varus Derotation Osteotomy)	2
Derotation osteotomy+Salter innominate osteotomy	2
Salter innominate osteotomy	12
Extractio OSM (there is no data on the type of the performed operation)	10

– 1, Bitola – 1, Kichevo – 1, Kochani – 1 patient.

Discussion

The papers of Sewell, Clarke N. M et al., show that the ultrasound examination is the most reliable method for describing the anatomical characteristics of the hips of the children under 3 months of age.[8,9] Screening is crucial for the early diagnosis and treatment of the developmental disorders of the hip, and it should begin in the maternity ward where clinical examination must be performed and advice for orthopedic examination must be given. AP radiography is important in diagnosing and confirming the diagnosis in children above 3 months of age; it is not necessary before the age of 3 months due to the fact that ossification nuclei of the femoral head begin to appear at the age of 4-6 months.[10] Acceptable manner of treatment of developmental dysplasia of the hip in the literature is graded from the least invasive treatment to increasing the invasiveness of the treatment.[2] Pavlik harness remains the most acceptable and the most used method in children with developmental dysplasia under 6 months of age, with a high success rate. Should the Pavlik harness fail to provide stability of the hip, the next step is closed reduction of the hip under general anesthesia and placement of abduction plaster cast with flexion in the hips with or without arthrography.[10] The safe zone of Ramsey is the range between maximal passive abduction of the hip and the angle of abduction where the femoral head becomes unstable. Immobilization must not be placed in maximal abduction, because this increases the chances of AVN of the hip.[3,11]. The plaster cast immobilization is placed in 90-100 degrees of hip flexion and controlled abduction which is less than 70 degrees.[3] If the safe zone of Ramsey is wide, the hip is considered stably repositioned, while if greater abduction and internal rotation greater than 10-15 degrees are required to keep the hip in the acetabulum, it is considered unstable repositioning.[11]

In order to increase safe zone that would allow greater abduction, an open or closed tenotomy of m. adductor longus was performed depending on the size of the adductor contracture.[11] After the successful closed reduction, the residual dysplasia of the hips, when necessary, is usually treated with Salter innominate osteotomy and, less frequently, with Pemberton osteotomy or Dega acetabuloplasty.

Varus derotation osteotomy is performed in cases of severe femoral anteversion.[12] If the closed reduction failed, then the next solution was open reduction of the hip, if necessary, with pelvic osteotomy or femoral osteotomy.[10]

The purpose of the treatment of developmental dysplasia of the hip is to keep the reduced hip in order to obtain a concentric shape of the femoral head for better congruence of the joint which will reduce the risk of early AVN which leads to early osteoarthrosis of the joint.10 The rate of osteonecrosis of the femoral head after treatment with Pavlik harness ranged from 1% to 30% in the study of Al-Essa's. S. R et al.[10]

The risk of developing osteonecrosis is high in Graf type IV hips or in patients where the dislocation was proven with an anterior-posterior view radiograph (AP). Initial treatment above 3 months of age, delay in ossification of femoral head at the beginning of the treatment, prolonged treatment accompanied by strong adductor contracture of the hip are risk factors for development of AVN of the femoral head. The rate of development of osteonecrosis of the contralateral healthy hip in cases where the dislocation is unilateral and that are treated with Pavlik harness is 2.9%.[6] According to the literature, after beginning to walk, i.e., above 2 years of age, direct open reduction of the dislocated hip should be performed.

The metacentric study of Morina C et al. shows results from 15 centers where a total of 222 cases were treated with closed reduction in the last 20 years. In 5.3% of patients the reduction was unsuccessful, 8% of the had recurrent dislocation or subluxation, and 4.7% of them had post-reduction osteochondritis. Successful open reductions of the hip were performed on 120 patients. 7% of them had recurrent dislocations and subluxations and 13% of them had post-reduction osteochondritis.[12] The study of Hayazi M Al Shehri et al. shows that the successful closed reduction in congenitally dislocated hips within the recommended age (4-15 months of age) results in improved acetabular development, i.e., formation of the acetabulum within a minimum of 12 months after the closed reduction.[13]

Screening as a method of choice is confirmed by the fact that if abandoned, the rate of late detection will increase and there will be a significantly increased expected risk of avascular necrosis of the hips and less successful results, because the surgical treatment, i.e., the open reduction of the hips will be more common.

Conclusion

By presenting the cases within a period of 10 years in this study, we can conclude that most of the cases are diagnosed later, but also that the standard treatment of closed reduction is successful even in patients above one year of age. Surgical procedure of the acetabulum and the proximal femur is used to correct residual dysplasia. Open reduction can give rise to complications such as avascular necrosis of the femoral head (AVN).

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CLINICAL SCIENCE

EVALUATION OF (1,3)-β-D-GLUCAN ASSAY IN DIAGNOSIS OF INVASIVE FUNGAL INFECTIONS WITH ASPERGILLUS

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Key words: *Aspergillus*, invasive fungal infection, 1,3-ß-D-glucan panfungal marker, BAL culture, diagnosis

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Abstract

Invasive fungal infections caused by *Aspergillus* are a significant problem in immunocompromised and critically ill patients and associated with increased morbidity and mortality. Early diagnosis of invasive aspergillosis is still a big clinical and diagnostic challenge. Conventional methods are not sensitive enough, and therefore, there is a need for rapid, more sensitive methods for early diagnosis of invasive fungal infections with *Aspergillus*. The aim of this study was to evaluate the diagnostic performance, sensitivity and specificity of serological panfungal (1,3)-β-D-glucan marker compared to conventional method for diagnosis of invasive fungal infections with *Aspergillus*. Material and methods: Specimens of 125 patients divided into 4 groups (group I - immune deficiency, group II - prolonged ICU stay, group III - chronic aspergillosis, group IV - cystic fibrosis), classified according to clinical diagnosis and EORTC/MSG criteria, were analyzed at the Institute of Microbiology and Parasitology, with conventional and serological methods, during a period of two years. Results: A total of 71 isolates of *Aspergillus* were confirmed in this study. Four isolates were recovered from bloodculture of patients with primary immune deficiency. With BAL culture, *Aspergillus* was detected in the group of chronic aspergillosis (63.33%), followed by the groups of cystic fibrosis (56.67%), primary immune deficiency (51.43%), and the group with prolonged ICU stay (43.33%). Sensitivity and specificity of BAL culture were: 64.29% and 100%, 59.09% and 100%, 54.55% and 12.5%, 100% and 54.17%, in I, II, III and IV group, respectively. In 79.1% (53/67) from positive BAL cultures in all groups, *A. fumigatus* was confirmed, of which, 32.1% (17/53) in group III, followed by group I – 26.42% (14/53) and group IV – 26.42% (14/53), and 15.1% (8/53) in group II. Other species confirmed in BAL were *A. flavus* 16.42% (11/67) and *A.terreus* 4.48% (3/67). Sensitivity and specificity of the serological panfungal (1,3)-β-D-glucan (BDG) marker were: 64.71% and 85.71%, 50% and 87.5%, 36.36% and 50%, in groups I, II and III, respectively. No positive findings of the panfungal (1,3)-β-D-glucan (BDG) marker were found in the group with cystic fibrosis. Conclusion: The results obtained in this study have demonstrated that a positive (1,3)-β-D-glucan assay highlights the value of this test as a diagnostic adjunct in the serodiagnosis of invasive fungal infections with *Aspergillus*, and along with the results from conventional mycological investigation, helped in reaching a timely antifungal treatment with a favorable clinical outcome.

КЛИНИЧКИ ИСТРАЖУВАЊА

ЕВАЛУАЦИЈА НА (1,3)-β-D-ГЛИКАН ЕСЕЈ ВО ДИЈАГНОЗА НА ИНВАЗИВНИ ИНФЕКЦИИ СО ASPERGILLUS

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Извадок

Инвазивните фунгални инфекции со *Aspergillus* претставуваат сериозен проблем кај имунокомпромитираните лица и критично болните лица, и се асоцирани со зголемен морбидитет и морталитет. Рана дијагноза на инвазивната аспергилоза е сè уште голем клинички и дијагностички предизвик. Конвенционалните методи не се доволно сензитивни, и заради тоа, се наметнува потреба за брзи и посензитивни методи за рана дијагноза на инвазивни фунгални инфекции со *Aspergillus*. Целта на оваа студија беше да се евалуира дијагностичкиот перформанс, сензитивноста и специфичноста на серолошкиот панфунгален маркер (1,3)-β-D-гликан споредено со конвенционалниот метод за дијагноза на инвазивните фунгални инфекции со *Aspergillus*. Материјал и методи: Примероци од 125 пациенти, поделени во 4 групи (група I - имун дефицит, група II - пролонгиран престој во ЕИЛ, група III - хронична аспергилоза, група IV - цистична фиброза), и класифицирани според клиничката дијагноза и EORTC/MSG критериумите, беа анализирани на Институтот за микробиологија и паразитологија, со конвенционални и серолошки методи, во тек на две-годишен период. Резултати: Вкупно 71 изолат на *Aspergillus* беа потврдени во оваа студија. Четири изолати беа докажани во хемокултура, кај пациенти со примарен имун дефицит. Со култура на БАЛ, *Aspergillus* најчесто беше детектиран во групата на хронична аспергилоза (63,33%), по што следуваа групите со цистична фиброза (56,67%), примарен имун дефицит (51,43%), и групата лица со пролонгиран престој во единиците за интензивно лекување (43,33%). Сензитивноста и специфичноста на културите на БАЛ беа: 64,29% и 100%, 59,09% и 100%, 54,55% и 12,5%, 100% и 54,17%, во I, II, III и IV група, соодветно. Во 79,1% (53/67) од позитивните култури на БАЛ во сите групи, беше докажан *A.fumigatus*, од кои, 32,1% (17/53) од група III, потоа 26,42 % (14/53) од група I и 26,42% (14/53) од група IV, како и 15,1% (8/53) од група II. Други специеси потврдени во БАЛ беа *A.flavus* 16,42% (11/67) и *A.terreus* 4,48% (3/67). Сензитивноста и специфичноста на серолошкиот панфунгален (1,3)-β-D-гликан (BDG) маркер беа: 64,71% и 85,71%, 50% и 87,5%, 36,36% и 50%, во групите I, II и III, соодветно. Не беа детектирани позитивни наоди од панфунгалниот (1,3)-β-D-гликан (BDG) маркер во групата со цистична фиброза. Заклучок: Резултатите од оваа студија покажаа дека позитивен наод на (1,3)-β-D-гликан ја истакнува вредноста на овој тест како дијагностичко надополнување во серодијагнозата на инвазивните фунгални инфекции со *Aspergillus*, и заедно со резултатите од конвенционалните миколошки испитувања, помагаат во навремена примена на антифунгална терапија, и постигнување поволен клинички исход.

Introduction

Invasive fungal infections are significant causes of morbidity and mortality, especially in immunocompromised patients undergoing steroid treatment, chemotherapy resulting in severe neutropenia, hematopoietic stem cell and solid organ transplantation.[1] AIDS and malignant diseases can also contribute to development of this opportunistic fungal infection. Aspergillosis usually affects the respiratory system and manifests as a broad-spectrum of diseases including aspergilloma, chronic pulmonary aspergillosis, allergic bronchopulmonary aspergillosis and invasive aspergillosis, which is the most aggressive and rapidly spreading form of infection to the brain, heart, liver, and kidneys, with a very high mortality rate.[2] Criteria for diagnosis of invasive aspergillosis have greatly benefited from the European Organisation for the Research and Treatment of Cancer (EORTC) and Mycoses Study Group (MSG) recommendations for defining invasive fungal infections including invasive aspergillosis.[3] To achieve a favorable prognosis of these life-threatening fungal infections, an early initiation of an antifungal therapy is necessary. It relies on a timely and accurate diagnosis, which in turn is still a big laboratory challenge, because clinical symptoms and signs as well as radiological signs are often non-specific. Histopathologic demonstration of microorganisms in tissue specimens or growth of fungal agents in culture media is still the "gold standard" method.[4] However, invasive procedures for specimen collection may be sometimes contraindicated, especially in patients with profound respiratory insufficiency. Conventional methods are time-consuming and relatively insensitive, since they are positive in less than 30% of all invasive *Aspergillus* infections, and they depend on the quality of the specimen submitted. Also, some fungal pathogens require prolonged incubation, which could further delay the mycological diagnosis.[5]

Due to all these limitations, a lot of work has been done in recent years for development of alternative nonculture-based diagnostic assays for detection of invasive fungal infections, like detection of fungal biomarkers. Serum (1,3)-β-D-glucan (BDG) is a panfungal marker which is a cell wall polysaccharide, found in many pathogenic fungi including *Aspergillus* species, that can be present early in the blood and body fluids in patients suffering from invasive fungal infections. Serum β-D-glucan concentrations show a constant rise even before manifestation of clinical signs, and then start to decrease, and eventually become negative if patients respond well to antifungal treatment.[6] Conversely, patients not responding do not show a decrease or show a continuous rise of this marker. The Fungitell test (Associates of Cape Cod) is a chromogenic kinetic test that was approved in 2003 by the U.S. Food and Drug Administration for the presumptive diagnosis of invasive fungal infections.[7] It may allow earlier diagnosis of invasive fungal infections than is otherwise possible with other conventional methods. The Fungitell BDG assay is a chromogenic, quantitative EIA based on the clotting cascade of the *Limulus* or horseshoe crab. Unlike most other standard ELISA tests, this assay is a kinetic ELISA, meaning that each well for each patient sample, which

is run in duplicate, is read, and optical density values recorded every 30 seconds over a 40-minute period. Findings from 4 different meta-analyses performed over the years have shown that in patients with a higher risk of development of invasive fungal infections, single positive β-D-glucan testing is associated with sensitivity and specificity generally ranging between 60 and 90%.[6] Other studies, performed primarily in patients with hematologic malignancies, have shown that the presence of two consecutively positive β-D-glucan results increase specificity of the assay to almost 99%, suggesting that these results may be used as a diagnostic marker for the presence of an invasive fungal infection.[8]

The aim of this study was to evaluate the diagnostic performance, sensitivity and specificity of serum (1,3)-β-D-glucan BDG marker in comparison with conventional methods (culture) for diagnosis of invasive infections with *Aspergillus* species.

Material and methods

Study design

A prospective diagnostic study was performed at the Institute of Microbiology and Parasitology, Faculty of Medicine, Skopje, Republic of Macedonia, during a 2-year period (2014-2016).

Group of patients and mycological investigations

In this study, clinical specimens (from mucosal surfaces of respiratory tract and blood cultures) from 125 patients divided into 4 groups, according to clinical diagnosis and risk factors for invasive aspergillosis, were analyzed at the Laboratory for diagnosis of fungal infections of the Institute of Microbiology and Parasitology, Faculty of Medicine, Skopje, Republic of North Macedonia. These groups included patients with primary immune deficiency, critically ill patients treated in intensive care units, patients with chronic aspergillosis and cystic fibrosis patients. Invasive fungal infection was defined according to the revised definitions by the EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study group) consensus group, with the necessary modification that (1,3)-β-D-glucan panfungal marker was not included in the microbiological criteria.[3] The specimens were investigated with conventional mycological methods, by inoculation of specimens on culture media for support of fungal growth (Sabouraud and chromogenic CALB medium (Oxoid)). Blood culture was performed with automated BacT/Alert system (*bioMerieux*, France), Gram stain and culture on Sabouraud and selective chromogenic CALB medium (Oxoid). Identification of *Aspergillus* on species level was performed with macroscopic analysis of grown mold colonies and further microscopic analysis of the reproductive elements (conidia) with lactophenol cotton blue method. Detection of (1,3)-β-D-glucan panfungal marker was made by Fungitell assay (Associates of Cape Cod).[7] A total of 5 µl of serum were briefly pretreated with 20 µl alkaline reagent solution (0.125 M KOH/0.6 M KCl) for 10 min at 37°C and then 100 µl reconstituted Fungitell reagent was added to the sample placed into triplicate wells of a 96-well microtiter plate. The reaction was incubated for 40 minutes

at 37°C and the optical density was measured at 405/490 nm with spectrophotometer. The mean rate of optical density change was determined for each well, and the BDG marker concentration was determined by comparison to a standard curve. Interpretation of BDG marker values was as follows: <60 pg/ml, negative; 60 to 79 pg/ml, indeterminate; ≥80 pg/ml, positive. The test results of the BDG marker assay were not available for the clinicians' decision on treatment (BDG results were not used for the management or classification of IFI). Proven and probable IFI were considered to be true-positive cases for analysis. Patients with possible invasive fungal infection were considered to be true-negative cases.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows. The results of our study are presented as numbers and percentages. Differences in distribution of proven, probable and possible fungal infections with *Aspergillus* were compared by Pearson Chi square test. P value less than 0.05 was considered statistically significant.

Results

Specimens from mucosal surfaces of respiratory tract and blood cultures from 125 patients were divided in 4 groups (patients with primary immune deficiencies, critically ill patients treated in intensive care units, patients with chronic aspergillosis and cystic fibrosis) according to clinical diagnosis and EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study group) criteria (Fig. 1).

Gender analysis of study patients revealed that men were more frequently distributed in I, III and IV group (60%, 60%, 53.33% respectively), whereas in group II, both genders were equally distributed. The average age of patients in all groups were: 40.8±17.7, 59.7±13.3, 64.7±6.3, and 28.9±8.5 years, respectively (Table 1).

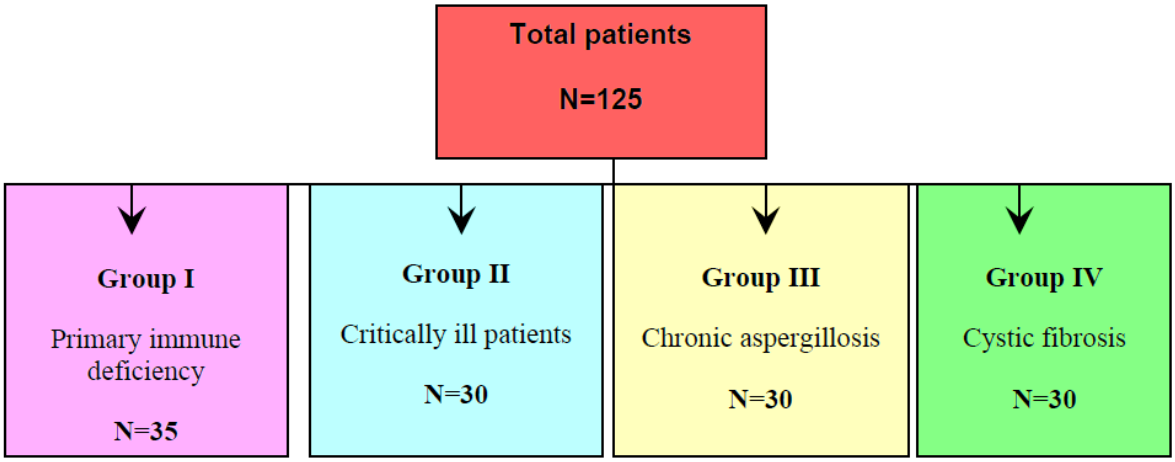

Fig. 1. Classification of patient groups according to clinical diagnosis and EORTC/MSG (European Organization for Researsh and Treatment of Cancer/Mycoses Study group) criteria

Table 1. Characteristics of patients according to gender and age

Aspergillus				
	Group I N=35	**Group II N=30**	**Group III N=30**	**Group IV N=30**
Gender	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Men 70 (56%)	21 (60%)	15 (50%)	18 (60%)	16 (53.33%)
Women 55 (44%)	14 (40%)	15 (50%)	12 (40%)	14 (46.67%)
	ap = 0.81			
Age (years) mean±SD, min-max				
	40.8±17.7 5-69	59.7±13.3 4-78	64.7±6.3 52-76	28.9±8.5 18-52

[a]p(Chi-square test)

Distribution of patients according to clinical diagnosis for proven, probable and possible fungal infection, with EORTC/MSG criteria (European Organization for Research and Treatment of Cancer/Mycoses Study group) are presented in Figure 2. According to EORTC/MSG criteria, only a small percentage of patients had proven infection with *Aspergillus*. Of these, 20% (7/35) of patients had some type of primary deficiency, and 10% (3/30) had a prolonged stay in an intensive care unit.

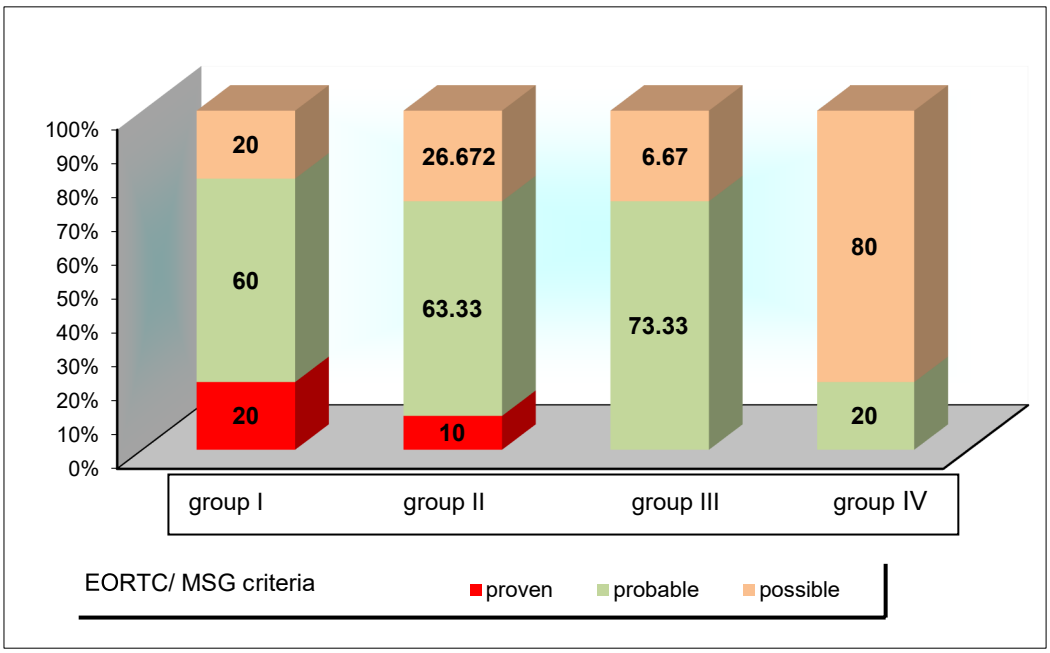

Fig. 2. Distribution of fungal infections according to EORTC/MSG criteria in all groups

Differences in distribution of proven, probable and possible fungal infection with *Aspergillus* were statistically significant between group I *versus* groups III and IV, and between group II *versus* groups III and IV (Table 2).

Table 2. Distribution of proven, probable and possible fungal infections according to EORTC/MSG criteria

Aspergillus	**Group I N=35**	**Group II N=30**	**Group III N=30**	**Group IV N=30**
Gender	**n (%)**	**n (%)**	**n (%)**	**n (%)**
proven 10 (8%)	7 (20%)	3 (10%)	0	0
probable 68 (54.4%)	21 (60%)	19 (63.33%)	22 (73.33%)	6 (20%)
possible 47 (37.6%)	7 (20%)	8 (26.67%)	8 (26.67%)	24 (80%)
	[b]p < 0.001 I vs II p=0.3 II vs III p = 0.345 III vs IV p < 0.001 I vs III p = 0.03* II vs IV p < 0.001 I vs IV p < 0.001			

[a]p (Chi-square test) [b](Fisher exact test) *p<0.05 **p<0.01

Mycological investigation of blood cultures in our patients demonstrated positivity only in 4 patients. All positive blood cultures were discovered from patients with primary immune deficiency. *A. fumigatus* was identified as an etiological agent in all positive blood cultures (Table 3).

Table 3. Positive blood cultures in four groups of patients

Aspergillus	**Group I N=35**	**Group II N=30**	**Group III N=30**	**Group IV N=30**
Blood cultures	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Negative 121 (96.8%)	31 (88.57%)	30 (100%)	30 (100%)	30 (100%)
Blood cultures – species				
***A. fumigatus* n=4**	4	0	0	0

Differences in positivity of blood cultures were insufficient for analysis of the statistical significance (p=0.46).

With cultural analysis of bronchoalveolar lavage (BAL), presence of *Aspergillus* was most frequently found in the group of chronic aspergillosis (63.33%), followed by the CF group (56.67%), the group with primary immune deficiency (51.43%), and 43.33% of patients hospitalized in ICU.

Regarding the presence of fungi in positive BAL specimens, the most frequently identified species (79%) was *A. fumigatus* (53/67). Thirty-two percent of the isolates (17/53) of *A. fumigatus* originated from specimens of patients with chronic aspergillosis, and 26% (14/53) were identified in specimens from patients with primary deficiency and cystic fibrosis (Table 4).

Table 4. Bronchoalveolar lavage (BAL) culture and identified fungal species

	Group I N=35	Group II N=30	Group III N=30	Group IV N=30
Blood cultures (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
negative 58 (46.4%)	17 (48.57%)	17 (56.67%)	11 (36.67%)	13 (43.33%)
positive 67 (53.6%)	18 (51.43%)	13 (43.33%)	19 (63.33%)	17 (56.67%)
Chi-square: 2.59 p = 0.46				
Identified mold species in BAL				
A. fumigatus n=53	14	8	17	14
A. flavus n=11	2	4	2	3
A. terreus n=3	2	1	0	0

[a]p(Chi-square test)

Investigation of presence of panfungal marker (1,3)-beta-D-glucan (BDG) in serum was performed in parallel with blood culture and BAL culture. Positive findings of panfungal marker, in parallel with positive blood culture and BAL culture, were detected in 19 (54.29%) patients in group I, and 12 patients (40%) in both II and III group (Table 5). The differences in the distribution of positive and negative specimens were confirmed as statistically significant between the group with primary immune deficiency and cystic fibrosis group (p=0.0000016).

Table 5. Detection of BDG marker in serum

	Group I N=35	Group II N=30	Group III N=30	Group IV N=30
BDG	**n (%)**	**n (%)**	**n (%)**	**n (%)**
negative 82 (65.6%)	16 (45.71%)	18 (60%)	18 (60%)	30 (100%)
positive 43 (34.4%)	19 (54.29%)	12 (40%)	12 (40%)	0
I vs II vs III [a]p=0.25 I vs IV [a]p=0.0000016**				

[a]p (Chi-square test) [b](Fisher exact test) **p<0.01

Results of the descriptive statistics for the concentration of the BDG marker are presented in Table 6. Along with blood culture and BAL culture, a statistically significantly lower concentration of panfungal BDG marker was measured in the group of cystic fibrosis compared to all other groups (p<0.0001). The average concentration of BDG panfungal marker was highest in the first group (93.17±55.3 pg/ml), followed by II, III and IV group (70.1±50.0, 68.6±48.1, 4.2±1.1 pg/ml respectively). The median value of con-

centration of BDG panfungal marker in all four groups was 112 pg/ml (range 36-133), 44 pg/ml (range 33–96), 42.5 pg/ml (range 34–96), and 4 pg/ml (range 4–5), respectively.

Table 6. Descriptive statistics for the concentration of the BDG marker in serum

	Aspergillus **BDG concentration (pg/ml)**			
	mean ± SD	min-max	median (IQR)	p-value
BDG				
group I	93.17±55.3	32–254	112 (36–133)	H=7.34 [d]p<0.0001
group II	70.1±50,0	17–211	44 (33–96)	I vs IV [c]p<0.0001
group III	68.6±48.1	29–199	42.5 (34–96)	II vs IV [c]p<0.0001
group IV	4.2±1.1	1–6	4 (4–5)	III vs IV [c]p<0.0001

[c]p (Mann0Whitney U test) [d]p (Kruskal-Wallis test)

Comparative diagnostic performances of conventional (blood culture and BAL culture) and panfungal BDG marker for diagnosis of invasive infections with *Aspergillus* in the group with immune deficiency are presented in Table 7.

Table 7. Diagnostic performances of conventional (blood culture and BAL culture) and serological methods in the group with immune deficiency

Method	Se(%)	Sp(%)	PPV(%)	NPV(%)	LR+(%)	LR-(%)
Blood culture	14.29	100	100	22.58	/	0.86
BAL culture	64.29	100	100	41.18	/	0.36
BDG in serum	64.71	85.71	94.74	37.5	4.5	0.42

Comparative diagnostic performances of conventional (BAL culture) and serological methods for diagnosis of invasive infections with *Aspergillus* in the group with prolonged ICU stay in critically ill patients are presented in Table 8.

Table 8. Diagnostic performances of conventional (BAL culture) and serological methods in the group with prolonged ICU stay

Method	Se(%)	Sp(%)	PPV(%)	NPV(%)	LR+(%)	LR-(%)
BAL culture	59.09	100	100	47.06	/	0.41
BDG in serum	50	87.5	91.67	38.89	4	0.57

Comparative diagnostic performances of conventional (BAL culture) and serological methods for diagnosis of invasive infections with *Aspergillus* in the group with chronic aspergillosis are presented in Table 9.

Table 9. Diagnostic performances of conventional (BAL culture) and serological methods in the group with chronic aspergillosis

Method	Se(%)	Sp(%)	PPV(%)	NPV(%)	LR+(%)	LR-(%)
BAL culture	54.55	12.5	63.16	9.09	0.62	3.64
BDG in serum	36.36	50	66.67	22.22	0.73	1.27

In the group with cystic fibrosis, only BAL culture was analyzed, and this method had the following diagnostic performances: sensitivity 100%, specificity 54.17%, positive predictive value 35.29%, negative predictive value 100%, likelihood ratio for positive finding was 2.18%, likelihood ratio for negative finding was 0.

Discussion

Invasive fungal infections present an increasing global burden in immunocompromised and critically ill patients. Early mycological diagnosis with adequate detection and identification of the etiological agent and antifungal susceptibility profile is critical for favorable clinical outcome.[1]

In our study, we detected only 4 positive blood cultures caused by *A. fumigatus*, and all of them were from patients with primary immune deficiencies. Blood culture, as a diagnostic test for invasive aspergillosis, with aspergillemia, according to EORTC/MSG classification, had 14.29% sensitivity and specificity 100%. The significance of positive blood culture with *Aspergillus* species varies depending on the patient population. In the study of Kontoyiannis et al, positive blood cultures with *Aspergillus* species represented pseudofungemia in all 12 patients with solid tumors, whereas proven or probable aspergillosis was registered in 12 of 24 patients with hematological malignancies.[9] In another study, which analyzed patients with pulmonary aspergillosis, aspergillemia was registered in 10.1% of patients of 89 patients examined.[10] Transplantation of hematopoetic stem cells was the main predisposing condition for the development of invasive aspergillosis.[11] According to literature, there are no studies investigating the significance or importance of positive blood cultures with *Aspergillus* in this high-risk group of patients. In a retrospective study of Simoneau et al., of a total of 525 patients with transplantation of hematopoetic stem cells, 377 received allogenic, and 148 autologous transplantations. Aspergillemia was registered 23 times in 21 patients. According to Simoneau, positive blood cultures with *Aspergillus* are very rare and usually clinically insignificant, despite the capability of this fungus to cause invasion of vascular compartments in immunocompromised patients. *Aspergillus* fungemia in this study was represented with 17% of all fungemia cases (23/131) during a 23-year-follow-up of all fungemia cases in this medical center.[12] In a similar medical center, during a 17-year follow-up, fungemia with *Aspergillus* was registered in 4% of all cases with fungemia. Still, in this study, non-transplant patients with hematological malignancies were also included.[10] In the study of Simoneau and collaborators, only one of 19 cases of fungemia with *Aspergillus* was confirmed as true fungemia. All cases of aspergillemia were detected during a period of 11 years, with a system based on lysis–centrifugation.[12] Out of 23,000 blood cultures analyzed, only 0.2% demonstrated positivity with growth of *Aspergillus*. Despite the fact that all blood cultures were investigated with a biosafety cabinet, still, contamination with conidia of filamentous fungi couldn't have been prevented. During recent years, many studies have analyzed true aspergillemia with automated systems, and none of these documented aspergillemia.[12,13] In the study of Simoneau,

experimental inoculation of blood culture bottles was performed, with BacT/Alert system, and growth with *Aspergillus* was confirmed, which additionally adds to the capability of the system to support growth of filamentous fungi.[12] According to Lopes-Bezerra, vascular endothelial cells exposed in vitro to kill hyphae of Aspergillu were continuously destroyed.[14] Probably, viability of endocytosed hyphae of *Aspergillus* species is deeply compromised, which contributes to small chances for recovery of fungi by blood culture. Although A. fumigatus can grow in blood culture bottles, still, blood cultures from patients with invasive aspergillosis are usually negative, and reasons for this are still unclear.[15] Girmenia et al. presented a small number of positive blood cultures (10%) in patients with invasive aspergillosis, which contributed to the general perception of a very low sensitivity of blood cultures for diagnosis of invasive aspergillosis.[10] Most scientists agree that positive blood cultures with *Aspergillus* are very rare, even in high-risk patients, like transplant patients with hematopoetic stem cells, hence most positive blood cultures are actually pseudofungemia, and are not connected with real invasive aspergillosis. Also, some studies suggest that DNA of *Aspergillus* is free in the blood, so most likely that is the reason for the low sensitivity of blood cultures for diagnosis of invasive aspergillosis.[16] As previously discuissed, clinical and radiological presentation, as well as the number of positive blood cultures and the system of blood cultures used, should be taken into consideration when analyzing the significance of positive blood cultures with *Aspergillus*. Ussully only one positive blood culture with the automated system means pseudofungemia.

In our study, the culture of BAL specimens demonstrated growth of *Aspergillus* most frequently in the group of chronic aspergillosis (63.33%), followed by 56.67% of patients with cystic fibrosis, 51.43% of patients with primary immune deficiency, and 43.33% of patients with prolonged ICU stay. Sensitivity and specificity of BAL culture was: 64.29% and 100%, 59.09% and 100%, 54.55% and 12.5%, 100% and 54.17%, in I, II, III and IV group respectively. In the study of Tashiro *et al*., 165 isolates of *Aspergillus* species were detected in culture of respiratory tract of 139 patients. Of these, 62 (45%) were colonized with *Aspergillus*, but didn't demonstrate clinical symptoms of aspergillosis, and the other 77 patients (55%) had some type of pulmonary aspergillosis classified as chronic (48%), aspergilloma (29%), invasive (13%), or ABPA (10%). In the study of Tashiro, patients with chronic necrotizing aspergillosis or aspergillom, most frequently had COPD, tuberculosis or cancer of the lungs. Some of them had received systemic immunosupresive drugs for a prolonged period, or had some chronic diseases like diabetes, cancer or hepatic chirrosis.[17] In patients with invasive aspergillosis, the main predisposing factor had been hematological malignancy, and they were subsequently treated with immunosupresive drugs. Patients with ABPA frequently demonstrated signs of bronchial asthma (88%) or other atopic diseases (63%). In our study regarding the distribution of species from positive BAL cultures, in all four groups, *A. fumigatus* was identified in 79.1% (53/67), and from these, 32.1% (17/53) in patients with

chronic aspergillosis. *A. fumigatus* was also identified in an equal number of patients in I group - 26.42% (14/53) and IV group - 26.42% (14/53), and 15.1% (8/53) in the group of critically ill patients. Other species confirmed in our study, in positive BAL cultures, were *A. flavus* (16.42% (11/67) and *A. terreus* 4.48% (3/67)). Of these, 36.4% (4/11) were due to isolates of *A. flavus*, confirmed in patients treated in ICU, and 27.3% in the group with cystic fibrosis. Two isolates of *A. terreus*, (66.7%) were confirmed in patients with AIDS, and one isolate in a patient with metastatic tumor of the brain, treated in ICU. Still, in our study, *A. fumigatus* was a dominant fungus in AIDS patients (4/6), who had their CD4 numbers below 50/mm3 and 10/mm3. Similar data were presented in the study of Meyohas *et al.*, who confirmed CD4 numbers below 50/mm3 in their patents with positive BAL culture.[18] In the study of Lortholary, 28 out of 33 patients (84.8%) had a positive BAL culture for *Aspergillus*.[19] In the study of Menninkx-Kersten, distribution of *Aspergillus* among 165 confirmed isolates in BAL cultures, demonstrated presence of 41% of *A. fumigatus* and 32% A. niger, but also A. versicolor (12%), A. terreus (6%), *A. flavus* (5%), A. nidulans (2%), A sydowii (1%) and unidentified *Aspergillus* species (0.6%).[20] In this study, A. fumigatus was the predominant species in patients with invasive aspergillosis (82%), aspergilloma (68%), and chronic aspergillosis (54%), while A. niger was on the second place. Zarrinfar et al. demonstrated presence of A. flavus, A. niger and one case with mixed infection with two species (A. flavus/A. niger) in positive (23 %) BAL cultures.[21] In contrast to our study, where A. fumigatus was predominant species, the most frequent agent in the study of Zarrinfar was A. flavus.[21] In our study, we did not isolate A. niger in BAL cultures of our patients. Although *A. fumigatus* is considered as the most pathogenic species, still this species can frequently be a colonizer of the respiratory tract without any clinical manifestation of invasive aspergillosis, which was also registered in our study, especially in those patients categorized as possible infections according to EORTC/MSG criteria. Diagnostic value of *Aspergillus* identification in respiratory specimens is sometimes questionable, since it is very difficult for the clinican to differentiate between colonization and infection. According to Ader, discovery of the same species of *Aspergillus* in more specimens during an antibiotic treatment, without favorable pharmacological response, in patients with a high risk, should raise a concern for the development of invasive aspergilosis.[22] Therefore, isolation of *Aspergillus* from respiratory tract specimens in critically ill patients with high risk and clinical signs of pneumonia requires a faster decision for a prompt initiation of antifungal treatment.[23,24] Although in some cases colonization is transient in the respiratory tract, still it could present as a serious warning sign of an infection with *Aspergillus*.[25] In 63.33% of our patients with chronic aspergillosis, BAL culture confirmed presence of *Aspergillus*, and all were due to *A. fumigatus*. Similar data were found in the study of Tashiro, where *A. fumigatus* was the predominant species (54%), followed by *A. niger* (24%), *A. terreus* (10%), *A. versicolor* (6%), *A. flavus* (4%), and A. *nidulans* (2%) (17). Perfect *et al.* also confirmed *A. fumigatus* (69%) as the

most frequent isolate in positive BAL cultures, followed by *A. niger* (13%), *A. flavus* (2%), and other species (5%) among their patients[26]. ABPA is an allergic form of aspergillosis due to hypersensitivity to *Aspergillus*, where the predominant cause is *A. fumigatus*.[27] In our study, all isolates of CF specimens were positive for *A. fumigatus* - 82.4% (14/17), and only 10% due to *A. flavus* (17.6%).

The serological diagnosis of infection with *Aspergillus* species was performed with detection of the panfungal (1,3)-beta-D-glucan (BDG) marker in patients' sera. The concentration of BDG marker in all four groups was 112 pg/ml (range 36–133), 44 pg/ml (range 33–96), 42.5 pg/ml (range 34–96), and 4 pg/ml (range 4–5), respectively. BDG panfungal marker in serum from immune deficiency patients demonstrated sensitivity of 64.71% and specificity 85.71%. In contrast to our results, with median values of this marker 112 pg/ml, Lahmer et *al*. demonstrated much higher concentrations of BDG marker in 22 out of 30 critically ill patients with hematological malignancies (median value 306 pg/ml).[28] According to values of BDG marker and mycological evidence, 10 patients were classified as probable invasive aspergillosis (34%) and 12 patients (40%) as possible aspergillosis. The overall sensitivity of the assay was 90% and specificity 85% in patients with invasive aspergillosis, in contrast to our results, where we demonstrated a lower sensitivity (64.71%) and specificity (85.71%).

The panfungal BDG marker in sera of critically ill patients in our study showed lower sensitivity compared to the group with primary immune deficiency (50%), and specificity was 87.5%. Similar results were obtained by Cai *et al*., who demonstrated lower sensitivity of BDG marker in their study, with sensitivity of 48.1% and specificity of 78.8%.[29] In the study of Lahmer *et al*., 49 immunosupressed patients with respiratory insufficiency and treated in ICU were analyzed. Thirteen of these patients (26%) had probable invasive aspergillosis. The BDG marker assay in these patients demonstrated much higher concentrations compared to patients without probable invasive aspergillosis (375 [103-1000 pg/mL; P<.001] in contrast to 64 [30-105 pg/mL; P<.001]).[30] Data from literature on BDG marker concentrations in serum in critically ill patients treated in ICU are very few and insufficient, since they show that serum concentrations of BDG marker do not always correlate with invasive aspergillosis and are not specific (if cut-off is 20 pg/mL).[31]

BDG in serum in the group with chronic aspergillosis showed sensitivity of 36.36% and specificity of 50%. In the study of Kami *et al*. 10/16 patients with proven aspergillosis, 8/14 with probable aspergillosis, and 44/185 control patients demonstrated positive findings with BDG panfungal marker in serum. Three of eight patients with localized invasive aspergillosis, and 7/8 patients with disseminated aspergillosis were positive for the BDG panfungal marker. Sensitivity and specificity of the panfungal BDG assay were 63% and 76%, respectively. Sensitivity was 88% in patients with disseminated aspergillosis, but only 38% in those patients with localized invasive aspergillosis.[32] Similar results were obtained in our study, with sensitivity of 36.36% and specificity of 50%, in patients with localized invasive aspergillosis. Sensitivity was

lower in patients with localized aspergillosis compared to patients with disseminated infections, and there was a statistically significant difference (p=0.0406). In another study, 29/178 patients with proven invasive aspergillosis, 33/210 probable cases of aspergillosis and 117/1877 specimens from patients without invasive aspergillosis were positive for BDG marker. Three of 99 specimens from patients with localized invasive aspergillosis and 26 of 79 specimens from patients with disseminated invasive aspergillosis were positive for BDG marker. In this analysis, sensitivity and specificity of the BDG assay was 16% and 94%, respectively. Sensitivity was 33% in patients with disseminated aspergillosis, but only 3% in patients with localized infection. Lower sensitivity of the assay was registered among patients with localized infection with *Aspergillus* compared to those with invasive form. This difference was statistically significant (p<0.0001).[32] In the group of cystic fibrosis, no elevated values of the panfungal marker was registered. Theel *et al*., evaluated the performance of the BDG assay in serum, for identification of invasive fungal infections in immunocompromised patients with proven, probable and possible aspergillosis according to EORTC/MSG criteria.[33] Among 109 patients, the BDG assay demonstrated a low positive predictive value for serological diagnosis of invasive fungal infections with serum analysis of BDG marker (26.7%). Still, the negative predictive value of the assay was much higher (84.8%). Mutschlechner *et al*. evaluated the BDG assay with sera obtained from non-selected transplant patients with solid organs suffering from proven and probable aspergilosis according to EORTC/MSG criteria. In 109 sera from 135 patients with proven, probable aspergillosis or without evidence of invasive aspergillosis, with cut-off of 100 pg/mL, sensitivity, specificity, positive and negative predictive value of the BDG assay were 79.2%, 81.8%, 69.2%, and 83.1%, respectively.34 Ahmad *et al*. evaluated diagnostic value of the BDG marker in immunocompromised mice, with intravenous injected conidia of *A. terreus*. The culture of lung specimens showed growth of *A. terreus*. Positivity of the BDG assay in serum was 43%.[35]

Conclusions

The results of this study have indicated that no single method could provide definite etiological diagnosis of invasive fungal infection caused by *Aspergillus*. When using a conventional method, it is neccessery to provide more specimens from each patient, in frequent time intervals, and cautiously interpret the results obtained, since colonisation with fungi without clinical signs of infection is possible. Still, clinicians should be aware that these methods are time-consuming, with low sensitivity, and depend on the quality of the specimen submitted.

Analysis of the serological panfungal (1,3)-beta-D-glucan marker has demonstrated that this assay could be an additional useful diagnostic tool for screening of invasive fungal infections, but results should be interpreted alongside other clinical and laboratory findings.

In conclusion, implementation and analysis of different microbiological methods, as well as appropriate interpretation of results, in collabora-

tion with clinicians, is the most important aspect towards accurate and precise etiological diagnosis of invasive aspergillosis and earlier start of antifungal treatment in order to achieve favorable clinical outcome.

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ORAL HEALTH

EVALUATION OF THE ORAL HEALTH STATUS IN GERIATRIC PATIENTS

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Abstract

The geriatric population in R. Macedonia presents a specific group that needs continuous evaluation of their oral health. According to WHO data in 2010, 12 % of the population was aged 65+ years in Macedonia. Aging is the process with different specific changes in all systems and organs, including the orofacial system. The most common conditions associated with age in the geriatric population are teeth loss, parodontopathy, precancerous lesions and oral carcinomas, xerostomia, resorption of the residual alveolar ridge, and overall dysfunction of the orofacial system. There is a great influence of the performed prosthodontic therapy in geriatric patients on the overall and general health. The aim of this study was to evaluate the condition of the soft tissues in geriatric patients, especially in patients with prosthodontic treatments, their oral health, and the influence of oral health on life quality. Material and methods: Observational cross-sectional study was conducted in geriatric patients and Geriatric Oral Health Assessment Index (GOHAI) was used for self-assessment of their oral health and the impact of oral conditions and performed dental treatment on quality of life. Results: Participants witha mean age of 72.88 years reported several general and systemic diseases, and the main risk factors for their oral mucosal changes were smoking and drinking alcohol. Total anodontia was observed in 37.5% of respondents and partial anodontia in 62.5%. The average period of wearing dentures was 7.8 years. The total scoreof the quality of life and oral health of the respondents varied in the interval 1.93 ± 0.65, and the average value in the subjects with prosthetic constructions for p> 0.05 (p = 0.19) was slightly higher in relation to the subjects without any prosthodontic device. Conclusion: GOHAI-12 score in the study had a low value, less than 50 indicated that the respondents were in poor oral health. According to the results of the self-assessment, there was a weak to moderate perception of oral health. An integrated approach is needed to achieve a critical positive level of general and oral health in geriatric patients.

ОРАЛНО ЗДРАВЈЕ

ПРОЦЕНКА НА ОРАЛНОТО ЗДРАВЈЕ КАЈ ГЕРИЈАТРИСКИ ПАЦИЕНТИ

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Извадок

Геријатриската популација во Македонија претставува специфична група која има потреба од континуирана евалуација на нивното орално здравје. Според податоците на СЗО во 2010 година, 12 % од населението во Македонија било на возраст 65+ години. Стареењето е процес со различни специфични промени во сите системи и органи, вклучувајќи го и орофацијалниот систем. Најчестите состојби поврзани со возраста кај геријатриската популација се губење на забите, пародонтопатија, преканцерозни лезии и орални карциноми, ксеростомија, ресорпција на резидуалниот алвеоларен гребен и целокупна дисфункција на орофацијалниот систем. Големо е влијанието на извршената протетичка терапија кај геријатриските пациенти врз нивното целокупно и општо здравје. Целта на оваа студија беше да се процени состојбата на меките ткива кај геријатриските пациенти, особено кај пациентите со протетички третмани, нивното орално здравје и влијанието на оралното здравје врз квалитетот на животот. Материјал и методи: Спроведовме опсервациона студија на пресек кај геријатриските пациенти, а геријатрискиот индекс за проценка на оралното здравје (GOHAI) беше употребен за да се изврши евалуација на нивното орално здравје и влијанието на оралните состојби и извршениот дентален третман врз квалитетот на животот. Резултати: Испитаниците со просечна возраст од 72,88 години пријавиле повеќе општи и системски заболувања, а главните фактори на ризик за промените на оралната мукоза биле пушењето и пиењето алкохол. Вкупна анодонција е забележана кај 37,5% од испитаниците и делумна анодонција кај 62,5%. Просечниот период на носење протези изнесуваше 7,8 години. Вкупната оценка за квалитетот на животот и оралното здравје на испитаниците вариираше во интервалот 1,93 ± 0,65, а просечната вредност кај субјектите со протетички конструкции за p> 0,05 (p = 0,19) беше нешто повисока во однос на субјектите без било каква протетичка изработка. Заклучок: Резултатот на GOHAI-12 во студијата имаше ниска вредност, помалку од 50 што покажа дека испитаниците беа со слабо орално здравје. Според резултатите од самооценувањето, имаше слаба до умерена перцепција за нивното оралното здравје. Потребен е интегриран пристап за да се постигне критично позитивно ниво на општото и оралното здравје кај геријатриските пациенти.

Introduction

Aging of the population is a natural process and reality, both in developed and underdeveloped countries in the world. According to Eurostat in 2008 in Europe over 20% of the population was old. The World Health Organization (WHO) in 2010 for the first time established a database on oral health in 163 of 193 registered countries. The data from the last census in 2002 in the Republic of Macedonia, showed that the geriatric population from 65 to 85 years was 214,915, of which 96,752 were men and 118,163 women.According to the WHO data in 2010, 12% of the population was over 65 years oldin Macedonia[1].The data for the capital city Skopje indicated 72,968 people at this age, of which 50,428 men and 22,540 women[2].

The geriatric population in the Republic of Macedonia is a specific group that needs continuous evaluation of their oral health. There is not much data on the state of oral health in the geriatric population in our country, and the cross-sectional study that covered 8 rural and urban areas (Skopje, Vardar, Eastern, Northeastern, Southeastern, Southwestern, Pelagonia, and Polog region)conducted in 2015/2016on a representative sample of432people (age>65 years) showed a high prevalence of anodontia of 45.1%, poor oral hygiene, and even 60-80% of respondents needed some urgent prosthetic treatment[3].

Aging is a process with different and specific changes in all systems and organs, and it affects the human bodyincluding the orofacial system too. In the elderly population, the number of remaining teeth is reduced, and their condition is changed. The changes of the teeth occur physiologically and gradually over the years, and are manifested at all layers of enamel, dentin, pulp, and cement. Oral soft and hard tissues are also affected by the aging process. These changes in the mouth are not pathological, and they are manifested on a macro and microscopic level[4].

The most common conditions associated with aging are tooth loss, periodontitis, precancerous lesions, and oral cancers, xerostomia, resorption of the residual alveolar ridge, and complete dysfunction of the orofacial system[5]. Oral hygiene habits are also age-dependent, and oral hygiene maintenance is often irregular or not performed, and is a result of impaired vision and reduced manual and cognitive capacity in the elderly[6].In this population, it is very important to discover all those factors that lead to the appearance and development of leukoplakia and other precancerous lesions as early as possible[7]. Precancerous lesions and oral cancers are much more common in the elderly than in the younger population, and screening tests are an important tool for asymptomatic patients in everyday practice[8]. The effectiveness of screening tests is evaluated according to the diagnostic value in terms of their sensitivity, specificity, and the number of cases detected with them[9,10].

Poor and inadequate prosthetic treatment in geriatric patients does not provide good masticatory function, and the masticatory forces in these patients can be reduced by up to 60%[11]. Therefore, careful planning of prosthetic treatment, improve-

ment of oral hygiene, and proper diet are very important factors for proper assessment of the quality of life of the geriatric population related to oral health[12].

The aim of this study was to assess the condition of oral status in geriatric patients with and without prosthetic devices, their general and dental health, and the impact of oral health on quality of life.

Material and methods

The data for the paper was obtained by clinical and epidemiological examination, observational cross-sectional study conducted in the geriatric population - patients over 65 years of PHI UDCC "St. Panteleimon", Skopje (Picture 1). Eighty respondents who were included in the study signed an informed consent form. The examination was approved by the Ethics Committe for examination at the Faculty of Dentistry, UKIM in Skopje.

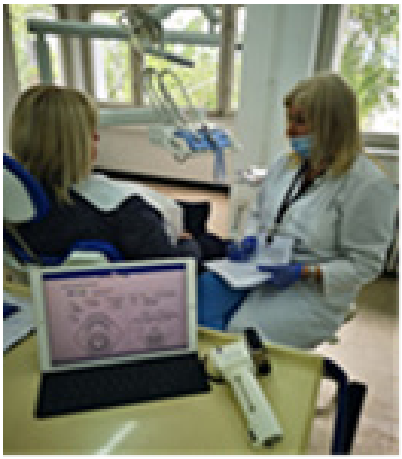

Figure 1. Epidemiological survey and clinical examination

Respondents were divided into 2 groups according to the presence or absence of prosthetic construction in the mouth: 40 respondents at the Clinic for dental prosthetics with prosthetic constructions and 40 respondents without prosthetic constructions.

All participants completed a questionnaire with anamnestic data on their general health status - medical history and oral health status - dental history, as well as data from the analysis of risk factors and oral hygiene, and completed a GOHAI - questionnaire (Global / General Oral Health Assessment Index).The GOHAI questionnaire for self-assessment of oral health and the impact of oral conditions on quality of life consists of 12 questions such as functional limitation, aesthetic dissatisfaction, discomfort during chewing, avoidance of certain types of food, avoidance of social contacts, and more. The questionnaire covers the problems of the elderly in three dimensions: physical functioning such as eating, speaking, and swallowing; mental functioning such as oral health concerns, dissatisfaction with appearance and avoidance of social contacts; pain and discomfort, use of pain medication or discomfort in the mouth.The questions are written positively or negatively, to stimulate the respondents to give their assessment of their oral health. The answers are evaluated with number 1-5 where 1 = never, 2 = rarely, 3 = sometimes, 4 = often and 5 = always. The overall score on the scale is the sum of all the values for each question, and the low value indicates the presence of an oral health problem. A higher GOHAI score indicates better oral health status. The values also show three levels of subjective perception of respondent's oral health: poor, moderate, and good perception. At the Clinic for prosthodontics, a clinical examination (ex-

tra and intraoral) was performed to evaluate the oral condition, the presence of mucosal changes, dental and prosthetic status[13-16].

Results

The socio-demographic characteristics of respondents are an important indicator with high significance in epidemiological research (Table 1). The mean age of our respondents was72.88 years, most of them32.5%, were aged 75-79 years and 1.25%at least were over 85 years. Gender distribution showed a higher presence of female respondents (57.5%) - compared to male respondents (42.5%). According to the place of residence, most of them originate from urban environments 82.5%, 16.25% from the peri-urban environment, and the smallest number live in rural areas (1.25%). Only 20% of our geriatric patients had completed universityeducation, most of them had secondary education (57.5%), while persons without education or completed primary education were 22.5%.

Table 1. Socio-demographic characteristics

RISK FACTORS		PHI UDCC
numberpercent		
GENDER		
male	34	42,5%
female	46	57,5%
AGE/years		
65-69	24	30%
70-74	25	31,25%
75-79	26	32,5%
80-84	4	5%
85-90	1	1,25%
Over 90	/	/
language		
Macedonian	72	90%
Albanian	3	3,75%
other	5	6,25%
education		
without	/	/
4 grade	/	/
primary	18	22,5%
secondary	46	57,5%
university	16	20%

Respondents also had several general and systemic diseases, mostly cardiovascular diseases such as hypertension (47.5%), rheumatic cardiomyopathy and angina pectoris (15%), hypotension (12.5%), and arrhythmias (7.5%). Prevalence of the eye diseases and cataracts was registered in 12.5% and reduced vision in 22.5%of respondents. Diseases of the gastric mucosa and ulcer were present in 20%, 20%had diseases of the bones and joints, and 12.5% of female patients were diagnosed with osteoporosis, for which they received therapy with bis-phosphonates. Of the endocrine diseases, the most common were diabetes mellitus (25%) for which the patients most often used therapy with Glucophage tablets or insulin ampoulec, and 12.5% of patients suffered from thyroid disease.

Risk factors for oral disease are hereditary predisposition and conditions or risks that depend on lifestyle and some behaviors (smoking, excessive alcohol consumption, drug use, tattooing and piercing, and HPV-16 virus infection).

Data were analyzed and the results obtained are displayed in Table 2. Respondents did not provide information that any of them used illegal substances, got a tattoo, or had a piercing. Risk factors were smoking and alcoholconsumption, and there were no data on HPV infection. Forty-five percents smoke or smoked, of which 61.1% werw men and 38.8%women. On average, everyone smoked 1-2 packs a day, and 40% stopped more than three years ago, or about 10 years ago. Regarding alcohol as a risk factor, 47.5% drank alcoholic beverages 6-11/week, and 5% drank 1-5 drinks/week, most of the respondents still drink some beer or brandy when they have the opportunity, and only 20% gave data that they no longer consume alcoholic beverages.

Table 2. Prevalence and distribution of risk factors

SMOKING male female	36(45%) 22(61,1%) 14(38,8%)
HOW MANY CIGARETTES? HOW LONG? WHEN DID YOU QUIT?	1-2 boxes 20 years Quit more than 3 years ago
ALCOHOL / AVERAGE AMOUNT OF ALCOHOL	38(47,5%) 6-11 drinks/week
ABUSE OF PROHIBITED SUBSTANCES	no
TATTOOS / PIERCINGS	no
INFECTION / HPV VIRUS	no

Most of the respondents did not know the exact reasons for the extraction of the largest number of their teeth, so fractures, a large dental caries process, and periodontitis were most often mentioned. Total anodontia or no teeth in the upper and lower jaw were observed in 37.5% of patients, while partial anodontia had 62.5%. More than 53.33% of patients with complete anodontiawere women. Of the patients with partial anodontia, 72% were females and 28% were males. The average age of patients with total anodontiawas 72.63 ranging from 65 to 80 years. The average age of patients with partial anodontiawas 72.66 ranging from 65to 80 years.

Regarding the number of remaining teeth as an important indicator of the oral healthstate, the average number of remaining teeth in the upper and lower jaw in patients was 14.5 ranging between 4and 23 teeth. The most common cause of tooth extraction was loosening or periodontitis, followed by large carious lesions and fractures of the teeth. The periodontal status of the patinets with partial edentulousness was noted by recording the presence/absence of gingival bleeding, the presence/absence of periodontal pocket, and the lost attachment from 0-3mm to 12mm. Inflammation and gingival bleeding, at least one periodontal pocket 4-5 mm deep and a lost 0-3mm attachment to at least one tooth were observed in all patients with residual teeth.

Prosthodontic constructions present in the mouth are total prosthesis, partial prosthesis, skeletal prosthesis, crowns, bridge, and combined prosthetic rehabilitation (bridge/prosthesis). Of all respondents 93.33% hadtwo total prostheses, 6.66% had one total prosthesis in the upper jaw and partial edentulousness with lower partial acrylic prosthesis and in 3.33% prosthetic rehabilitation was performed in combination with a lower total prosthesis, and partial edentulousness in the upper jaw with a visceral skeletal prosthesis (Table 3).

Table 3. Prosthetic rehabilitation

PROSTHETIC REHABILITATION	number	%
2 total dentures	28	35%
1 total denture	/	/
Total/partial denture	2	2,5%
Partial/partial denture	10	12,5%
Skeletal denture	6	7,5%
Bridges	4	5%
Bridge/Partial denture	18	22,5%
Bridge/Total denture	2	2,5%
Upper total denture/bridge/lower partial denture	4	5%
Bridge/partial skeletal denture/silicone denture	5+1	7,5%
Total	**80**	**100%**

Patients had a total of 60 total acrylic prostheses and 26 partial acrylic prostheses. The average wearing dentures time was 7.8 years ranging in an interval of 3-20 years (Figure No. 2).

Figure 2. Total prostheses

Calculation and results of the questionnaire for the GOHAI index

The GOHAI Questionnaire consists of 12 items/questions: T1(How often do you limit the amount of food you eat because of problems with your teeth or dentures?); T2(How often do you have problems with biting or chewing any kind of food (solid meat or apples)?); T3(Do you have difficulty swallowing?); T4 (How often have your teeth or dentures prevented you to speakthe way you wanted?); T5 (How often you were able to eat without feeling discomfort?); T6(How often have you avoided contact with people because of the condition of your teeth or dentures?); T7(How satisfied are you with the look of your teeth, gums or dentures?); T8(How often have you used medication to relieve pain or discomfort from around your mouth?); T9(How often have you been concerned about the condition of your teeth, gums or dentures?); T10(How often do you feel nervous or aware of problems with your teeth, gums or dentures?); T11(How often did you feel uncomfortable eating in front of people because of problems with your teeth or dentures?); T12(How often were your teeth or gums sensitive to heat, cold or sweets?).

Responses to the questions are scored according to the Likert scale and a GOHAI score is obtained, according to which the oral health is divided into three categories: high - good oral health 57-60; moderate - secondary oral health 51-56; low - poor oral health less than 50.

The obtained score can be categorized for easier and faster determination of the level of psychometric characteristics according to the oral health self-perception: less than 50 as “low perception, 51-56 as” moderate perception ”for oral health, 57-60 as“ high perception ”. Table 4 and Figure 3 show descriptive statistics of the total score and the average score for the quality of life and oral health of respondents.

Table 4. Quality of life and oral health/total, average score / Descriptive statistics

GOHAI	No	Average	Confidence -95,00%	Confidence +95,00%	Median	Sum	Min.	Max.	Std.Dev.
Sum Total	80	15,48	14,32	16,63	14,50	1238	6	32	5,19
Average	80	1,93	1,79	2,08	1,81	154,75	0,75	4,00	0,65

The total score that refers to the quality of life and oral health in respondents from group 1 varied in the interval 15.48 ± 5.19; ± 95.00% CI: 14.32-16.63; the median was 14.50; the sum of the total score was 1238; the minimum value was 6 and the maximum value was 32. The average score referring to the quality of life and oral health of the respondents from group 1 varied in the interval 1.93 ± 0.65; ± 95.00% CI: 1.79-2.08; the median was 1.81; the sum of average score was 154.75; the minimum score was 0.75 and the maximum score was 4.00.

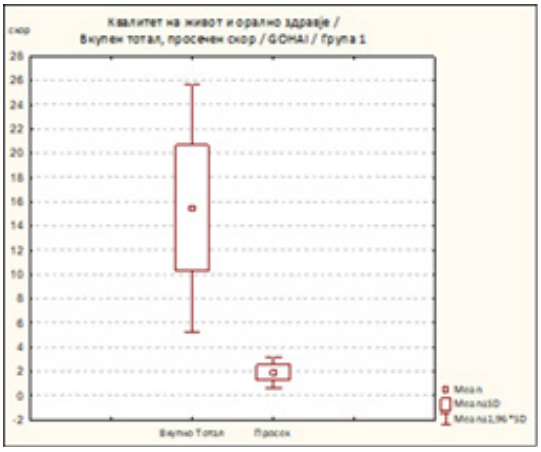

Figure 3.

Table 5 presents the difference in the quality of life and oral health of respondents in relation to gender. The average value of quality of life and oral health in male respondents (x = 2.05) for t = 1.40 and p> 0.05 (p = 0.17) was slightly higher thanin female respondents (x = 1 , 85).

Table 5. Quality of life and oral health / Gender

Variable	Mean Male	Mean Female	t-value	df	p	Valid N Male	Valid N Female	Std.Dev. Male	Std.Dev. Female
Average*	2,05	1,85	1,40	78	0,17	34	46	0,63	0,66

There was an insignificant correlation between the average value of quality of life and oral health and their age (72.48-5.25). For r = -0.21 (p> 0.05) a moderately weak negative insignificant correlation was found. Namely, with a single increase in the age of the respondents by one year, the quality of life and oral health decreases insignificantly by 0.03 units. The average value of quality of life and oral health in the respondents in peri-urban environment (x = 2.27) for t = - 2.17 and p <0.05 (p = 0.03) is significantly higher than in respondents in urban environment (x = 1.86).

Table 6. Quality of life and oral health / Environment

Variable	Mean Urban	Mean Periurban	t-value	df	p	Valid N Urban	Valid N Female	Std.Dev. Urban	Std.Dev. Periurban
Average*	1,86	2,27	-2,17	78	**0,03**	66	14	0,58	0,84

For F = 0.57 and p> 0.05 (p = 0.57), there was no significant difference in the quality of life and oral health when it comes to the education of respondents. Table 7 shows the difference in the quality of life and oral health of respondents in relation to smoking. The average value of quality of life and oral health in smokers (x = 2.15) for t = 2.74 and p <0.01 (p = 0.008) was significantly higher than in non-smokers (x = 1.76).

Table 7. Quality of life and oral health / Smoking

Variable	Mean Smokers	Mean Nosmokers	t-value	df	p	Valid N Smokers	Valid N No smokers	Std.Dev. Smokers	Std.Dev. No smokers
Average*	2,15	1,76	2,74	78	**0,008**	36	44	0,72	0,53

The average value of quality of life and oral health in respondents who drank alcohol (x = 2.03) for t = 1.30 and p> 0.05 (p = 0.20) was slightly higher than in the respondents who did not drink alcohol (x = 1.85). The average value of quality of life and oral health in respondents with prosthetic constructions (x = 2.03) for t = - 1.32 and p> 0.05 (p = 0.19) was slightly higher in relation to respondents without prosthetic structures (x = 1.84).

Discussion

Oral health is important for general health and well-being and has a major impact on quality of life. It is defined as a state of absence of pain in the mouth and face, oral diseases, and disorders that limit individual capacities for chewing, biting, laughing, talking, and psychosocial well-being. About 30% of the European population aged 65-74 do not have natural

teeth and have reduced function and quality of life[13]. The average life expectancy of people is constantly increasing due to better living conditions, education, and better health care. Life expectancy in 1900 was 45 years, and in 2000 it was twice higher(85 years). Aging, on the other hand, is associated with higher rates of morbidity, disability, and lower quality of life. Oral diseases and the reduced number of teeth affect the orofacial system and its functions in elderly patients[14]. They have problems with chewing, decreased sense of taste, bad breath (fluoride), dry mouth (hyposalivation and xerostomia), burning syndrome, speech and communication problems, pain in TMJ, etc.[15]. Age is not always directly related to tooth loss and is most likely the result of periodontitis, caries, poor general health, and socioeconomic factors[16]. However, the number of elderlywith anodontia in different countries is quite high (6-78%), and this has a negative impact on the quality of life related to oral health (OHRQoL)[17]. According to the WHO, anodontia is a severe physical disability that causes several clinical, functional, and psychological difficulties. In this study, partial anodontia was recorded in all patients missing more than one tooth. Studies in some Western European countries show a higher number of remaining teeth than data obtained from our geriatric respondents (37.5% partial and 62.5% total edentulousness). A study conducted in Germany gives data on an average of 14 remaining teeth in subjects from the age group 60-65, and only 3 remaining teeth on average in the group 75-79 years[18]. A study conducted in Sweden after the continuous implementation of measures to improve oral health showed a reduction in the rate of toothlessness from 14% in 1973, to 8% in 1993 and only 1% in 2003[19]. This confirms that the attitude towards age and the number of remaining teeth have changed, and today it is known that regular maintenance of oral hygiene, proper diet, and visit to the dentist give positive results in preserving natural teeth. Prosthetic constructions (total and partial dentures) successfully restore mastication, phonetics, and aesthetic function, but also contribute a lot to the improvement of social life. Proper chewing function is of great importance because it also affects the effect of digestion. During aging, the secretion of gastric juice decreases, and proper preparation of the bolus is especially important, because the masticatory efficiency of dentures is 16-50% compared to chewing with natural teeth[20].

Health-related quality of life (HRQoL) and oral health-related quality of life represent the condition of the teeth and mouth and general health of patients, and their assessment is performed using several indices. The GOHAI General Oral Health Assessment Index measures people's perceptions of the social impact of oral disorders on their general well-being[21]. The index specializes in the evaluation of oral functional problems in elderly patients and the effects of dental treatment[22]. It consists of 12 questions related to the ability to do social activities and lack of pain and infection. If the patient does not answer more than 3 questions, his data are invalid and are not used for statistical analysis. The total points are 0-60, and the validity of the index was checked in a study conducted on a sample of 1775 patients, which showed great

reliability and accuracy[23]. The total Cronbach's Alpha = 0.65 in our study was high and indicated a very strong internal consistency between responces to 9 questions regarding functional limitations of patients. The total score that refers to the quality of life and oral health of the respondents varied in the interval 15.48 ± 5.19 (22.84 with all values included) the minimum value was 6 and the maximum 32. GOHAI-12 score in this study was very low value, less than 50, and indicated that respondents from group 1 were with poor oral health and according to the results of the self-assessment, there was a weak to moderate perception of oral health.

Conclusion

Evaluating problems in geriatric dentistry alone is certainly not always enough. It is necessary to find appropriate solutions to the problems that exist today not only in terms of dental practice but also in terms of education and social care. As the population ages and part of it become institutionalized, the incidence of caries and periodontal disease will increase, with an increase in the degree of partial or total anodontia. An integrated approach is needed to achieve a critical positive level of general and oral health, especially for patients placed in homes and institutions for their care. Coordinated medical care is as vital as support from different dental specialties. An adequate number of professionally trained medical personnel and adequate education of the dental staff is of great importance.

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REVIEW

IDENTIFICATION AND MANAGEMENT OF CHILD DEVELOPMENT -PRACTICE PARAMETERS

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Abstract

The main characteristics of children are phenomena of growth and development. Child development could be defined as a complex unfolding of a series of skills and adaptations, with very predictable stages, that occur in multiple dimensions at approximately the same time and in approximately the same order.There are several types of developmental delays in children. These delays can affect child's physical, cognitive, communication, social, emotional, or behavioural skills. Developmental delays are common in childhood, occurring in 10%-15% of preschool children in different forms. Global developmental delays are less common, occurring in 1%-3% of preschool children. The article gives some practice parameters for identification and management of child development based on the newest published articles included in the PubMed database.

ПРЕГЛЕД НА ЛИТЕРАТУРА

ИДЕНТИФИКАЦИЈА И УПРАВУВАЊЕ СО ДЕТСКИОТ РАЗВОЈ- ПРАКТИЧНИ ПАРАМЕТРИ

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Извадок

Главна карактеристика на децата е феноменот на раст и развој. Детскиот развој може да се дефинира како комплекс од серија вештини и адаптации, со предвидливи стадиуми, кои се јавуваат во разни димензии на приближно слично време и со приближно ист редослед. Постојат неколку вида застој во развојот кај децата. Може да го зафатат физичкиот, когнитивниот, комуникативниот, социјалниот, емоционалниот развој или поведението. Застојот во развој е чест во детството и се јавува кај 10-15% претшколски деца во разни форми. Глобалниот застој на развојот е поредок и се јавува кај 1-3% од претшколските деца. Овој напис дава некои практични насоки за идентификација и постапки за справување со детскиот развој базирани на најнови публикации соржани во базата ПубМед.

Introduction

Being a long-term paediatrician and psychologist, as well as an educator, I feel an obligation to give some suggestions about issues related to the public health. In this context I think that the developmental delay is not enough evaluated in the curricula of medical studies in our country and this article is devoted to this issue.

The main characteristics of children are phenomena of growth and development, processes that permit to rich maturity and functioning of the whole organism. Child development stages are theoretical milestones, some of which are asserted in nativist theories. As a reminder, nativist theorists are based on the hypothesis from Noam Chomsky and argue that children are born with an **innate ability** to organize laws of language, which enables them to easily learn a native language. They believe that children have language-specific abilities that assist them in mastering a language. Opposite to this, constructivism is based on a **theory of learning** in which the learners (children) construct the language through experiencing things and reflecting on those experiences. Cognitive constructivism was developed by Piaget, a well-known developmental psychologist.

However, development is quite different than growth. Growth only refers to the child getting bigger in size (changes in quantity). When we talk about normal development, we are talking about changes in quality, i.e., developing skills like: gross motor, fine motor, language, cognitive and social skills. Still, children reach developmental milestones at their own pace, and some move faster than others. It is known that two siblings in the same family, even tweens, may reach milestones at different rates.

Developmental delays are common in childhood, occurring in 10%-15% of preschool children in different forms. Global developmental delays are less common, occurring in 1%-3% of preschool children. In this way, developmental delay is really the problem of the public health[1,2,3].

The main obligation of the paediatricians is to assess the development of every child and to alarm even minimal deviation of the norm. Minor, temporary delays are usually no cause for high concern, but an ongoing delay or multiple delays in reaching milestones can be a sign for different problems later in life.

For the purpose of this article a systematic search was conducted using PubMed and retrieving published articles in the last two decades. In addition, a bibliography of 160 articles available at the American Academy of Neurology Web site (http://www.aan.com/) were identified and reviewed for preparation of parameters discussed in this article. The following key words were used: developmental delay, children, screening. Important results obtained from this review are presented in this article.

Epidemiology

Globally, approximately 53 million children are supposed to have identifiable developmental problems delay. Since 95% of the population resides in low and middle-income countries, there is an increased risk of developmental delays and disorders. Although the exact prevalence of developmental delay is unknown, according to the World Health Organization (WHO), 10% of the population in each country has a disability of one or another kind. In the United States, roughly 15% of children have been reported to have at least one developmental problem. In England, the prevalence of intellectual delay in children under the age of five and

adults is 2.7% and 2.17%, respectively. The incidence rate for general developmental delay is 1% to 3% in school-age children or younger. Autism prevalence is approximately 2.5%. These numbers change each year, but unfortunately, they are increasing[4,5].

The prevalence of delay in development involving respective domains among children is based on data reported in children getting services by USPSTF (United States Preventive Services Taskforce). For the United States, they are as follows: cognitive (1% to 1.5%); learning disability (8%); speech and language (2% to 19%) and any delay (15%)[6].

According to Drakenstein Child Health Study (DCHS) conducted in Western Cape, South Africa, the risk of low developmental performance in the high-risk environment was higher among boys. Likewise, several other studies have also reported a slightly increased incidence in males, possibly due to genetic variability on the X-chromosome[7].

There are several types of developmental delays in children. These delays can affect child's physical, cognitive, communication, social, emotional, or behavioural skills. Often, developmental delays affect more than one area of a child's development. When a child has delays in many or all of these areas, it is called global developmental delay.

Aetiology

Some developmental delays have an identifiable cause. However, for many children, the cause of the delay, or multiple delays, is not clear. Boxes 1 and 2 show common aetiologies for delay, as well as test needed for the evaluation.

Box 1. Common aetiologies of developmental delay:[2,8]

Prenatal

- Genetic disorders: Down syndrome, fragile X syndrome, chromosomal microdeletion or duplication
- Cerebral dysgenesis: microcephaly, absent corpus callosum, hydrocephalus, neuronal migration disorder
- Vascular: occlusion, haemorrhage
- Drugs: cytotoxic, anti-epileptic
- Toxins: alcohol, smoking
- Early maternal infections: rubella, cytomegalovirus, toxoplasmosis
- Late maternal infection: varicella, malaria, HIV

Perinatal

- Prematurity, intrauterine growth retardation, intraventricular haemorrhage, periventricular leucomalacia
- Perinatal asphyxia: hypoxic-ischaemic encephalopathy
- Metabolic: symptomatic hypoglycaemia, bilirubin-induced neurological dysfunction

Postnatal

- Infections: meningitis, encephalitis
- Metabolic: hypernatraemia, hyponatraemia, hypoglycaemia, dehydration
- Anoxia: suffocation, near-drowning, seizure
- Trauma: head injury, either accidental or non-accidental
- Vascular: stroke

Others

- Social: severe understimulation, maltreatment, malnutrition (deficiency of iron, folate and vitamin D)
- Maternal mental health disorder
- Unknown

Box 1: *Common causes for developmental delay*

Box 2. Additional tests for children referred to a Child Development Unit:

Genetic evaluation
- Child appears syndromic
- Clinical findings suggestive of any genetic condition
- Family history of developmental delay/intellectual disability

Creatine phosphokinase test
- Gross motor delay, especially in boys

Screening for inborn errors of metabolism
- Unexplained global developmental delay and a history of regression

TORCH (toxoplasmosis, rubella cytomegalovirus, herpes simplex and HIV) screen
- Macrocephaly/microcephaly

Neuroimaging
- Focal neurological deficits/abnormal neurological findings

Electroencephalography
- History suggestive of seizures/regression

Box 2: *Needed evaluations for global developmental delay*

Routine screening for inborn errors of metabolism in children with global developmental delay has a yield of about 1% that can increase up to 5%, in particular situations such as relatively homogeneous and isolated populations. When stepwise screening is performed, the yield may increase to about 14%. In our country, unfortunately due to financial deficit and disorganization, screening programs are not regularly performed in all obstetric settings[8].

Forms of delay

Having in mind all written before, child development could be defined as "a complex unfolding a series of skills and adaptations, with very predictable stages, that occur in multiple dimensions at approximately the same time and in approximately the same order." To assess whether an infant or a child is developing at a healthy and normal pace, paediatricians and child development experts consider four domains (or aspects) of development:

- Motor skills, including large (or gross) motor skills, such as rolling over, crawling and learning to walk and run, and fine motor skills, such as the ability to pick up and eat small pieces of food or hold a pencil and draw or write.
- Sensory skills, including how a child uses the senses (taste, smell, touch, sound and sight) to learn about the environment.
- Social skills, including how an infant interacts with parents and caregivers, and then with others, including siblings, extended family and strangers.
- Cognitive skills, including how child's attention, memory, thinking and learning skills develop and grow.

A significant delay is defined as a performance two standard deviations or more below the mean on age-appropriate, standardized norm-referenced testing. The term global developmental delay is usually reserved for younger children (i.e., typically less than 5 years of age), whereas the term mental retardation is usually applied to older children when IQ testing is more valid and reliable.

Cognitive delays may affect child's intellectual functioning, interfering with awareness and causing learning difficulties that often become apparent after a child begins school. Children with cognitive delays may also have difficulty communicating and playing with others.

Shaken baby syndrome, seizure disorders, and chromosomal disorders that affect intellectual development, such as Down syndrome, may increase the risk of a cognitive delay. This type of delay may occur also in children who have experienced a brain injury due to an infection, such as meningitis, which can cause swelling in the brain known as encephalitis. In most cases, however, it is not possible to identify a clear reason for this type of delay.

Motor skills' delay interfere with a child's ability to coordinate large muscle groups, such as those in the arms and legs, and smaller muscles, such as those in the hands. Infants with gross motor delays may have difficulty rolling over or crawling; older children with this type of delay may seem clumsy or have trouble walking up and down stairs. Those with fine motor delays may have difficulty holding onto small objects, such as toys, or doing tasks such as tying shoes or brushing teeth. Some motor delays result from genetic conditions, such as achondroplasia, which causes shortening of the limbs, and conditions that affect the muscles, such as cerebral palsy or muscular dystrophy. They may also be caused by structural problems, such as a discrepancy in limb length.

Social, Emotional, and Behavioural Delays are mainly related with neurobehavioral disorders such as autism spectrum disorder and attention deficit hyperactivity disorder. Due to differences in brain development, they may process information or react to their environment differently than children of the same age. These delays can have an impact on a child's ability to learn, communicate, and interact with others.

Some **speech delays** are receptive language disorders, in which a child has difficulty understanding words or concepts. Children with this type of speech delay may have trouble identifying colours, body parts, or shapes. Others are expressive language disorders, in which a child has a reduced vocabulary of words and complex sentences for his or her age. A child with this type of speech delay may be slow to babble, talk, and create sentences. Often, a child with a speech delay has a combination of receptive and expressive delays.

Children may have speech delays due to physiological causes, such as brain damage, genetic syndromes, or hearing loss. Other speech delays are caused by environmental factors, such as a lack of stimulation. In many instances, however, the cause of a child's speech delay is unknown.

The **evaluation of the developmental delay** is based on one-on-one diagnostic play sessions and evidence-based measurement tools such as the Bayley Scales of Infant and Toddler Development and the Mullen Scales of Early Learning.

Delay in development is generally determined when a child does not attain developmental milestones as compared to peers from the same population. Statistical terms are often used to classify the degree of delay into mild (functional age (FA) <33% below chronological age (CA), moderate (FA 34% to 66% of CA), and severe (FA <66% of CA). "De-

velopmental delay" is a general descriptor of a broad phenotype that must then be specified by carefully determining one or more elements linked to the area of disrupted development.

Most developmental disabilities occur before a child is born, but some, as mentioned before, can occur after birth due to infection, injury, or other factors. In this context the first step in the evaluation of developmental delay is **metabolic screening as well as cytogenetic studies**.

In the group of innate causes for global developmental delay, in addition to Down syndrome, Rett syndrome is believed to be the most common cause of developmental delay in females. Seizures, autistic-like behavior, ataxia, intermittent hyperventilation, and stereotypic hand movements occur in most patients with Rett syndrome mainly after the age of 18 months together with microcephalia. Rett syndrome is believed to be one of the leading causes of global developmental delay/mental retardation in females and is caused by mutations in the X-linked gene encoding methyl-CpG-binding protein 2 (*MECP2*). About 80% of patients with Rett syndrome have *MECP2* mutations. The prevalence of Rett syndrome in the general population is approximately 1 to 3 individuals per 10,000 live births.

The accumulated data suggest that cytogenetic studies will be abnormal in 3.7% of children with global developmental delay, a yield that is likely to increase in the future as new techniques are employed. In mixed populations (both males and females), a yield of between 0.3% and 5.3% (average yield of 2.6%) has been demonstrated for fragile X testing. The higher range of this yield exists for testing amongst males. There is a suggestion that clinical preselection for the fragile X syndrome amongst males may improve diagnostic testing beyond routine screening.

Having in mind the mentioned facts, the main recommendation is to conduct a routine metabolic screening for inborn errors of metabolism together with some cytogenetic testing of child with developmental delay even in the absence of dysmorphic features or clinical features suggestive of a specific syndrome. In children with unexplained moderate or severe developmental delay, additional testing using newer molecular techniques (e.g., FISH, microsatellite markers) to assess for subtelomeric chromosomal rearrangements (6.6%) may be considered.

What is the role of **lead and thyroid screening** in children with global developmental delay?

Lead is the most common environmental neurotoxin. Studies over several decades have shown a relation between marked elevations in serum lead levels, clinical symptoms and cognitive deficits (but not definitively mental retardation). Our team (paediatricians together with public health professionals) evaluated children in the Veles region. Our assessment confirmed a negative correlation between blood lead level and IQ in a sample of school children from Veles region where the lead factory was active (Fig.1)9. Additionally, some other direct negative effects from lead poisoning were proven. The pressure of scientists and public health professionals was so hard ending with the closure of the lead factory in Veles. Still, some consequences from lead toxicity are present.

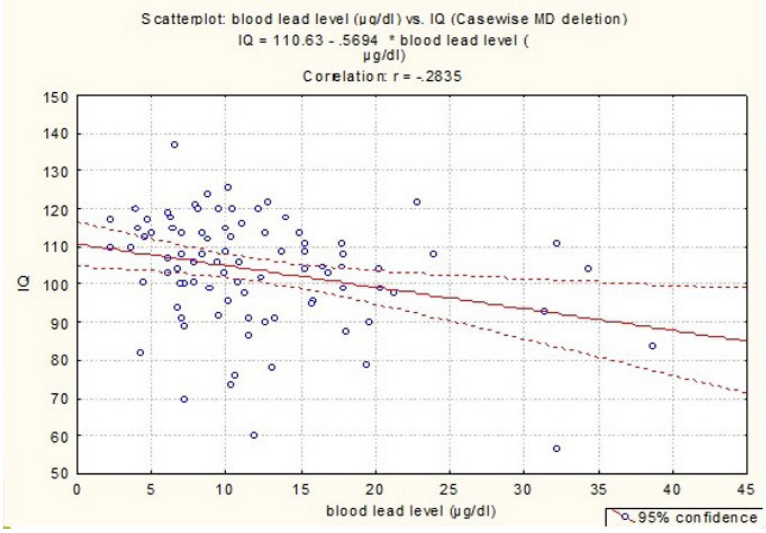

Figure 1: Correlation of blood lead level and IQ

Unrecognized congenital hypothyroidism is a potentially treatable cause of later developmental delay. Delay in diagnosis and treatment beyond the newborn period and early infancy has been clearly linked to later often substantial, neurodevelopmental sequelae. Implementation of newborn screening programs has been extremely successful in eliminating such sequelae.

What is the diagnostic yield of **EEG** in children with global developmental delay?

An EEG can be obtained when a child with global developmental delay has a history or examination features suggesting the presence of epilepsy or a specific epileptic syndrome. Data are insufficient to permit making a recommendation regarding the role of EEG in a child with global developmental delay in whom there is no clinical evidence of epilepsy.

What is the diagnostic yield of **neuroimaging** in children with global developmental delay?

Available data from some studies show that CT contributes to the etiologic diagnosis of global developmental delay in approximately 30% of children, with the yield increasing if physical examination findings are present. MRI is more sensitive than CT, with abnormalities found in 48.6% to 65.5% of children with global delay with the chance of detecting an abnormality increasing if physical abnormalities, particularly cerebral palsy, are present.

In this context, the presence of physical findings (e.g., microcephaly, focal motor findings) increases the yield of making a specific neuroimaging diagnosis, and physicians are advised to consider obtaining a scan in this population. If available, MRI should be obtained in preference to CT scanning when a clinical decision has been made that neuroimaging is indicated.

Are vision and hearing disorders common in children with global developmental delay?

Several studies have shown that children with global developmental delay are at risk to have primary sensory impairments of vision and hearing. Estimates of vision impairment or other visual disorders range from 13% up to 50% whereas significant audiological impairments occur in about 18% of children based on data in one series of patients[10].

However, it is recommended that children with global developmental delay undergo appropriate vision and audiometric assessment at the time of their diagnosis. Vision assessment can include vision screening and a full ophthalmologic examination (visual acuity, extra-oculo-movements, fundoscopic). Audiometric assessment can include behavioral audiometry or brainstem auditory evoked response testing when feasible.

Treatments for developmental delays vary according to the specific delay. Some treatments include physical therapy for help in motor skill delays, and behavioural and educational therapy for help with ASD and other delays. A new report shows that a severe developmental brain disorder due to fragile X syndrome might be treated with drugs that inhibit a neurotransmitter receptor called mGluR5. The idea, that mGluR5 stimulates excessive protein synthesis in fragile X neurons disrupting their functions, became well validated by experiments in the lab of David et al.11 and some others worldwide, using several animal models of the disease. In the future some other new approach in the treatment of developmental delay might appear.

Issues related to quality of life and social support of families who have children with developmental delay need also further studies. They should include the benefits that medical testing confers by reducing parental concerns related to determining a specific etiology and by providing important information regarding prognosis, genetic counseling, alleviation of parental anxiety, and planning future educational and treatment needs.

Conclusion

There are different forms and causes for developmental delay. The incidence of development delay globally is about 1-10% in the school period. The regular neonatal screening and cytogenetic studies are needed for early and exact diagnosis. The earlier diagnosis gives better prognosis based on specific therapeutic approach. In order to help these children some different therapeutic methods are available. For early diagnosis and prevention massive neonatal screening are needed.

This paper has presented an overview of the common etiological factor as well as of some parameters in diagnostic approach. Further studies in this field are important and needed.

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REVIEW

PHONOLOGICAL AWARENESS IN CHILDREN WITH DEVELOPMENTAL LANGUAGE DISORDER

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Abstract

Children with developmetal language disorder have impaired developmental pattern of language structure. Literature data speak in favor of delay and/or difficulties in development of phonological, lexical, morphological and syntactic structure, but the nature of developmental language disorder (DLD) has still not been elucidated. The aim of this paper was to present and analyze data about phonological awareness in children with DLD based on a systematic literature review. Also, we wanted to point out some methods of assessment and stimuli/encouragement in development of phonological abilities. The research presented in the analyzed literature have shown that current knowledge regarding phonological awareness in children with DLD is mainly obtained from comparative stuides of children with developmental language disorder and children with normal language development. A large number of results has revealed that different components of phonological awareness in children with DLD are less developed compared to their peers with typical development. Studies have also presented current assessment techniques and importance of phonological awareness preventive stimulation progams, which are an important indicator/parameter for the development of reading and writing as well as for onset of impairments in learning these skills.

ПРЕГЛЕД НА ЛИТЕРАТУРА

ФОНОЛОШКА СВЕСНОСТ КАЈ ДЕЦА СО РАЗВОЈНО ЈАЗИЧНО НАРУШУВАЊЕ

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Извадок

Децата со развојно јазично нарушување имаат изменет образец на развојот на јазичната структура. Податоците од литературата сведочат во прилог на доцнење и/или абнормалности во развојот на фонолошката, лексичката, морфолошката и синтаксичката структура, во природата на развојното јазично нарушување (РЈН) сеуште е непозната. Цел на овој труд е врз основа на преглед на литература, на систематски начин да се прикажат и анализираат податоци за фонолошката свесност кај децата со РЈН. Исто така сакавме да истакнеме некои методи на проценка и поттикнување на развојот на фонолошките способности. Резултатите од анализата на податоци од литературата покажуваат дека современите сознанија за фонолошката свесност кај децата со РЈН воглавно потекнуваат од компаративните студии на достигнувања на децата со развојнојазично нарушување и деца со типичен развој. Поголемиот број резултати покажуваат дека различните компоненти на фонолошка свесност кај децата со РЈН се развиени во помала мерка во споредба со нивните врсници со типичен развој. Исто така, прикажани се актуелните техники на проценка и истакнато е значењето на превентивните програми за поттикнување на развојот на фонолошката свесност, која претставува важен показател на развојот на читање и пишување и покава на пречки ва учењето на овие вештини.

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Клучни зборови: развојно јазично нарушување, фонолошка свесност, типичен јазичен развој, деца

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Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Introduction

Phonological awareness is the consious awareness of the phonological structure of words in one's language which along with phonological representation presents a unique construct.[1] The concept of phonological representation is an abstract one and in a broader sense it means storage of phonological information in the long-term memory.[2] There is considerable debates in the scientific literature about distinctive features of phonological processes. Regarding phonological abilities, no clear distinction exists in determination and usage of the terms phonemic and phonological awareness and very often they are used as synonyms in the literature. Phonemic awareness means segmenting words into phonemes and blending phonemes into words, and it is a part of the concept of phonological awareness. Phonological awareness is a wider construct than phonemic awareness.[3,4] It is the ability to analyze and synthesize syllables and words, i.e., longer language units than phonemes, but also manipulation with phonological elements of the words. In other words, phonological awareness is defined as the ability of a child to recognize words as parts of a sentence, to recognize and reproduct words that rhyme, and to recognize syllables in a word.[5] It is considered that phonological awareness is established when a child develops the ability to identify and reproduce words that rhyme, to identify sounds in the words and to segment a word into sounds.[6] Its development and the development of the other components of phonological awareness are thought to be very important for children before they start going to school. However, phonological awareness is a narrower constuct than meta-linguistic awareness.3,4 Phonological skills include usage of phonological representations along with consciousness and metacognitive skills byfast and serial identification and working and short-term memory.[7]

Until recently, developmental language disorder (DLD) has been referred to as specific language impairment (SLI) while in the past this type of impairment was called developmental dysphasia. It is defined as a developmental language disorder found in children without intelectual disabilites, visible cerebral pathology, sensory and serious motor disorders.[8] Diagnosis is established in children who present with at least a 12-month expressive language delay, a 6-month receptive language delay and in situations when there is a 12-month difference between mental and language maturity. In addition, in children with DLD the intellegence coefficient is above 85, which means it ranges from average to above the average intellectual abilities.[9]

Children with developmental language disorderexhibit altered developmental patterns of particular linguistic categories, that is, disharmonious language development. In fact, there is a significant delay and abrnormalities in the development of certain elements of language structure. Children manifest lexical deficts by expressing themselves with shorter words; they haverestricted vocabulary and evident difficulties in using pollysylabic words. Grammar deficitsare manifested at the level of morphology and syntax. Phonological disorders are manifested by making reversal, inversion and metathesis

of phonemes in the words, and very ofter a larger number of sounds are either spoken or used.[10]

The aim of this study was to make a literature review and analyses of empirical data about phonological awareness in children with developmental language disorder (DLI). Also, current techniques for assessment of phonological awareness as well as methods of stimulation the development of phonological awareness in these children have been presented.

Material and methods

A systematic literature search was made by using the following databases: Google Scholar, KoBSON, Cross Reference and PubMed. The following keywords were used: *developmental language disorder, specific language disorder, phonological disorder, phonological deficits in children with specific language disorder, assessment of phonological abilities.*

Phonological awareness in children with DLI

In order to better understand the phenomenon of DLI, different assumptions were formulated so as to describe syntactic, phonological, semantic and speech disorders. Literature review has shown that nowadays there has been considerable debate about the most appropriate theoretical approach regarding the nature of developmental language disorder. As a result, several hypotheses were formulated. Some of them speak in favor of the existence of various deficits such as deficit in the specialized module for learning a language, disorders in auditory perception, memory deficit and disorders in the domain of information processing.[11,12]

Studies that investigated phonological awareness in children with disorders in the language development showed that these children performed significantly weaker results in different types of tasks of phonological awareness than children with typical language development (TLD). For example, in the study conducted by Milosevic and Vukovic (2018) statistically significant differences were observed in identification and production of rhyme between children with DLD and children with TLD.[13] Having in mind that the ability of finding words that rhyme is one of the earliest components of phonological awareness which is developed in children, the authors made a comparative analysis where they compared children with DLD with their peers with TLD. They found out that children with DLD had weaker performance than their peers with TLD. The authors concluded that the ability of identifying and production of rhyme is an important indicator of the phonological development, but also an important component of prereading skills.[13]

Certain emprical data show that children with DLD in preschool period have no developed ability of more complex phonological word processing. Therefore, children achieve better results in simpler tasks relying solely on their working memory (synthesis and segmentation at the level of phonemes and syllables) and weaker performance in more complex tasks (deletingphonemes, substitution of phonemes, production of rhyming words).[14]

Colic (2015) confirmed that preschool children with DLD diagnosis showed statistically significantly worse results on complex elements of phonological awareness (rhyming, deleting phonemes, substitution of phonemes, segmentation, synthesis of phonemes, syllables and words) when compared to children with TLD. However, the author emphasized that children with DLD successfully accomplished tasks that required simpler aspects of phonological processing (analysis and synthesis of words in/to syllables and words) probably owing to the developed phonological memory, although they showed poorer results compared to children with TLD.[3]

In a study by Australian authors, a more detailed comparative analysis was made between phonological awareness in children with DLD and children with TLD. Children with DLD were compared to their peers with TLD matched for age (one subgroup) and matched for receptive language skills (the other subgroup). The authors noticed that children with DLD were more successful in the tasks of naming speed than younger children matched for linquistic skills, but still less successful than their peers with TLD. As for the tasks of phonological short-term memory and working memory, as well as the tasks of phonological representation, children with DLD had weaker performance than both subgroups of typicially-developing children.[15]

Farquharson et al. (2014) in their study demonstrated that children with DLD had the same pattern of phonological processing as the children without language impairment regarding tasks of repeating and deleting sounds in the words and non-words, although children with DLD performed less wellthan children with TLD. Children with DLD were very successful in the task of phonologically similar words and in cases when the initial and final two sounds were different. The authors concluded that the difference between typically-developing children regarding language skills and children with DLI were of quantitative rather than of qualitative character.[16]

In the literature, phonological and lexical influences on phonological awareness are explained by two theories. According to the first theory, in which frameworks the hypothesis of phonological deficit was formulated, children with poor phonological skills have difficulties in storing and processing sounds in words. The other theory is based on the lexical restructuring model and is focused on the role of phonemic features that enable children to discern similar words from one another. It is supposed that as the vocabulary grows an increased phonemic processing is required.[16]

Literature data show that some cognitive processes influence on performing language tasks in children with DLD. Some researchers think that the primary deficit in DLD is in the memory (sensory, short-term, working and long-term memory), which might explain the weaker performance in phonological awareness of children with this impairment. It is almost certain that all three memory systems are necessary for phonological processing of words. Sensory or perceptual memory stores information obtained through the senses, in this case auditory, from half a second to several seconds, whereby this piece

of information is not transformed and processed. Having in mind these assumptions, some authors believe that children with DLD probably have the same achievements in the task of identifying the initial sound in a word as children with TLD since this task does not depend on memory function.[17,3] More complex tasks of phonological awareness, such as eliminating the initial phoneme in a word, require a good sensory short-term and long-term memory and, hence, children with DLD perform less well in these tasks than children with TLD due to phonological memory deficit.

In spite of the large number of studies conducted on phonological memory, lexical approach and phonological awareness in children with DLD, there is a lack of comparative studies of these skills in order to determine which one is the most developed and which one isaffected.Such findings might contribute in creating targeted intervention plans, but also in reducing the negative impact on the development of reading in children with DLD due to deficit of the mentioned skills.

Numerous studies have emphasized the correlation of phonological awareness with subsequent literacy difficulties in children. One of them is the longitudinal study of Zourou et al. (2010) presenting interesting results.18 The authors found improved phonological awareness in their examinees after certain time interval. However, the fragile nature of phonological awareness was also shown as well as the fact that children with DLD failed to cope with the acquiredreading and spelling skills that require a high level to manipulate phonemes.[18]

Research conducted in Serbia has revealed a high correlation between phonological ability expressed through phonological awareness and syntactical awareness with initial reading.[19] A recent study conducted in the Serbian-speaking area has also shown that children with difficulties in reading have weaker phonological awareness than children with typical-reading development.[20] Other studies have also indicated the risk of impairment in literacy acquisition due to limited phonological awareness.[21] It is considered that children with reading problems have weaker phonological awareness compared to children with normal reading development. In spite of the fact that phonological awareness is not fully developed before mastering reading and writing, there is still no precise answer to the question to what level phonological awareness in children is developed before they master these skills.[22] The development of reading skills, as we all know, requires much more activity than only encoding (transformation of sounds into letters) and decoding (transformation of letters into sounds).

The study of Ramus et al. (2013) examined the phonological abilities in children with DLD and children with dyslexia by using a broad battery of tests. It was found out that children with DLD did not necessarily have phonological deficit or reading difficulties, and that the nature of phonological disorder was different in these two groups of children. In other words, the authors of this study suggest that DLD and developmental dyslexia do not necessarily appear as comorbidities, i.e., they can appear independently of each other. Children with DLD show impairments

in both phonological representations and phonological skills at the same degree, whereas children with dyslexia show significant disorders in phonological skills.[23] Also, the authors think that deficits in phonological representation are rather a result of involving cognitive skills that are associated with phonological representationthan of the representation themselves. This means thatthere is a relationship between impairments in phonological representationswith deficits in focusing attention, short-term and long-term memory, metacognitive skills, understanding instructions, etc.[23]

Assessment of phonological awareness

Some of the tasks that assess phonemic and phonological awareness are extracting the initial sound in a word, extracting the final sound in a word, finding a word in a group of words that differs from the others by the initial or final phonemes, segmentation of one word into constituent phonemes and syllables, blending phonemes into syllables and words.[4,24] Tasks for assessment of phonological awareness include finding rhyming words, i.e., identifying rhyming pairs of words in a group of words or providing a rhymewith a given word. The analysis of these tasks suggests no clear boundary between those that measure or assess phonemic awareness from those that assess phonological awareness. In the English speaking countries, phonological awareness in children is assessed by Phonological Awareness Test-2 – PAT-2 (from 5 to 9.11 years), Sutherland Phonological Awareness Test – Revised SPAT-R, Comprehensive Test of Phonological Processes – CTOPP and Pre-Literacy Skills Screening – PLSS.[25-28] Also, screening tests have been developed such as Phonological Awareness Screening Test – PAST.[29]

One of the operational models or tests of phonological awareness developed in the Serbian speaking area and is widely used is the FONT test. It consists of seven subscales: blending syllables, identifying the final syllable, recognizing rhyme, phoneme segmentation, identifying the final phoneme, phoneme substitution and phoneme elimination/deletion. Having in mind that the validation of the test is still an ongoing process, the authors have suggested framework norms for children aged five to nine year.4 However, when they applied this test in children with TLD, it was not possible to make a general division into less and more demanding tasks with which phonological awareness was examined in children with speech and language disorders. It was assumed that the majority of tests would be more difficult to be performed by children with language disorders regardless of their age.[30]

One of the instruments that is used in phonological awareness in children is the Emerging Literacy & Language Assessment - ELLA.31 ELLA is an American test translated and adjusted for the research needs in the Serbian language and where three important features (length of words, frequency of words, combination of vowels and consonants in words) have been taken care in order to find adequate substitutions for the original text that would match the Serbian language. It consists of three parts, each of which contains several scales. The first part refers to examination of phonological

awareness, the second examines decoding and the third is intended for examination of memory.[19]

One valuable method for testing naming speed in children with DLD is PredČiP test aimed at a more detailed inspection of phonological skills in children with DLD.[32] PredČiP is a test for evaluation of pre-skills of reading and writing, i.e., a screening test for assessment of children's linguistic readiness to master initial academic skills. This test contains tasks for assessment of phonology, phonological memory, pragmatics and visual perception.[33]

Stimuli/encouragement for the development of phonological ability

It is generally accepted that phonological awareness and naming speed are good predictors of reading and writing in children with normal development of speech and language skills. Naming speed is important for the development of fluent reading (holistic word recognition) and for reading comprehension and is associated with reading speed. Good skills in naming speed are a good predictor of later recognition of graphemes. Results obtained in studies discussing naming speed show that children with DLD significantly slower perform task of this kind than children with TLD. Empirical evidence show that naming speed deficit is associated with reading deficit, and hence, it is believed that the assessment of these skills in preschool children may be of preventive character. Therefore, some researchers of language disorders in children emphasize the importance of therapeutic program contents in children with DLD. Taking into account their own research, state that treatment program of children with DLD should contain a larger number of tasks aimed at development of naming speed skills.[32]

Finally, during the development of the mother tongue structure individual differences are mainly seen at the level of language expression, which is important since individual deviations in the normal development of language expression should not be characterized as delayed development or language disorder. Knowledge about any problems in phonological awareness has resulted in experts' increased interest in creating programs directed to encouraging the development of phonological abilities in typically-developing children, but also in children who show deficits in speech and language development. Some authors suggest targeted programs that would encourage development of phonological awareness, which would be performed two to three times per week in sessions of 10 to 30 mintues during preschool period. Also, it is recommended to perform these activities throughout plays/games and in accordance with the age.[34]

Conclusion

Literature review has shown that former knowledge regarding phonological awareness in children with DLD is primarily a result of comparative studies involving these children and children of normal language development. A large number of studies has demonstrated that children with DLD have weaker performance in phonological awareness tasks, especially in the more complex ones. According to empirical evidence, simpler types of tasks such as analysis and synthesis of sounds and syllables in words, do

not pose difficulties for children with DLD. Furhter analysis of empirical data has shown that the delayed phonological awareness development in preschool children is associated with difficulties later in acquring academic skills, especially the reading skill.

For the assessment of phonological ability different types of tasks are being used and they measure different components comprised by phonological awareness. Literature review has revealed that the FONT test is a valuable tool for assessment of phonological ability in children whose mother tongue is Serbian having in mind the vast amount of empirical findings based on the application of this test, mainly in children with TLD. Also, important insturments for examination of phonological abilities are the PredČip and Emerging Literacy & Language Assessment (ELLA)tests, which have been used in both, children with DLD and children with delayed/slower progression in initial reading.

Finally, literature data give evidence about risks that exist in children with phonological awareness disorders regarding their mastering of school skills, that is, reading and writing. Given the fact that children with reading difficulties have delayed phonological awareness development, it is assumed that intervention during preschool period could be of crucial importance to pevent or reduce literacy difficulties.

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CASE REPORT

VENTRICULAR FIBRILLATION AFTER ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY IN PATIENT WITH LEFT VENTRICULAR ASSIST DEVICE – A CASE REPORT

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Abstract

Congestive heart failure is a growing global health problem. Left ventricular assist device (LVAD) is a method used to extend the life of patients with congestive heart failure as a definitive treatment or to "bypass" the period until heart transplantation. Ventricular arrhythmias in patients with LVAD are not uncommon. The aim of this paper is to present the case of a patient with an already implanted LVAD and the need for appropriate interdisciplinary medical treatment. Case report: We present the case of a 54-year old patient, with implanted LVAD - HeartMate 3 due to severe congestive heart failure. The patient was admitted with jaundice at the PHIU Clinic for Gastroenterohepatology with performed endoscopic retrograde cholangiopancreatography (ERCP)) procedure and a stent was placed in the choledochus duct. Immeasurable blood pressure and pulse were recorded in this patient. The ECG was approaching VF (ventricular fibrillation) and it was all asymptomatic by the patient. LVAD mechanical pump leads to continuous blood flow, which means that patients with LVAD not infrequently have no pulse or measurable blood pressure. Also, in patients with LVAD, ECG pulses are with electrical disturbances. VF and ventricular tachycardia (VT) are ventricular arrhythmias that are often seen on ECG in patients with implanted LVAD. Usually these arrhythmias occur with unknown duration and terminate spontaneously. Conclusion: Patients with LVAD are prone to cardiac arrhythmias. The continuous development of medical devices leads to a continuous educational and clinical approach to patients.

ПРИКАЗ НА СЛУЧАЈ

ВЕНТРИКУЛАРНА ФИБРИЛАЦИЈА ПО ЕНДОСКОПСКА РЕТРОГРАДНА ХОЛАНГИОПАНКРЕАТОГРАФИЈА КАЈ ПАЦИЕНТ СО ВГРАДЕН УРЕД ЗА ЛЕВО ВЕНТРИКУЛАРНА АСИСТЕНЦИЈА – ПРИКАЗ НА СЛУЧАЈ

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Извадок

Конгестивната срцева слабост е растечки глобален здравствен проблем. Уредот за лево вентрикуларна асистенција (LVAD) се користи за продолжување на животот на пациентите со конгестивна срцева слабост како дефинитивен третман или за премостување на периодот до трансплантација на срце. Вентрикуларните аритмии кај пациентите со LVAD не се невообичаени. Целта на овој труд е да се прикаже случајот на пациент со веќе вграден LVAD и потребата од соодветен интердисциплинарен медицински третман. Приказ на случај: Ви претставуваме случај на 54-годишен пациент, со вграден LVAD - HeartMate 3 поради тешка конгестивна срцева слабост. Пациентот е примен со иктерус на ЈЗУ Клиниката за гастроентерохепатологија по што е извршена ендоскопска ретроградна холангиопанкреатографија (ERCP)) и е поставен стент во холедохусниот канал. Кај овој пациент е регистрирано немерлив крвен притисок и пулс. На ЕКГ е регистрирана VF вентрикуларна фибрилација (VF) и сето тоа беше асимптоматски од страна на пациентот. Механичката пумпа на LVAD води до континуиран проток на крв, што значи дека пациентите со LVAD не ретко немаат пулс или мерлив крвен притисок. Исто така, кај пациентите со LVAD, ЕКГ импулсите се со електрични нарушувања. VF и вентрикуларна тахикардија (VT) се вентрикуларни аритмии кои често се гледаат на ЕКГ кај пациентите со имплантиран LVAD. Најчесто овие аритмии се јавуваат со непознато времетраење и спонтано завршуваат. Заклучок: Пациентите со ЛВАД се склони кон срцеви аритмии. Континуираниот развој на медицинските помагала води кон континуиран едукативен и клинички пристап во третманот на пациентите.

Introduction

Congestive heart failure (CHF) is a global health problem. Around 26 millions peoples in the world have this growing health problem. Long time congestive heart failure was treated only with medicaments. But with the increase in the incidence of CHF, especially in the elderly population, the need has arisen for the development of devices with mechanical circulatory support such asLVAD[1,2].

The first LVAD was set by Dr. DeBakey in the distant 1966. Since then, technological LVADs have been greatly improved. In Europe, about 500 LVADs are implanted annually, while in the USA over 1700 devices. Today LVAD is used to extend the life of these people with CHF. LVAD's are used as a definitive treatment or to bridges the period until cardiac transplantation.The use of LVAD has doubled the survival rate and significantly improved the quality of life of these patients with this health problem[3,4].

Episodes of ventricular arrhythmias are not uncommon in patients with LVAD.Ventricular fibrillation (VF) is a malignant arrhythmia that causes chaotic electrical activity of the heart with a lack of ventricular activity and a sharp drop in cardiac output. It leads to hypoperfusion in all organs of the human body and if you do not react quickly with CPR and DC defibrillation, rapid death occurs. VF is the number one cause of sudden cardiac death in the world[5].

We report for our experience with a patient with LVAD after performing endoscopic retrograde cholangiopancreatography(ERCP) who survived a sustained VF of unknown duration and all of this asymptomatic.

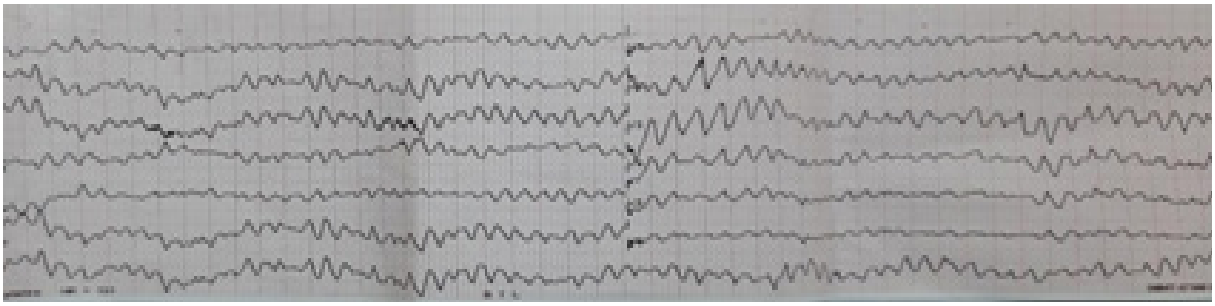
Case report

We describe the case of patient A.D., born in 1973, with implanted LVAD - HeartMate3 (picture 1) due to severe congestive heart failure. The patient had a myocardial infarction three years ago when he had a coronary angiography with three stents placed on the coronary arteries. He has a history of hypertensive diseases, he is diabetic and he was also operated on for anulcusventriculisanguans. He smoked cigarettes for 30 years, until three years ago when he quit. The patient was on regular cardiological, diabetic and gastroenterological therapy.

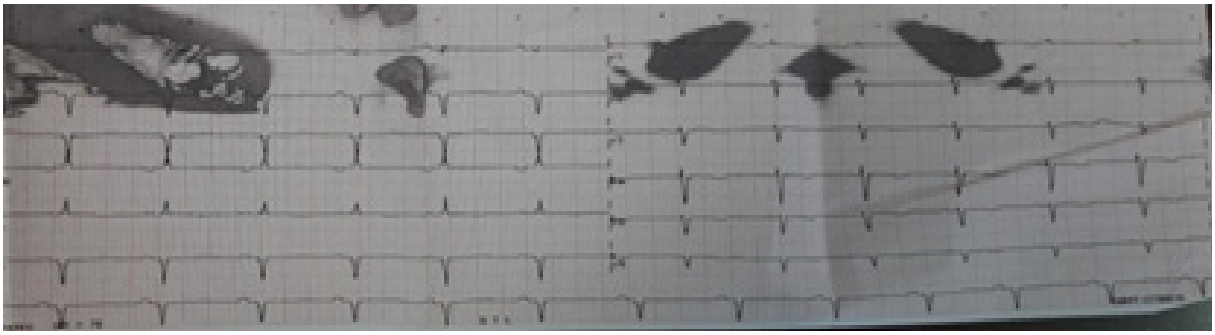
Picture 1. Patient with LVAD

The patient was admitted with jaundice at the PHIU Clinic for Gastroenterohepatologywith hyperbilirubinaemia (total bilirubin 88 μmol / L and direct bilirubin 76 μmol / L), elevated cholestatic parameters (alkaline phosphatase 88 U / L, GGT 867 U / L). Ultrasound revealed a finding of an inflamed calculous gallbladder and also intra and extrahepatic dilatation of the biliary trunk.It was indicated and performed in the patientERCP procedure and a stent was placed in the choledochus duct.

The request for an urgent cardiac consultation was due to the patient's immeasurable blood pressure and abnormal ECG. The cardiac examination revealed that the patient had LVAD implanted almost 2 years ago. There was immeasurable blood pressure and pulse, the ECG was approaching sustained VF (picture 2)and it was all asymptomatic by the patient. After twenty minutes, VF spontaneously terminates in a normal stable sinus rhythm (picture 3).



Picture 2. ECG with VF in patient with LVAD



Picture 2. Spontaneous termination of VF in sinus rhythm

Discussion

A medical examination of a patient with immeasurable blood pressure and pulse, with an ECG showing VF and all of it asymptomatic by the patient is a truly dramatic experience. Especially if you have no previous experience with patients with implanted LVAD. Cardiologists usually triage patients with CHF forcardiac surgery implantation of LVAD. But many cardiologists do not follow these patients after LVAD implantation. The possibility of sudden cardiac death in these patients is a reason for cardiologists and clinicians in general to be cautious in the treatment of these patients and that is why we present this case report.

LVAD enables continuous flow to patients. Indications for LVAD implantation are patients with a low left ventricular ejection fraction (<25%) who ware inotrope dependent or were persistently NYHA functional class IIIb or IV despite optimal medical therapy. Also, maximal oxygen consumption under 12 ml/kg/min was often used as an inclusion criterion.Implantation of LVAD it's being used to extend the life ofpatients with congestive heart failure as a definitive treatment or to "bypass" the period until heart transplantation.

HeartMate 3 heart pump is a small, implantable mechanical circulatory device that serves to support patients with heart failure.This pump utilizes technology known as Full Maglev (full magnetically-levitated) Flow technologywhich reduces the damage to the blood flowing through the pump6. The pump is implanted at the apex of the heart where it receives blood from the left ventricle and transmits it through the tube to the aorta. It works by pumping blood in a continuous flow from the left ventricle to the aorta and further to the whole organism.External parts of the LVAD are the controller which is the brain of the whole system and batteries which are the energy of the system.The pump is connected to a cable driveline that runs through the skin of the abdomen and is connected to the controller externally.Parameters that are monitored on HeartMate 3 LVAD are: speed (normal range is 8600 to 9800 rpm), flow (normally 4-6 L/min), power (normal range is 4-7W) and pulsatility index (PI typically range from 3 to 7). It has been medical proven that there is a significant improvement in the ejection fraction after one year of using LVAD[1,6,7,8].

The impeller in a mechanical pump rotates thousands of times per minute. This leads to continuous blood flow, which means that patients with LVAD not infrequentlyhave no pulse or measurable blood pressure. Patients with LVADs not infrequentlydo not have a palpable pulse. Because of that traditional blood pressure measurement by auscultation or automated cuff is less reliable.LVAD guidelines recommend the mean arterial blood pressureto be in the range of 70 to 80 mm Hg. It should not exceed 90 mm Hg.And all this is a usual and expectedcondition in patients with implanted LVAD[9].

In patients with LVAD, ECG pulses are with electrical disturbances. These patients have ECG changes that did not precede implantation normally occur.VF and VT are ventriculararrhythmias that are not infrequentlyseen on ECG in patients with implanted LVADand strangely they are often well tolerated3,5. But there are also cases in which sudden cardiac death occurs. Most often due to continuous flow and electrical interference these arrhythmias occur with unknown duration and terminate spontaneously.Sacha P. Salzberget al., describe a case report of a patient who survived a seven-hour sustained VF10. In our case the patient converted to sinus rhythm after twenty minutes but we have no data when VF started because the patient was not placed on continuous ECG monitoring.

The rapid technological development in the world especially in medical technology leads to constant changes in the treatment of patients. However, VF is a deadly arrhythmia. Patients with LVAD who are exposed to

other medical procedures must be very carefully monitored and specifically monitor their clinical condition. Of course, it should be considered that there is no possibility of electrolyte imbalance that needs to be corrected with fluid and electrolyte. Most patients with LVAD due to CHF already have pre-implanted ICD, in which case the level of defibrillation of the implanted ICD in these patients should be checked and eventually reprogrammed. Also, patients or medical staff should perform a daily self-test on the LVAD to ensure that the device is working properly[3,9,11,12,13]. The approach to these patients should be multidisciplinary.

Conclusion

We presented this case report to emphasize the specificity as a medical case and awareness of the need for special treatment of these patients. Patients with LVAD should be closely monitored for arrhythmias before / for / after any other more serious medical intervention. The occurrence of VF requires professional supervision and appropriate medical management.The continuous development of medical devices leads to a continuous educational and clinical approach to patients.

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CASE REPORT

AUTOIMMUNE HASHIMOTO THYROIDITIS WITH CONCOMITANT AUTOIMMUNE HEPATITIS

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Key words: autoimmune thyroiditis, autoimmune hepatitis, antinuclear antibodies, antithyroid antibodies

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Abstract

So far, the literature data have presented a combination of several autoimmune triggered disease in patients, but the research is scarce and very limited. In this context we present a rare case of autoimmune thyroiditis with a concomitant autoimmune hepatitis. Hashimoto thyroiditis is an autoimmune disorder in which immune cells lead to impairment, destruction of the thyroid hormone producing cells and tissue fibrosis with consecutive primary hypothyroidism. Autoimmune hepatitis is a chronic liver disease with unknown etiology, which is assumed to be T cell mediated condition where immune cells produce autoantibodies responsible for inflammation, destruction and fibrosis of the hepatic parenchyma. In this case report, we discuss the possible correlation in the spectrum of autoimmune diseases concerning Hashimoto thyroiditis and autoimmune hepatitis.

ПРИКАЗ НА СЛУЧАЈ

АВТОИМУН ХАШИМОТО ТИРОИДИТИС АСОЦИРАН СО АВТОИМУН ХЕПАТИТИС

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Цитирање: Маневска Н, Стојковска Н, Ташева Љ, Јовановски-Срцева М, МаказлиеваТ, Стојаноски С. Автоимун Хашимото тироидитис асоциран со автоимун хепатитис. Арх. Ј Здравје 2022;14 (1) 151:156.

doi.org/10.3889/aph.2022.6042

Клучни зборови: автоимун тироидитис, автоимун хепатитис, антинуклеарни антитела, антитироидни антител

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Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

До сега, во литературата се среќаваат податоци за комбинација од неколку автоимуни болести кај различни пациенти, но студиите од ова поле на истражување се оскудни и ограничени. Во овој приказ на случај, претставуваме редок случај на автоимун тироидитис со истовремен авотимун хепатитис. Хашимото тироидитис е автоимуно заболување во кое клетките на имуниот систем доведуваат до оштетување и уништување на клетките коишто го произведуваат хормонот на тироидната жлезда и ткивна фиброза со последователен примарен хипотироидизам. Автоимуниот хепатитис е хронично заболување на црниот дроб со непозната етиологија, за кое се претпоставува дека е состојба посредувана од Т-клетките каде што имуните клетки произведуваат автоантитела одговорни за воспаление, уништување и фиброза на хепаталниот паренхим. Во овој приказ на случај ја дискутираме можната корелација во спектарот на автоимуни болести кои се однесуваат на Хашимото тироидитисот и автоимуниот хепатитис.

Introduction

Autoimmune thyroid diseases (AITD) are organ specific autoimmune disorders, where both genetic and environmental factors are included into the etiological spectrum[1]. Patients with AITD are predisposed to develop other autoimmune disorders. Autoimmune hepatitis (AIH) is a disease of unknown etiology in which destruction of the liver tissue occurs, resulting in a permanent liver tissue damage that eventually leads to liver failure. AIH occurs in children and adults of all ages; has a female predominance and affects different ethnic groups[2].

In this paper we report a rare case of AIH in a patient with preexisting Hashimoto thyroiditis (HT).

Case report

We present a 58-year-old female referred to our Institute of Pathophysiology and Nuclear Medicine in June 2013 with symptoms of difficulties in swallowing and tachycardia, for assessment of possible thyroiditis. Initial examination excluded subacute thyroiditis. The laboratory findings revealed normal sedimentation rate and TSH and FT4 levels. However, levels of aTPO were increased 195 μIU/mL (reference values <10 μIU/mL), which was an indicator of AITD – Hashimoto thyroiditis, in the euthyroid phase. The ultrasound (US) of the thyroid gland presented hypoechoic gland structure with hyper-echoic reflections which additionally pointed to the AITD. Since the US detected also a thyroid nodule, a fine needle aspiration biopsy (FNAB) was performed. The results of the FNAB showed a combination of benign thyrocytes and lymphocyte infiltration.

The patient was scheduled for annual follow check-ups and treatment with Selenium (50 μg per day) was initiated. In 2016, TSH levels increased above the reference range and hypothyreosis was diagnosed. Anti-thyroglobulin antibodies (aTG) were also highly elevated (>3000 μIU/mL). Treatment with 25 μg of levothyroxine was initiated.

In 2017, the patient gave data that she was more prone to tiredness in the last year and she felt a constant pain under the right rib arch. She was referred to the University Clinic for Gastroenterohepatology for further examination. The results from the blood analysis showed increased levels of the liver enzymes AST 100 (normal ranges 7-52 U/L) and ALT 86 (normal ranges 13-39 U/L). Ultrasound of the abdomen was performed presenting liver inhomogeneous structure with fibrotic changes. Additional analysis suggested and confirmed the diagnosis behind the liver changes, such as serum auto-antibodies level and liver biopsy. Serum levels of the antinuclear antibodies (ANA) were elevated seven times above

reference value. ANA screen was 7.08 IE/mL (reference value < 1 negative).

The enzyme status profile is presented in Table 1.

Table 1. Enzyme status profile

Enzymes	U/L	Reference value
Alkaline phosphatase	136	36-126 U/L
Aspartate aminotransferase	26	10-34 U/L
Alpha amylase	76	30-110 U/L
Lactate dehydrogenase	142	< 248 U/L
Gamma-glutamyl transferase	136	9-64 U/L
Alanine aminotransferase	33	10-45 U/L

Liver biopsy was additionally performed and confirmed the diagnosis of autoimmune chronic active hepatitis. The patient was also put on a hepatoprotective treatment and scheduled for regular check-ups at the Gastoentorohepatology Clinic, in addition to regular examinations at the Institute of Pathophyisology and Nuclear Medicine.

Discussion

The increased liver biomarkers in patients with autoimmune thyroiditis can indicate an underlying autoimmune hepatitis, as was the case we herein presented. Our patient had elevated liver biomarkers (AST and ALT) five years after the initial diagnosis of AITD. Autoimmune serology also confirmed presence of antinuclear antibodies, which were seven times above the reference range. The levels of anti-cytoplasmatic and other analyzed autoantibodies of the IgG class were within the reference range. The seronegativity for the already mentioned auto- antibodies did not rule out the AIH. The seropositivity for ANA was a diagnostic factor that led to the necessity of performing a liver biopsy. The biopsy results were in favour of autoimmune chronic active hepatitis.

Hashimoto thyroiditis is the most frequent autoimmune disease that affects the thyroid cells by developing antibody mediated processes, lymphocytic infiltrations, formations of antithyroid antibodies and consecutive fibrosis of the tissue[3, 4].

Clinical evidence that highlights the coexistence of two or more autoimmune diseases in one patient is abundant. Since Hashimoto thyroiditis is the most common thyroid autoimmune disease (AD), it is frequently associated with another organ specific or organ nonspecific AD[5, 6].

In several studies, patients who have been suffering from rheumatoid arthritis (RA) are known to have multiple autoimmune disorders including HT. The prevalence of AITD and RA varies between regions and countries such as 37% in Columbia (America), 30% in Egypt (North Africa), 24.4% Scotland (Europe), 15.9% in Turkey (Asia). A subject of controversy for some authors is the increased prevalence of AITD in patients with systemic lupus erythematosus (SLE). The prevalence of HT in SLE, mixed connective tissue diseases, Sjögren's syndrome and polymyositis/dermatomyositis were much higher than in the general population[7, 8, 9].

Autoimmune hepatitis is an inflammatory condition of the liver with

chronic progressive characteristics. It is presented with elevated amino transferases, persisting antinuclear antibody, high levels of IgG and infiltration with plasma cells and lymphocytes. There is no specific evidence about its etiology up to date. There are two types of autoimmune hepatitis described in the literature. The first one is known as type 1, which is characterized with the presence of anti-smooth muscle antibodies in which antinuclear antibodies could be but it is not obligatory to be present. The other type is type 2, associated with anti-liver microsomal type 1 antibodies or anti-liver cytosol type 1 antibodies[10, 11].

Antinuclear antibodies are the first autoantibodies to be related with AIH, but they are not disease specific. Scientific studies showed that 50-75% of AIH patients are ANA-positive. ANA can sometimes also be found in healthy persons or patients with other liver diseases including fatty liver disease, drug produced liver lesions or viral hepatitis. Antinuclear antibodies in autoimmune hepatitis attack the nuclear chromatin, histones, centromere, double-(ds) and single-(ss) stranded deoxyribonucleic acid (DNA) and other constituents of the cell nucleus.

However, testing for ANA antibodies is necessary for AIH diagnosis[12].

In some studies, the authors confirm that patients with AH are more likely to develop concomitant autoimmune disease of the thyroid gland. Patients who had AITD and AILD showed higher levels of IgG, since IgG was positively correlated with thyroid antibodies and thyroperoxidase antibodies[13, 14].

Since AIH is a progressive disease, a missed diagnosis can have serious consequences. If untreated, AIH can have a fatal outcome due to changes of the liver tissue that might lead to cirrhosis and consecutive liver failure. Elevated levels of liver enzymes, alanine transaminase (ALT) and aspartate transaminase (AST) are common findings in asymptomatic patients. Even though history and physical examination of the patient might not suggest an underlying condition, a stepwise analysis should begin based on the prevalence of diseases that cause elevations of transaminase levels. Most common causes that can lead to liver enzymes elevations are excessive alcohol consumption, family history of hemohromatosis, hepatitis B and C and medications. Various medications are known to cause liver damage. Many of these are often included in daily practice such as NSAID, antibiotics, anti-seizure drugs, anti- tuberculosis drugs, antidepressants. The absence of specific signs and lack of symptoms and specific criteria makes the diagnosis of drug-induced liver damage (DILI) difficult. DILI occurs via several known mechanisms. Among these mechanisms are impairment of the structural and functional integrity of the liver, production of a metabolite that affects the liver structure, beginning with a systemic hypersensitivity response, production of a reactive drug metabolite that binds to liver proteins to produce new antigenic drug-protein adducts, which are subsequently targeted by hosts' defenses. Liver biopsy is used and might be quite a helpful diagnostic tool when there is an undefined liver disease or possible autoimmune hepatitis[15].

The marking of injury and typical characteristics of AIH are imprecise, thus the differential diagnosis is very comprehensive. In AIH cases with an acute hepatitis presentation of tissue deterioration, the differential diagnosis predominantly

includes acute viral hepatitis and drug- induced liver injury (DILI). In cases with a chronic hepatitis pattern, chronic viral hepatitis, other autoimmune diseases and/or Wilson disease should be appraised. Idiosyncratic DILI can mimic the clinical, biochemical and serological constitution of AIH. In non-acute AIH, non-alcoholic steatotic hepatitis (NASH) is a foremost clinical differential diagnosis. Positive autoantibody serology, usually with low levels, is present in 20-48% of NASH patients. It is necessary to exclude infection with hepatotropic viruses before the diagnosis of definite or potential AIH. Serological testing is recommended in all patients with this differential diagnosis, especially for hepatitis virus A and hepatitis virus E (HEV) infection[16].

Conclusion

Patients with HT who report symptoms of liver involvement and have high levels of aTG and aTPO autoantibodies should be referred for further investigation for possible concomitant AIH, since there could be a possible correlation and overlap in the spectrum of autoimmune diseases.

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CASE REPORT

MORNING GLORY SYNDROME

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Abstract

Morning Glory Syndrome (MGS) is an uncommon congenital anomaly of the eye nerve (optic nerve) that resembles a flower known as morning glory, impairs vision, and may be associated with both ocular and non-ocular abnormalities. It has a characteristic fundoscopic appearance consisting of a large funnel-shaped cavity on the optical disc. We register an unusual congenital anomaly of the optic disc in a three-year-old female child.

ПРИКАЗ НА СЛУЧАЈ

СИНДРОМ НА “MORNING GLORY”-

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Клучни зборови: Синдром на “Morning Glory”, оптички диск.

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Извадок

Синдромот на “Morning Glory” (MGS -Morning Glory Syndrom) е невообичаена конгенитална аномалија на оптичкиот нерв кој наликува на цвет познат како „morning glory“, го нарушува видот и може да биде поврзан и со окуларни и неокуларни абнормалности. Има карактеристичен фундоскопски изглед кој се состои од голема празнина во форма на инка на оптичкиот диск. Во овој труд презентираме невообичаена вродена аномалија на оптичкиот диск кај три годишно дете од женскиот пол.

Introduction

DMorning Glory Syndrome (MGS), first described by Kindler[1], is a congenital defect, a malformation of the optic nerve that resembles a flower known as morning glory. It is characterized by an enlarged funnel-shaped cavity in the optic disc, the part of the eye where the optic nerve fibers leave the retina. The disc is enlarged and has a white center (which gives the appearance of a white pupil). The number of blood vessels that are twisted is increased because they come from the enlarged disc that has a white center, which results in this malformation to look like the petals of a flower[2] . In the medical literature, most reported and documented cases are unilateral (affecting only one eye), sporadic (without other cases in the family), and occur in females [3-6] .

Symptoms include very poor eyesight with poor visual acuity. MGS can occur on its own or in combination with other eye abnormalities, such as strabismus or lazy eye (amblyopia) or other non-ocular problems such as brain disorders[7-9]. Typically, individuals with non-ocular findings also have a broad head, a suppressed nasal bridge, and a defect or cleft in the middle of the upper lip[9]. MGS appears to be caused by the failure of the optic nerve to fully form as the baby develops. Manschot considers MGS to be a mesoderm disorder10. According to Lee & Traboulsi MGS is not inherited and the genetic defects associated with it have not been confirmed[11].

The most severe complication is retinal detachment and can occur in about 26-38% of people with MGS[12]. MGS is sometimes misdiagnosed as optic nerve coloboma[8].

The prevalence of MGS is unknown, a study conducted in Stockholm, Sweden registered a prevalence of 22.6 / 100,000[3].

Treatment involves surgery and may result in some vision recovery. Depending on other related abnormalities, some patients require referral to several specialties such as neurosurgery, interventional neuroradiology, otolaryngology, and dentistry. All people diagnosed with “morning glory” disc anomaly should have a CT scan and MRI of the head [3-4].

Case report

Child 3 years old, girl, was scheduled at the Department of Pediatric Ophthalmology at the Clinic for Eye Diseases Skopje with Dg.OD Esotropia cum hypertropia by a specialist ophthalmologist from secondary health care.

During taking the anamnesis from the girl’s mother, it is found out that the curvature of the right eye inside the nose is from birth. Pregnancy was normal and the baby was born on time.

During the examination, the child is visibly upset and it is not possible to determine the visual acuity of both eyes and to examine the fundus, but the curvature of the right eye is visible.

Due to the age of the child, it was decided to examine the fundus under general anesthesia in the operating room with the help of a fundus camera.

An examination of the fundus under anesthesia diagnoses Morning Glory Syndrome of the right eye.

Bottom of the right eye: Papilla nervi optici (optic disc) enlarged to pale white. There are no blood vessels

through the gliosis tissue. Macula Lutea (point of clear vision) has a clear reflex. The retina is neat (Picture 1).

Left eye's left eye: Papilla nervi optici is at the level of the retina with clear boundaries, blood vessels with normal lumen and fullness. Macula Lutea has a clear reflex

Therapy: try to close the better eye (left eye) for 3 hours consecutively per day.

Advice is given for ENT examination and consultation with a neurophthalmologist.

Picture 1. Fundus of the right eye

Discussion

The etiology of the Morning Glory anomaly is poorly understood. There are some similarities with coloboma on the optical disc.

The visual prognosis in individuals with an anomaly of morning glory is poor. In addition to the abnormal disc itself and the propensity for serous retinal detachment, there is an added variable of complexity of high refractive errors, amblyopia, and strabismus. Although surgery for eye strabismus and treatment of anisometropic amblyopia is recommended and may result in some vision restoration, dramatic improvements are rare5. Treatment of other related abnormalities requires an interdisciplinary approach, often including neurosurgery, interventional neuroradiology, otolaryngology, and dentistry. All patients who are found to have a disc anomaly on a routine ophthalmologic examination should have a MRI of

the brain, MRI, and timely referrals to an appropriate subspecialist.

Conclusion

Patients with MGS need to be explained the need to wear goggles for two compelling reasons. Because the individual with MGS usually has beneficial vision in only one eye, preserving normal eye vision is essential. The strong link between MGS and retinal detachment also means that contact sports should be avoided, and if this is not possible, goggles designed to reduce the risk of ocular trauma should be worn. Educating the patient about the symptoms of retinal detachment will also be helpful as emergency medical care can prevent the detachment from worsening and allow for careful monitoring of the condition.

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CASE REPORT

STRAIGHT WIRE AND SEGMENTED TECHNIQUE IN CANINE RETRACTION

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Abstract

Correct positioning of the canines after their retraction is of great importance for the function, stability and esthetics. Aim: Two case reports were presented to compare the efficiency of two techniques for canine retraction, segmented mechanics using 0.017 x 0.025 TMA T-loop vs sliding straight-wire mechanics using elastomeric chains. Material and methods: The first case describes orthodontic treatment with 0.017 x 0.025 TMA T-loop whereas the second case describes a 9 mm canine retraction using elastomeric chains. Results: Depending on the type of malocclusion both techniques for canine retraction can be used. Post treatment results showed canine retraction with good anchorage control and no mesial movement of the molars.Conclusion: Both techniques provide an optimum rate of tooth movement and none of the methods can be considered superior in terms of tooth movement or side effects, including rotation, tipping, root resorption, anchorage loss, as well as associated pain.

ПРИКАЗ НА СЛУЧАИ

ТЕХНИКА НА ПРАВ ЛАК И СЕГМЕНТИРАНА ТЕХНИКА ПРИ РЕТРАКЦИЈА НА КАНИН

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Извадок

Правилна позиција на канините по нивната ретракција е од голема важност за функцијата, стабилноста и естетиката. Цел на трудот: Приказ на два случаи со цел да се спореди ефикасноста на две техники за ретракција на канините, сегментирана техника користејќи 0.017 x 0.025 TMA Т-омча версус техника на прав лак користејќи еластомерни ланци. Материјал и метод: Првиот случај е приказ на ортодонтски третман со 0.017 x 0.025 TMA Т-омча, додека вториот случај е приказ на 9мм ретракција на канин со еластомерни ланци. Резултати: Во зависност од типот на малоклузија можат да се користат и двете техники за ретракција на канинот. Добиените резултати по ретракција на канинот покажуваат добра контрола на анкоражата без мезијално движење на моларите. Заклучок: Двете техники покажуваат оптимална стапка на движење на забите и ниеден метод не може да се смета за супериорен во однос на другиот во поглед на движење на забите или несакани ефекти, вклучувајќи ротација, инклинација, ресорпција на коренот, губиток на анкоража, како и придружена болка.

Introduction

Anterior dental crowding with the need of canine retraction is the most frequently encountered condition in orthodontic practice[1]. Teeth alignment plays an important role in facial esthetics and facial harmony and the presence of maxillary dental crowding is esthetically less acceptable when the 4 maxillary incisors are misaligned[2]. The presence of crowding associated with canine ectopic eruption due to arch length tooth material discrepancy further motivates patients to seek orthodontic treatment[3, 4]. On the other hand there is malocclusion like Angle Class II division I, where the choice of treatment depends on patient's age, etiology of the deep bite, skeletal and dental morphology, vertical dimension, the relationship of the teeth to the surrounding soft tissue structures, length of lip and occlusal plane[5]. Not all patients with deep overbite and increased overjet should be treated with the same mechanics[6]. Canine retraction is a very important step in treatment of patients with crowding, an ectopically erupted canine and first premolar extraction cases. Correct positioning of the canines after retraction is of great importance for the function, stability, and esthetics. Canines can be retracted by friction (sliding) and frictionless (non-sliding) mechanics, using T-loops for tooth movement. Both techniques depend on the type of malocclusion. Continuous mechanics in severely crowded cases results in round tripping with proclination of the anterior teeth during leveling and aligning. This is followed by en-masse retraction of the entire anterior segment thereby increasing treatment time. On the contrary, the segmental mechanics involves placing brackets only in the posterior segment and initially and individually retracting the canine into the premolar extraction space[7]. This provides space for unraveling the crowding in the upper and lower arch without proclining the anterior teeth. The segmented arch has been designed to deliver relatively light constant forces with reasonable control over the anchor units[8,9]. The aim of this paper was to present two case reports and to compare the efficiency of the two techniques used.

Case report 1

In this case report, we describe a 16-year-female patient presented with a chief complaint of irregularly placed upper and lower front teeth. The patient was diagnosed as severe Angle's Class II malocclusion with maxillary prognathism and skeletal deep bite. She had dental Class II division 1 malocclusion associated with an increased overjet, 14 mm, and excessive gingival display on smile, 4 mm overbite and super-eruption of maxillary incisors, with occlusal cant, presence of bad oral habits and infantile swallowing. Both arches exhibited minor crowding (Fig.1 and Fig. 2).

Figure 1. Pretreatment facial photographs.

Figure 2. Pretreatment intraoral view of the patient.

Treatment objectives

The primary objective was to correct the deep bite because of its potentially detrimental effects on periodontal health, temporomandibular joint function, as well as esthetics. Due to the patient's vertical maxillary excess, the large interlabial gap and the long lower facial height the treatment objectives were to correct the increased overjet and to reduce the maxillary incisor proclination with retraction of the incisors and canines in the space of the extracted first premolars. Treatment objectives for the occlusion were to correct molar and canine relation and to achieve canine guidance with anterior disclusion. For the soft tissue the treatment objective was to achieve lip competency and ideal facial profile.

Treatment plan and progress

Due to the fact that the patient avoided surgical method for her malocclusion correction, our treatment plan in this case was alternative (camouflage) with upper premolars extraction. The upper first premolars were extracted to reduce the overjet and to align canines properly in the arch form. 0.022 × 0.028 MBT prescription was used. Alignment was done by 0.014 and 0.016 Ni-Ti and active tiebacks. Most of the extraction space was utilized for alignment of canines. In the first phase, we did a 9 mm canine retraction with preserved vertical dimensions of upper incisors (Fig. 3). Canine retraction incorporated new forces and moments into the system so the good anchorage control to overcome the side effects of the mechanics was crucial. In the second phase of our treatment, we established Class I canine and Class II molar relationship and we achieved ideal overjet and overbite by correcting the incisor inclination along by en-masse retraction of the incisors and their intrusion. Due to the forces and moments created by the system of incisor intrusion and canine retraction, the largest number of posterior teeth was incorporated into posterior segments and a good anchorage control was achieved. For incisor intrusion and canine retraction with elastomeric chains in order to prevent incisor bite deepening we used 0.017 × 0.025 Connecticut intrusion arch and 0.019 x 0.025 stainless steel as base archwire7. We ligated and tied the intrusion arch at the lateral incisors and between the central incisors to prevent the loss of distal anchorage and to prevent the extrusive force generated on the incisors when the canine retraction was done[11]. Molar relation was corrected by light Class II elastics. Finishing was accomplished with coordinated upper and lower 019×.025 stainless steel wire (Fig. 4).

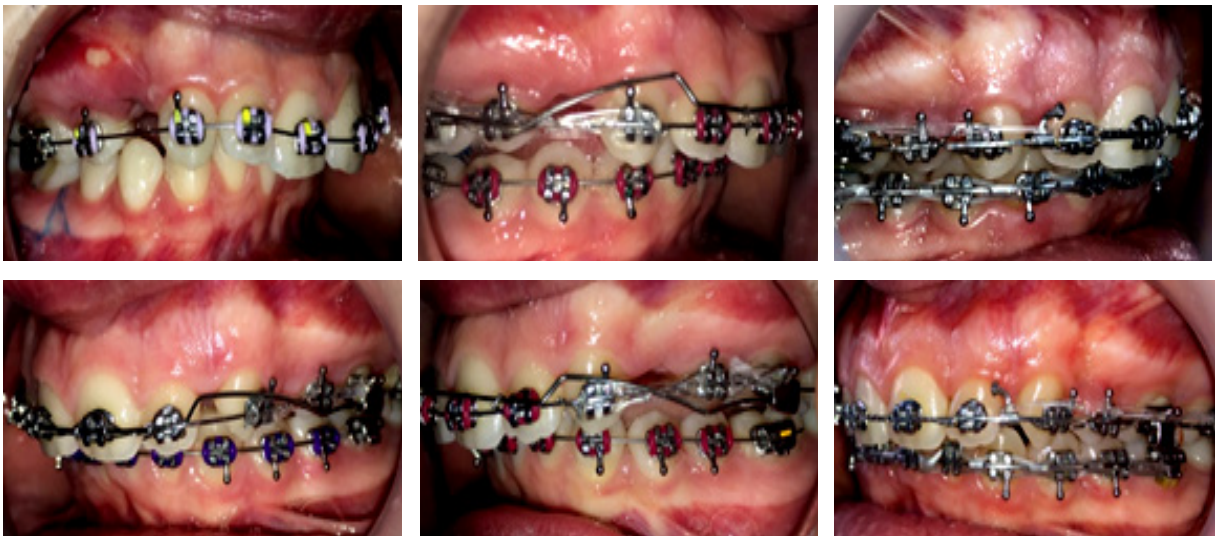

Figure 3. First phase: canine retraction in the extraction space on both sides.

Figure 4. Second phase: incisor intrusion and Class I canine and Class II molar relation shipestablished.

Treatment results

The change in our patient's smile was the most impressive part of the treatment. Outstanding results were achieved with an improved facial profile and smile harmony (Fig 5). With extraction of the first upper premolars, 9 mm retraction of upper canines was achieved.

The Class II molar relation was fixed and Class I canine relationship was corrected and occlusal contacts were obtained between all of the other teeth, especially the canines. A mutually protected occlusion was obtained with stable contacts in centric relation and efficient protrusive movements, as well as right and left lateral movements (Fig. 6).

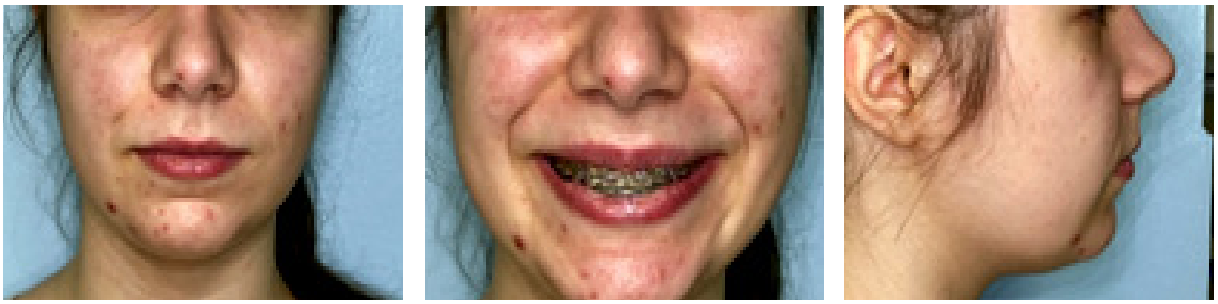

Figure 5. Facial and smile photographs at the end of the treatment

Figure 6. Intraoral view at the end of the treatment.

Case report 2

In the second case report we describe a 17-year-old female patient with chief complaintof her unpleasant smile, anterior bimaxillary crowding, an ectopically erupted upper left canine,buccally positioned and dental arch asymmetry (Fig. 7).

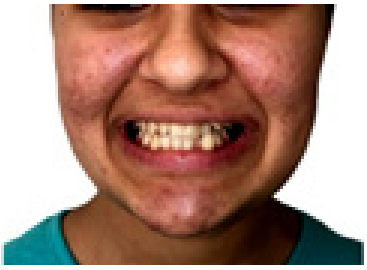

Figure 7. Extraoral view of patient's smile before orthodontic treatment.

Intraoral examinatiot described Angle class I on both sides, III Class tendency on the left side in the canine region, bimaxillary crowding and palatinally placed left lateral incisor (Fig8).

Figure 8. Intraoral view of the patient before treatment.

Ortopantomographic radiograph showed ectopically erupted tooth 23, not erupted teeth 18, 28 and 38 and 48 already in occlusion (Fig.9).

Figure 9. Orthopantomografic radiograph of the patient before treatment.

Treatment plan and progress

Due to space deficiency for canine retraction the upper left first premolar was extracted. Segmented technique involved placing braces only on the teeth of the posterior segment and retracting the ectopically placed canine at the site of the extracted first premolar. This provided space in the arch for leveling the teeth in the anterior segment without their proclination as would have been the case if a straight-wire technique was applied and all teeth were aligned at the same time. An absolute anchorage for canine retraction and no mesial movement of the molars was planned. Properly aligned teeth (upper left lateral incisor and upper right central incisor) were not included in the leveling phase in order to prevent their inclination and to prevent the generation of unfavorable interbracket geometry resulting in the formation of an occlusal cant and thereby in reducing treatment time. With 0.017 x 0.025 segmental titanium molybdenum alloy T-loop, the horizontal force acted on the tooth performing its bodily distalization and its retraction by closing the extraction space. For this case of mesial typing of the canine, the T-loop was activated horizontally until canine correction was achieved. Once the canine correction was achieved, the activation of the standard T-loop began with a moment of reactivation and horizontal activation, which produced a translatory bodily canine movement. Depending on the position of the canines in the dental arch, anti-rotation bends are used to overcome the tendency for the canines to rotate. The T-loop was positioned closer to the canine so that it occupied an asymmetric position relative to the middle of the distance between the canine and the molar. For a T-loop with a height of 7 mm, a horizontal length of 10 mm with an activation of 3 mm, strength of 100 g was obtained (Fig10). After 5 months of individual canine retraction with 3mm activation at each visit and leveling of teeth with 0.014 nickel titanium arch, an arch protocol was used: 0.016 nickel titanium, 0.016 stainless steel and 0.016 x 0.022 nickel titanium and 0.017 x 0.025 stainless steel. After the treatment with segmented arch and achieving correction of the ectopically positioned canine in Angle class I relationship in 5 months, the second phase of our treatment was continued with straight wire technique in order to correct the maxillary and mandibul crowding, to achieve ideal overjet and overbite and to improve incisor inclination, which, led to improved occlusion and satisfactory

smile for the patient. By presenting this case report, we have highlighted the efficiency of segmented mechanics to optimize the orthodontic treatment, to reduce the duration of treatment time and to achieve ideal results without side effects on the surrounding teeth and tissues. The use of good biomechanical principles helped us to achieve all treatment goals and objectives in a very short period (Fig11).

Figure 10. Intraoral view of T-loop and initial phase of orthodontic treatment of canine retraction.

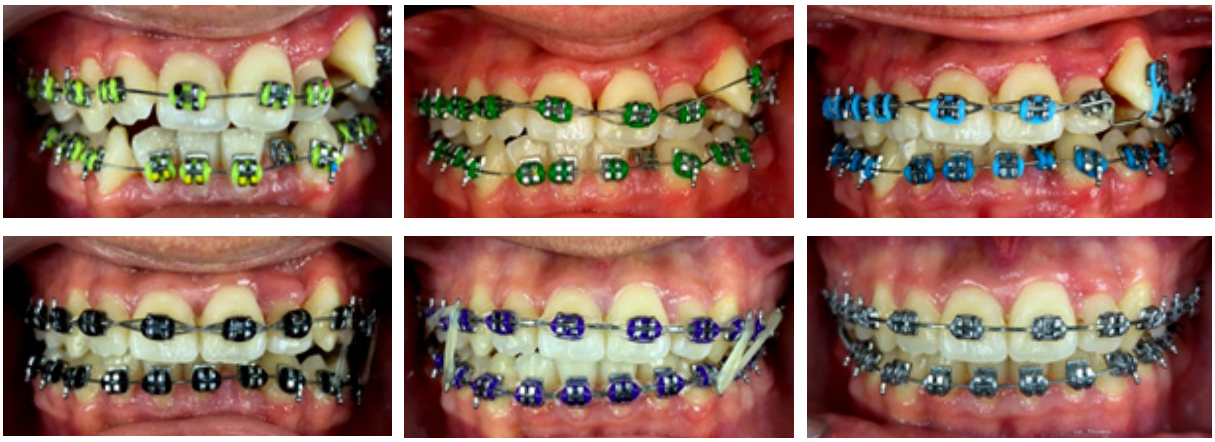

Figure 11. Intraoral view of second phase of orthodontic treatment.

Treatment results

The results of our treatment showed correction of the ectopic placement of the canine. By canine distalization for 7 mm in place of the extracted premolar, the first-class Angle was obtained as well as sufficient space to resolve the anterior maxillary crowding. The inclination of the incisors was improved, the dental midlines coincided with each other and with the face and an ideal overjet and overbite were obtained. We achieved improvement of the occlusion and a satisfactory smile for the patient by correcting the maxillary and mandibular crowding and good maintenance of the buccal occlusion on both sides, both in canine and molar regions. We achieved stable occlusal contacts in central occlusion as well as absence of occlusal interferences during mandibular excursions (Fig.12 and Fig.13).

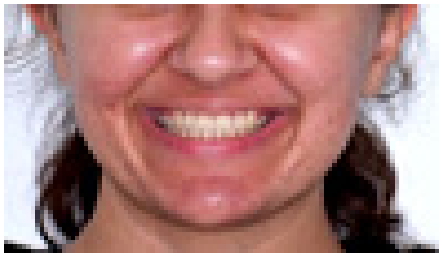

Figure 12. Extraoral view of the patient at the end of the treatment.

Figure 13. Intraoral view of the patient at the end of the treatment

Discussion

Since the canine retraction procedure takes the longest duration of the entire orthodontic treatment, the main goal is to achieve a rapid and controlled canine retraction with minimal anchorage loss. There are two main canine retraction mechanics: the sectional mechanics which involves frictionless tooth movement, and the continuous mechanics involving friction tooth movement. The friction persists between archwire and bracket when pulling the canine distally using sliding mechanics. On the other hand, frictionless mechanics imply the use of the sectional method such as the use of Burstone's T – loop. Different types of mechanisms have been described for correcting tooth. A controlled tooth movement is always the goal of an orthodontist especially during the phase of canine retraction. Depending upon the relationship of the line of action of the force to the center of resistance of the tooth, prediction of tooth movement in the three planes of space is possible[10-13]. Therefore, to preserve supporting tissues and prevent dental trauma and resorption, in addition to performing the treatment in a predictable way and within a shorter period of time, in both cases we decided to extract the first premolars to ensure the proper positioning of the maxillary canines in the dental arch. Segmented TMA T-loop showed three dimensional controls[14]. Segmented T-loop served as a retraction spring, which offered not only a distal driving force on the canine but also a moment for anti-distal tipping as well as torque control of canine[15-17]. As the retraction progressed, the ectopic tooth was moved distally from the root of the lateral incisor. In the last stage,

a vertical component of force operating on the canine became more desirable. On the other hand, many retraction devices could be used to represent the continuous mechanics technique. However the choice of elastomeric chains used in this study was based on the fact that due to the incisor torque control and the control of upper molars position, the force that they produced was favorable in space closure[18].

Conclusions

Based on the favorable results, it would be safe to assert that the treatment adopted in these clinical cases was the most appropriate one. Because of the large space deficiency for the ectopically placed canine and the facial features, one premolar extraction was critical to treatment success. Controlled movements of the canine with the aid of segmental T-loop and proper anchorage control enabled a simple and predictable approach. Due to the increased overjet and the other symptoms in the second described case, the alternative treatment with upper premolars extraction was crucial for treatment results. Both techniques described provided an optimum rate of tooth movement and none of the methods can be considered superior in terms of tooth movement or side effects, including rotation, tipping, root resorption, anchorage loss, as well as associated pain.

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