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Betimi i Hipokratit

Në çastin kur po hy në radhët e anëtarëve të profesionit mjekësor premtoj solemnisht se jetën time do ta vë në shërbim të humanitetit. Ndaj mësuesve do ta ruaj mirënjohjen dhe respektin e duhur. Profesionin tim do ta ushtroj me ndërgjegje e me dinjitet. Shëndeti i pacientit tim do të jetë brenga ime më e madhe. Do t'i respektoj e do t'i ruaj fshehtësitë e atij që do të më rrëfehet. Do ta ruaj me të gjitha forcat e mia nderin e traditës fisnike të profesionit të mjekësisë.

Kolegët e mi do t'i konsideroj si vëllezër të mi.

Në ushtrimin e profesionit ndaj të sëmurit tek unë nuk do të ndikojë përkatësia e besimit, e nacionalitetit, e racës, e politikës, apo përkatësia klasore. Që nga fillimi do ta ruaj jetën e njeriut në mënyrë apsolute. As në kushtet e kërcënimit nuk do të lejoj të keqpërdoren njohuritë e mia mjekësore që do të ishin në kundërshtim me ligjet e humanitetit. Këtë premtim po e jap në mënyrë solemne e të lirë, duke u mbështetur në nderin tim personal.

The Oath of Hippocrates

Upon having conferred on me the high calling of physician and entering medical practice, I do solemnly pledge myself to consecrate my life to the service of humanity. I will give my teachers the respect and gratitude which is their due. I will practice my profession with conscience and dignity. The health of my patient will be my first consideration. I will respect the secrets which are confided in me, even after the patient has died. I will maintain by all the means in my power, the honor and the noble traditions of the medical profession.

My colleagues will be my brothers.

I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient. I will maintain the utmost respect for human life from its beginning even under threat and I will not use my medical knowledge contrary to the laws of humanity. I make these promises solemnly, freely and upon my honor

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Original scientific paper

THE IMPORTANCE OF HPV VACCINATION IN THE PREVENTION OF CERVICAL CANCER

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ABSTRACT

Vaccination is one of the most effective and efficient measures of primary prevention.

Almost 95% of all cervical cancers are associated with HPV and most HPV-related morbidities and mortality belong to this type of cancer.

All three types of HPV vaccine (bivalent, quadrivalent, nine-valent) are effective in preventing HPV infections and are one of the first primary ways to prevent cancer, globally.

The HPV vaccine is a recombinant vaccine, which means that it does not contain live viruses but genetically engineered protein particles that resemble viruses. One of the main goals of the WHO immunization program in the European region, with which the goal of the immunization program in Republic of North Macedonia is harmonized, is to achieve and maintain high coverage by immunization with the recommended number of vaccine doses according to age, with special emphasis on children belong to vulnerable population groups.

Key words: cervical cancer, prevention, HPV vaccination.

INTRODUCTION

Vaccination is one of the most effective and efficient measures of primary prevention.

Regardless of the fact that human being stand out from other forms of life with his technological skill which is constantly progressively growing and which has enabled us to have 1000 times more of us on the planet than if there were no such insertion, the laws of nature apply to humans as well. Thus, written history says that more people perished from infections and contagions than from all other causes combined: wars, starvation, winters and natural disasters. Today, the achievements of civilization have made it possible to distinguish this image. However, we should know that along with human development, microorganisms are also improving - the causes of infectious diseases, so it is not an unknown claim that the greatest threat to human survival is not wars, not nuclear war, not unpredictable nuclear cataclysms, but viruses (from "The Truth About Vaccines", Prof. d-r Zoran Radovanovic).

OBJECTIVE

To emphasize the importance of HPV vaccination in the prevention of cervical cancer and to show the scope of

vaccination against HPV infection in Republic of North Macedonia in the period from 2014 to 2019.

MATERIAL AND METHODS

The data were taken from the database of the Institute of Public Health of RNM. A descriptive epidemiological method was used.

RESULTS

Human papillomaviruses (HPV) are a large group of viruses with more than 200 different types, and about 30 of them are sexually transmitted. Some of the HPV types cause the appearance of warts (condyloma acuminata), while some of the HPV types cause cervical dysplasia with the potential to transform into cervical cancer as well as cancer of the female and male genitals, mouth and pharynx. Infected individuals usually have no symptoms. The human beings are the only reservoir of infection. It is the most common sexually transmitted disease in the world and the most common cause of the cervical cancer, mouth and throat. Almost 95% of all cervical cancers are associated with HPV and most HPV-related morbidities and mortality belong to this type of cancer. Cervical cancer is usually preceded by cervical intraepithelial neoplasia – CIN that develops over a period of about 20 years after the initial infection with HPV. Within three years of initial HPV infection in 68% of young women with moderate dysplasia (CIN2) will come to regression, in about 15-22% of women with CIN2 will appear high-grade dysplasia (CIN3) and only in 0.2-4% of women with CIN3 there will be progression to squamous cell carcinoma.

HPV vaccination is important because in this way, almost completely prevents the development of cervical cancer in women, as well as condyloma, cancer of the external genitalia, anus and pharynx, caused by the HPV viruses, in both sexes.

The recommendation for HPV vaccination is to be performed at the age of 9 to 14 years, before the start of sexual activity. Vaccination can be performed later, for women up to 26 years of age and for men up to 21 years of age. So far, three types of HPV vaccines have been developed: bivalent, quadrivalent and ninevalent. The HPV vaccine is a recombinant vaccine, which means that does not contain live viruses but genetically engineered protein particles (VLP – virus like particles) that resemble viruses. Protein particles are not contagious and do not cause infection because they do not contain viral DNA and living biological parts. However, because these particles resemble viruses, after vaccination, the body produces antibodies against the HPV types present in the vaccine. Antibodies are also produced against other HPV types due to the existence of a cross-reaction.

The bivalent vaccine contains VLP HPV types 16 and 18, which cause more than 70% of all cervical cancers. The vaccine is registered for females aged 9 to 25 years.

The quadrivalent vaccine contains VLP HPV types 16 and 18, but also types 6 and 11 that cause condyloma, in both sexes. The vaccine is registered for use in both sexes at age of 9 to 26.

It is estimated that more than 200 million doses of these vaccines have been given so far in more than 80 countries worldwide.

The ninevalent vaccine contains VLP HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 and can be given to both sexes between the ages of 9 to 26.

HPV vaccines are given in the deltoid muscle and reactions after vaccination are usually mild and transient.

It has recently been determined that the vaccine is effective for a slightly older population, and the US FDA recommends it up to the age of 45.

It is important to say that no death or serious illness has been associated with the HPV vaccine.

Table 1: Coverage of HPV vaccination of girls aged 12 to 14 in Republic of North Macedonia in the period 2014 – 2019.

Year	2014	2015	2016	2017	2018	2019	Average
%	53.7	42.2	53.3	48.0	54.6	57.8	50.4

Graph 1: Coverage of HPV vaccination of girls aged 12 to 14 in Republic of North Macedonia in the period 2014 – 2019.

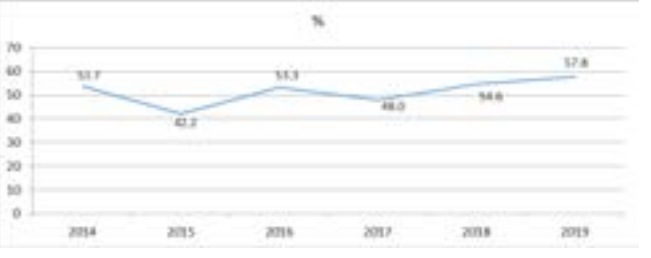

Table 1 and Graph 1 show the coverage of vaccination against HPV infections in the Republic of North Macedonia in the five-year period, from 2014 to 2019. We note that the coverage is very low and ranges from 42.2% in 2015 to 57.8% in 2019. Certainly, it is encouraging that

the trend of HPV vaccination coverage in RNM is on a slight increase and we will continue efforts and activities to increase coverage as much as possible.

Bivalent and ninevalent have been available for 9 years and have the most consistent data on efficacy in preventing HPV-induced cancer.

The bivalent vaccine was evaluated in a phase 3 clinical trials in Europe, called Papilloma Trial against Cancer in Young Adults, supported by the pharmaceutical company GlaxoSmithKleine. In this study, the vaccine showed 92.9% efficacy in the prevention of CIN2 in 18.000 women aged 15-25 years, with normal cytology or low-grade cervical dysplasia. CIN2 lesions are usually associated with HPV serotypes 16 and 18. The vaccines showed 33.6% efficacy in the prevention of CIN3 lesions in patients with a history of HPV infection.

Follow-up studies, after 6.4 years of follow-up in 776 women without previous HPV exposure, show 95.3% efficacy in preventing HPV 16/18 infection and 71.9% efficacy in preventing CIN 2 lesions. After 9 years of follow-up, the vaccine was 100% effective against HPV 16/18 infection, and there was no difference in the degree of prevention of CIN2 or CIN3.

The quadrivalent vaccine was evaluated in clinical trials supported by the pharmaceutical company Merck: Females United to Unilaterally Reduce Endo/Ectocervical Disease, "FUTURE" clinical trials. In the first smaller study, the vaccine showed 100% efficacy in preventing CIN2/3 in women without previous HPV exposure. However, in women with HPV history, there was no statistically significant difference in the incidence of CIN2/3 lesions. The follow-up clinical trial "FUTURE II", included 12.000 women aged 15-26 years with a history of abnormal Papanicolaou test and with less than 4 sexual partners in this group, the vaccine showed 98.0% efficacy in the prevention of CIN2/3, HPV 16/18 and adenocarcinoma in situ.

The efficacy of the ninevalent vaccine was evaluated in a phase IIb-III study supported by Merck. In 14.215 low-risk women, aged 16–26 years, were assigned to receive three doses of the ninevalent vaccine. The vaccine showed 96,0% efficacy in the prevention of high-grade CIN, high-grade vaginal intraepithelial neoplasia, vulvar and vaginal carcinoma, associated with the nine HPV types targeted by this vaccine (0.1 vs 1.5 cases per 1000 persons per year) and 96.0% efficacy in preventing persistent infections associated with the same HPV types (2.1 vs 52.4 cases per 1000 persons per year).

According to randomized clinical trials, all three types of HPV vaccine are effective in preventing HPV infections and are one of the first primary ways to prevent cancer globally.

DISCUSSION & CONCLUSION

The fear of the new is natural, whether it is justified or not. Fear is usually associated with the emergence of new vaccines, but the reasons for distrust of vaccines today are quite different than before. Namely, many infections are absent or very rare, thanks to vaccines and vaccination, so it seems to parents that today it is unnecessary to vaccinate children by exposing children to stings for the sake of vaccines. In addition, fears from postvaccination reactions and long-term harm from them take first place in parent's doubts due to the absence of diseases and infections that are prevented exactly with vaccines. Concern among parents arises only when an epidemic of a vaccine-preventable disease occur, certainly due to nonvaccination.

What is the antivaccination movement? From several definitions, I will list one from 2012: "A movement that opposes active immunization in an unscientific way with activities aimed at rejecting vaccination with denial and unjustified disparagement of peer-reviewed scientific literature, available evidence, and finally the honesty of the motives of people who produce, recommend and administer vaccines!"

A prominent British professor of genetics has commented the war on the truth about vaccines over Andrew Wefield's (discredited former British doctor, gastroenterologist, anti-vaccine activist, deleted from the British Medical Register for unethical behavior, scientific fraud and publishing a fake research paper claiming that the measles, mumps and rubella vaccine was linked to autism and intestinal disease) article and anti-vaccine activity: "It is almost incomprehensible to normal people that there is organized resistance to vaccines. A special place in hell should be set aside for people who want to kill or maim their children by not vaccinating".

Croatian epidemiologist, directed his anger at those doctors who spread fear of vaccination, who should have revoked their licenses and who should be sent for reeducation. When doctors with academic titles take an anti-vaccine stance, it must be subjected to a further blow

of criticism, not only because of unprofessionalism, but also because of unethical behavior and violation of the university code of professional ethics.

"We have resistance because of skepticism, beacause of the anti-vaccine environment that has been created in the world. When distrust of any vaccine starts, it is transmitted to everyone else. When it comes to the HPV vaccine, it is completely meaningless, because it is one of the safest vaccines according to all the data that currently exists", says Dr. Kon, a prominent Serbian epidemiologist.

Both, globally and locally, there is no reputable, honorable and recognized medical professional who is against vaccination.

I think that the senselessness of anti-vaccine movements (which are also represented by many medical experts), unfortunately is quite clear and that the benefit of this civilized achievement in the field of medicine, the vaccine, is also quite clear.

By saving a large number of human lives, which according to the most modest estimates is measured in millions, active immunization (vaccination) has achieved by far the greatest effect of all the achievements of scientific medicine in preserving the health and prolonging the life of the human species.Vaccination is largely credited, due to the fact that the mortality rate of children from infectious diseases in many countries today is less than one per mill, while only 100 years ago in the richest countries it reached up to 50%.

One of the main goals of the World Health Organisation immunization program in the European region, along with the goal of the immunization program in RNM is to achieve and maintain high coverage of immunization with the recommended number of vaccine doses according to age, with special emphasis on children who belong to vulnerable population groups.

The goal of systematic immunization in RNM is to achieve and maintain coverage of at least 95% by the mandatory immunization program at the level of the entire population of children who should be vaccinated according to the calendar in order to prevent diseases, possible complications requiring hospital treatment and deaths.

The basic precondition for successful immunization is safe immunization with use of vaccines that meet WHO standards.

The efforts and activities of all relevant institutions in the RNM will continue to maximize the coverage of HPV vaccination as one of the most effective ways to prevent cancer associated with HPV infections.

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Original scientific paper

KI67 EXPRESSION IN PAPILLARY THYROID CANCER

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ABSTRACT

Background. Papillary thyroid cancer is the most common thyroid cancer and accounts for over 70% of malignant thyroid diseases. In the last few decades the incidence of the papillary thyroid cancer (PTC) has increased worldwide. The aim of the study is to evaluate the Ki67 protein expression in papillary thyroid carcinoma and to correlate with clinicopathological parameters (age, gender, tumor size, vascular invasion, capsule invasion, lymph node metastasis, multifocality).

Materials and methods. The study population consists of 47 patients diagnosed with PTC, and benign thyroid changes. After standard surgical procedure formalin fixed paraffin embedded (FFPE) tissue sections for standard histological and immunohistochemically Ki67 analysis were obtained.

Results. Out of 47 patients, 24 (51.06%) were diagnosed with papillary thyroid cancer (Ki67expression varies in the range 8.58-5.76%) and 23 (48.94%) were benign changes of the thyroid gland (expression of Ki67 varies in the range 1.61±1.23%). For Z = 5.49 and p <0.001 (p = 0.000) the cancers had significantly higher Ki67 expression than benign tumors. There was no significant variation in Ki67 expression in papillary thyroid carcinoma in comparison to cervical lymph node metastases and tumor position. These parameters vary with tumor size and multifocality.

Conclusion. Ki67 is an appropriate biomarker used to distinguish papillary carcinoma from benign thyroid lesions. Ki67 expression was associated with tumor size and multifocality. High expression of Ki67 could be an important indicator for assessing the clinical course and prognosis of the disease itself.

Key words. Papillary thyroid cancer, expression and Ki67

BACKGROUND

Thyroid cancers are the most common tumors of the endocrine system and make up about 95% of all tumors of endocrine origin [1]. The development of thyroid cancers, similar to other cancers, uncontrolled cell proliferation must first occur. A number of hormones, growth factors, and steroids regulate the proliferation and function of normal and neoplastic thyroid tissue [2-4].

Cell proliferative activity is an important factor in evaluating the behavior of malignant cells, and Ki67 is one of the most commonly used markers for assessing the proliferative capacity of malignant cells. Ki67 protein expression is regulated by proteolytic processes, including mechanisms controlled by key regulatory complexes: cyclin B / cyclin-dependent kinases [5]. It is structurally similar to other proteins involved in cell cycle regulation [6].Ki67 is used in the evaluation of clinical progression and prognosis of malignant tumors. Relevant studies have reported strong protein expression of Ki67 in highly malignant tumors [7]. The prognostic value of Ki67 has been investigated in a number of studies in breast, thyroid, lung, prostate and central nervous system cancers [12-15].

The prevalence of papillary thyroid cancer is almost four times higher in women than in men [8,9] and decreases after menopause [10]. Papillary thyroid cancer is known to have a better prognosis than other malignant tumors of the human body, although about 10% show a worse clinical course than expected. Higher prevalence among women, especially during the reproductive period, is observed in all regions and in all ethnic groups [11].

MATERIALS AND METHODS

This study was performed at the University Clinic for Thoracic and Vascular Surgery at the University "St. Cyril and Methodius" in Skopje, Republic of Macedonia, while immunohistochemically and molecular analyzes of surgical specimens were analyzed at the Institute of Pathology, Faculty of Medicine, Skopje.

The study population consists of 47 patients that underwent thyroidectomy for PTC or subtotal thyroidectomy for benign thyroid disease (thyroid adenomas, goiter). Patients were separated in two groups: group A consists of 24 patients diagnosed with papillary thyroid cancer and group B consists of 23 patients (control group), patients with benign thyroid disease.

Preoperative examinations such as thyroid ultrasound, fine-needle biopsy, and gland scan are performed at the Institute of Nuclear Medicine and Pathological Physiology. Patients with papillary carcinoma are examined by CT scan of the neck with intravenous contrast at the Radiology Clinic, while laboratory tests are performed at the Institute of Clinical Biochemistry.

Surgical technique: Total thyroidectomy is performed under general anesthesia and endotracheal intubation in all cases. An incision of 4 to 6 cm is made in the lower parts of the neck. At that point the subcutaneous tissue and platysma are surgically dissected and we reach to a group of infrahyoid musculature that is dissected. As a result, we reach the thyroid gland, which is completely removed (for subtotal thyroidectomy we remove only the part of thyroid tissue that is pathologically altered) and we are careful to preserve the parathyroid glands and the n.laryngeus recurrens. When we have enlarged lymph nodes we continue with elective cervical dissection.

After gross dissection, formalin fixed paraffin-embedded (FFPE), 4 microns thick tissues sections were stained in standard protocol and used to determine: tumor location, tumor focality, size of the primary tumor, the presence of lymphatic or vascular invasion, extrathyroidal extension into perithyroidal soft tissue, number of lymph nodes with metastases, margin status and the stage of the disease. The stage of the disease was determined according to the criteria of the Union for International Cancer Control (UICC), 8th edition [19]. The Ki67 immunostaining was performed using DAKO monoclonal antibody (clone Mib1, dilution 1:150), by semi-automated PT Link immunoperoxidase technique. After deparaffinization and rehydration, samples were pretreated with Target Retrieval Solution for 20 minutes at 97°C and then incubated with primary antibody for 20 minutes at 25°C. For antibody detection EnVision FLEX, DAKO visualization system (20 minutes at 25°C) and chromogen -di–amino-benzene-DAB (5 minutes at 25°C) were used. At the end slides were counterstained with hematoxylin.

RESULTS

1. Gender

The study included 47 (100.0%) patients, of which 40 (85.1%) were women and 7 (14.9%) men (Table 1). Out of 40 (85.1%) women, 22 (46.8%) had benign changes in the thyroid gland and 18 (38.3%) were diagnosed with papillary thyroid cancer. Of 7 (14.9%) men, 1 (2.1%) had a benign finding and 6 (12.8%) were diagnosed with papillary thyroid cancer.

There was no significant difference in the cross-tabulation performed between the patient sex and the Fisher's Exact Test diagnostic finding p> 0.05 (p = 0.097) / Monte Carlo Sig, (2-sided).

Table 1. Gender / Crosstabulation

Benign Carcinoma			Type		Total
Gander	Female	Count	22	18	40
		%	46,8%	38,3%	85,1%
	Male	Count	1	6	7
		%	2,1%	12,8%	14,9%
Total		Count	23	24	47
%		48,9%	51,1%	100,0%	

1.1 Gender & Expression

In women, the expression value of Ki67 varies in the range 5.13-5.76% and in men the expression value of Ki67 varies in the range 5.43±3.46%. For Z = 00.96 and p> 0.05 (p = 0.34) men have a slightly higher expression of Ki67 than women (Table 1.1).

Table 1.1 Gender / Difference in expression

Variable	Rank Sum Female	Rank Sum Male	U	Z	p-level	Valid N Female	Valid N Male
Expression	928,00	200,00	108,00	-0,96	0,34	40	7

2. Age of patients

The age of the patients varies in the range 46.30 ± 12.48 years.

Out of a total of 47 (100.00%) patients, 22 (46.81%) were <45 years old (expression of Ki67 varies in the range 6.05-4.92%) and 25 (53.19%) had ≥ 45 years (expression of Ki67 varies in the range 4.40-5.97%). For Z = -1.63 and p> 0.05 (p = 0.10) patients who were <45 years of age had a slightly higher expression of Ki67 than patients who were ≥45 years of age (Table 2).

Table 2. Patient age / Ki67 expression

Variable	Rank Sum ≥ 45 yrs	Rank Sum < from 45 yrs	U	Z	p-level	Valid N	Valid N
Expression	523,50	604,50	198,50	-1,63	0,10	25	22

3. Tumor size

Tumor size varies in the range of 1.95-1.13 centimeters. Out of a total of 24 (51.06%) patients, 14 (29.79%) had tumor size <2 cm (expression of Ki67 varies in the range 7.43, 4.50%) and 10 (21.27%) had a tumor size ≥ 2 cm (expression of Ki67 varies in the range of 10.20 ± 7.10%). For Z = 00.88 and p> 0.05 (p = 0.38) patients who had a tumor size ≥ 2 cm had a higher expression of Ki67 than patients who had a tumor size <2 cm (Table 3).

Table 3. Tumor size / Ki67 expression

Variable	Rank Sum < from 2 cm	Rank Sum ≥ from 2 cm	U	Z	p-level	Valid N < from 2 cm	Valid N ≥ from 2 cm
Expression	160,000	140,000	55,00	-0,88	0,38	14	10

4. Capsule invasion

Out of a total of 24 (51.06%) patients, 13 (27.66%) did not have a capsule invasion (expression of Ki67 varies in the range 7.62-5.77%) and 11 (23.40%) had a capsule invasion (Ki67 expression varies in the range 9.73-5.80%). For Z = 11.10 and p> 0.05 (p = 0.27) patients who had capsule invasion had a slightly higher expression of Ki67 than patients who did not have capsule invasion (Table 4).
Table 4. Capsule Invasion / Expression of Ki67

Variable	Rank Sum No	Rank Sum Yes	U	Z	p-level	Valid N No	Valid N Yes
Expression	143,50	156,50	52,50	-1,10	0,27	13	11

5. Vascular invasion

Out of a total of 24 (51.06%) patients, 23 (48.93%) had vascular invasion of the tumor and in 1 (2.13%) patient vascular invasion was not established.

In patients with vascular invasion of the tumor, the expression of Ki67 varies in the range of 8.52-5.88%.

6. Lymph node metastases

Out of a total of 24 (51.06%) patients, 15 (31.91%) did not have lymph node metastases (expression of Ki67 varies in the range 7.93±4.28%) and 9 (19.15%) had metastases in lymph nodes (expression of Ki67 varies in the range 9.67±7.81%). For Z = 0.00 and p> 0.05 (p = 1.00) There was no significant difference in Ki67 expression between patients who had or did not have lymph node metastases (Table 5).

Table 5. Lymph node metastases / Ki67 expression

Variable	Rank Sum No	Rank Sum Yes	U	Z	p-level	Valid N No	Valid N Yes
Expression	187,50	112,50	67,50	0,00	1,00	15	9

7. Tumor Type & Multifocality

The results shown in Table 6. refer to the performed cross-tabulation between tumor type and multifocal tumors. Of the 23 (48.9%) benign tumors, there was no multifocality. Of the 24 (51.1%) diagnosed papillary thyroid cancer, 18 (38.3%) had no multifocality and 6 (12.8%) had multifocal tumors. In the performed cross-tabulation between tumor type and multifocality for Fisher' s Exact Test p <0.05 (p = 0.022) / Monte Carlo Sig, (2-sided) there is a significant difference.

Table 6. Tumor type & Multifocality

Yes No			Multifocality		Total
Type	Benign	Count	23	0	23
		%	48,9%	0,0%	48,9%
	Carcinoma	Count	18	6	24
		%	38,3%	12,8%	51,1%
Total		Count	41	6	47
%		87,2%	12,8%	100,0%	

8. Tumor type & / Ki67 expression

Out of a total of 47 (100.00%) operated tumors, 24 (51.06%) were diagnosed with papillary thyroid cancer (expression of Ki67 varies in the range 8.58-5.76%) and 23 (48.94%) were benign changes in the thyroid gland (expression of Ki67 varies in the range 1.61±1.23%). For Z = 5.49 and p <0.001 (p = 0.000) the cancers have significantly higher expression of Ki67 than benign tumors (Table 7).

Table 7. Tumor type & / Ki67 expression

Variable	Rank Sum Carcinoma	Rank Sum Benign	U	Z	p-level	Valid N Carcinoma	Valid N Benign
Expression	834,00	294,00	18,00	5,49	0,000	24	23

DISCUSSION

Thyroid carcinomas mainly develop from follicular cells, only medullary carcinoma develops from parafollicular cells. Papillary carcinomas belong to the group of well-differentiated thyroid cancers. Papillary carcinoma is the most common primary tumor of the thyroid gland and accounts for 70% to 80% of all thyroid cancers. It is more common in women (the ratio of women to men is 2-4: 1) and is less aggressive. However, biological behavior of the tumor is not always as such. Part of papillary thyroid carcinoma can manifest itself in an aggressive nature such as the presence of cervical lymph node metastases, recurrence of the disease itself, distant metastases and even death [16].

Ki67 is a type of protein that acts in DNA binding and is present during cell proliferation. As a marker of cell proliferation, a number of studies are investigating its use in the treatment of tumors. It is mainly located in the cell nucleus and plays an important role in maintaining a stable DNA structure during mitosis. Ki67 has become an important indicator of tumor cell proliferation activity. As Ki67 expression increases, the proliferative activity of tumor cells also increases. Ki67 correlates with the degree of differentiation, tumor invasion, metastasis, and prognosis of many tumors. Patients with high Ki67 expression have a poor prognosis [17]. In this study, the value of Ki67 expression in papillary thyroid cancer relative to benign thyroid changes was statistically significant. Some studies also confirm that Ki67 expression is useful in the differential diagnosis of papillary thyroid cancer [18].

This study showed that Ki67 expression in papillary thyroid cancer is more evident, and correlates with multifocality. While capsule invasion, tumor size, and patients younger than 45 years had slightly greater expression of Ki67, there was no correlation with sex, cervical lymph node metastases or tumor position. With increasing tumor size and multifocality, the intensity of expression and the positive rate of Ki67 are evidently increased.

We demonstrate that expression of Ki67 is increased in papillary thyroid cancer. Expression of Ki67 in papillary carcinoma has been associated with tumor size and multifocality.

CONCLUSION

Ki67 is an appropriate biomarker used to distinguish papillary carcinoma from benign thyroid lesions. Ki67 expression was associated with tumor size and multifocality. High expression of Ki67 could be an important indicator for assessing the clinical course and prognosis of the disease itself.

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Original scientific paper

THE ROLE OF RISK OF RENAL FAILURE, INJURY TO THE KIDNEY, FAILURE OF KIDNEY FUNCTION, LOSS OF KIDNEY FUNCTION AND END-STAGE RENAL FAILURE (RIFLE) CLASSIFICATION IN IDENTIFICATION AND PREDICTION SEVERITY OF THE KIDNEY INJURY IN NEWBORNS

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ABSTRACT

Objective: Acute kidney injury is a serious condition with various clinical manifestations ranging from minimal kidneys disordsers to kidney injury requiring substitution therapy. Because of need of timely diagnosis of kidney injury, RIFLE classification could be used. The aim of the study was to determine the role of RIFLE classification in detecting and follow up the progression of kidney injury in newborns. Methods: This study was realized at University Clinic of Pediatrics in Skopje from period of two years. It was analyzed the medical records of 80 newborns (40 with kidney injury and 40 without kidney injury) treated in intensive care unit. The severity of the disease was determined by RIFLE classification. Results: During the study period 6.25% of newborns have developed acute kidney injury acording standard clasification. Most of the newborns analyzed in the study were male (66 and 59%) and term (67% and 61%). RIFLE classification was applied in this study. We reported "risk" in 32%, "injury" in 57% and "failure" in 11% of newborns with AKI. Of these, 69% showed progression to "injury "and 15% to "failure". In 17% of newborns with verified "injury" the condition progressed to "failure". Conclusion: By using RIFLE classification we could not only identify kidney injury, but also detected the progression of the disease. Hence the significance of this classification as a solid tool in the diagnosis and follow-up of kidney injury in newborns.

Keywords: kidney injury, newborns, RIFLE classification

INTRODUCTION

Acute kidney injury (AKI) is a serious condition with various clinical manifestations ranging from minimal kidney disordsers to kidney injury requiring substitution therapy. Because of need of timely diagnosis as well as assessment of the severity of kidney injury, RIFLE (risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function and end-stage renal failure) classification is aplayed in newborns with AKI [1-7]. The diagnosis of kidney injury is based on serum creatinine and urine output. The both parameters are markers to identify the kidney damage. Because of need for timely and appropriate diagnosis of kidney injury, the Acute Dialysis Quality Initiative introduced in 2004 a classification system called RIFLE which indicates Risk, Injury, Failure, Loss, End-stage kidney disease. This classification is not designed to identify the causes

of kidney damage, but to diagnose the kidney damage itself. It is based on glomerular filtration (GFR), serum creatinine and 24 hours urine output. It consists of 3 levels that classify the severity of kidney injury (risk, injury, insufficiency) and 2 levels that classify the outcome of kidney injury (loss of renal function and terminal renal insufficiency) [8-11].

In 2007, the Acute Kidney Injury NETWORK (AKIN) modified the RIFLE classification to be useful to pediatric population. This classification is based on creatinine clearance calculated according to Schwartz's formula. [12-13].

One third of newborns with AKI develop neoliguric kidney injury. In them, considering only urine output as diagnosing criteria of AKI, while serum creatinine is not measured, kidney injury could be unrecognized. In newborns, especially in premature babies, total body water is accounts 80% of body weight. This body water content and tubules underdevelopment, explain why urine output in newborns is normally higher than in other population. Therefore, reference values of urine output in term newborns are above 1.0 ml/kg/24h and above 1.5 ml/kg/24h in premature babies [14-15]. Torres de Melo and colleagues described the neonatal RIFLE classification for the first time. They have modified the pediatric RIFLE classification because it has been found to be incompletely acceptable to neonatal kidney injury diagnosis. Taking into account the immaturity of tubular cells, high body water content and presence of maternal creatinine in newborn circulation, authors of neonatal RIFLE classification have corrected the values of serum creatinine and 24-hours urine output. So, the condition of oliguria has defined as urine output less than 1 to 1.5 5ml/kg/24h [16-17].The aim of the study was to determine the distribution of kidney injury in neonates according to RIFLE classification in terms of severity of the disease. The aim of the study was to determine the role of RIFLE classification in detecting and follow up the progression of kidney injury in newborns.

MATERIAL AND METHODS

This was prospective, clinical study performed in the period of two years, which included 80 newborns (40 with kidney injury and 40 without kidney injury) treated in intensive care unit (ICU) at University Clinic of Pediatrics in Skopje. In the study were included newborns up to 28 days of postnatal age, hospitalized in NICU due to certain pathological condition and development of kidney injury. AKI was defined by serum creatinine more than 130 Mmol/L in newborns younger than 33 weeks and more than 90 Mmol/L in newborns older than 33 weeks of gestation. Presence of oliguria was defined as urine output less than 1.0 mL/kg/h.

Data from medical records of the involved newborns were analyzed. The newborns were analyzed according to gender, birth weight and gestational age. In all newborns, the severity of the disease was determined according to the neonatal RIFLE classification using the criteria shown in Table 1.

Stage	Criteria	Urine output
R (risk)	>1,5 Cr, GFR< 25%	1,0ml/kg/24h, term newborns <1,5 ml/kg/24h, premature
I (injury)	> 2 Cr, GFR <50%	<1,0 ml/kg/24h.
F (failure)	> 3 Cr, GFR <75%	<0,7ml/kg/24h. or anuria 12h.
L(loss)	AKI >1 month	
E (endstage)	AKI >3 month	

Table 1. Neonatal RIFLE classification criteria

Laboratory examinations of serum creatinine were performed by use of a Kodak camera dry biochemistry at the Laboratory of Biochemistry, University Clinic of Pediatrics in Skopje.

The material was statistically analyzed using the methods of descriptive statistics. To determine the significance of differences in the parameters, the tests for independent samples were analyzed. Statistical significance was determined for the values of $p<0.05$.

RESULTS

The study was performed at the University Clinic of Pediatrics in Skopje in the period of 2 years. During study time 80 newborns with various pathological conditions were selected. In 40 of them acute kidney injury were detected.

Hence, the calculated prevalence of AKI in newborns was 6.25%. Another 40 newborns with comparable associated pathological conditions but no AKI were taken as a control (non AKI) group. In the group of newborns with AKI 66% were male and 34% female. Comparable values in the control group were 59% males and 41% females, retrospectively. Most of involved newborns in both group (AKI and non AKI) were born at term (67% and 61%). The

mean gestational age of newborns with AKI was 36.55 ± 3.1 weeks and 35.46 ± 3.8 weeks in control group. The mean birth weight of newborns with AKI was 2680.5 ± 898.1 grams; while in the control group was 2620.7 ± 894.6 grams. Demographic characteristics of newborns with AKI and non AKI are summarized in Table 2.

	Male	Female	Mean gestation age (w)	Mean birth weight (g)
AKI	66%	34%	36.55 ± 3.1	2680.5 ± 898.1
Non AKI	59%	41%	35.46 ± 3.8	2620.7 ± 894.6

Table 2. Demographic characteristics of newborns with AKI and non AKI

The neonatal RIFLE classification, which categorizes the severity of kidney injury, was applied in AKI and non AKI group. We evaluated "risk" in 32% of newborns with AKI, "injury" in 57% and "failure" in 11% of newborns. Additionally, using this classification, kidney injury were found in the control group too, with 27% registering "risk" and 4%"failure". The Figure 1 shows the distribution of newborns with AKI compared to the non AKI group according to the RIFLE classification.

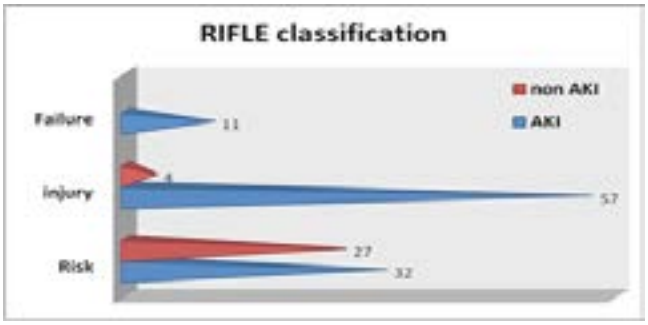

Figure1. Distribution of newborns with AKI and non AKI according to the RIFLE classification

In 13 neonates with AKI, in whom we registered risk (R) in 75%, progression of disease occurred, with injury (I) registered in 69% of newborns and failure (F) in 15% of newborns. Only 17% of the newborns with AKI in whom we reported subsequent injury (I), the experienced progressed of the disease to renal failure (F). Figure 2 shows the follow up results of RIFLE classification in newborns with or without acute kidney injury.

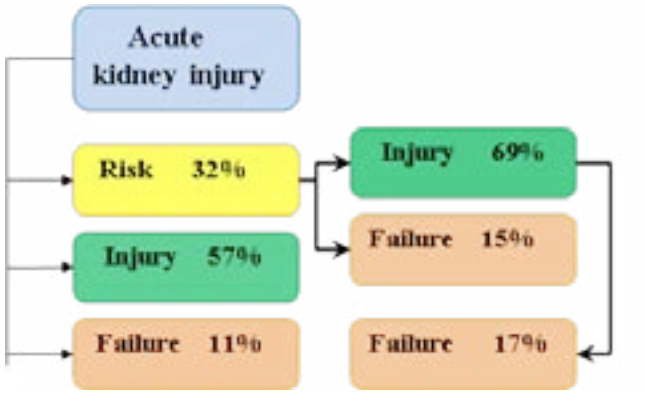

Figure 2. Flow up results of RIFLE classification in newborns with or without kidney injury

DISCUSSION

This is a clinical, epidemiological study that evaluated newborns who were hospitalized in the intensive care unit at the University Clinic of Pediatrics in Skopje due to various pathological conditions. The study analyzed 40 newborns with documented AKI, as well as another 40 newborns as a control group, with comparable associated pathological conditions but without AKI. Hence, the calculated prevalence of kidney injury in newborns was 6.25% [18-21]. This data correlates with the data presented in the literature, where the prevalence of AKI in neonatal age shows the highest rate (6-24%) compared to other age groups (infants, children and adults). The occurrence of AKI in newborns is influenced by various factors, such as: gestational age, birth weight and predisposing factors present during and immediately after birth. A similar finding as ours has been published in other studies. In the study of Vachvanichsanong et al. the prevalence of AKI in newborns is 6.3%, while in the studies of Bolat et al., and Stapleton et al. it is 8% and 8.4% [22-24].

Because of the need for timely diagnostics, as well as the assessment of the severity of the kidney injury, in newborns in this study, for the first time in our environment, was applied the RIFLE classification. This classification, introduced in 2004 by the Acute Dialysis Quality Initiative is based on the values of glomerular filtration, serum creatinine and urine output. Three years later, in 2007, Akcan-Arikan et al. they were modified in the pediatric classification to be applicable to the pediatric population, with the creatinine clearance value calculated according to the Schwartz formula. But pediatric classification has proved to be incompletely acceptable in diagnosing kidney injury in newborns.

Therefore Torres de Melo et al. adapted it to a neonatal RIFLE classification, which included criteria for corrected serum creatinine and 24-hour urine output [25-27]. Since our study addresses the problem of neonatal kidney injury, we opted for precisely the neonatal RIFLE classification, due to its high predictability and sensitivity to AKI recognition in newborns. In this classification, we used age-adjusted urine output values, with urine output lower than 1.0 ml / kg / h for term newborns and less than 1.5 ml / kg / h for preterm babies. Namely, urine output in newborns, especially in premature babies, normally exhibits greater values than other age groups. This is due to the immaturity and underdevelopment of the kidney tubules, as well as the high concentration of body water which in newborns accounts for 80% of total body mass [28-30].

The results of our study showed that 32% of the newborns had "risk", 57% had "injury", and 11% had "renal failure". In 33% of newborns with a registered risk, there was a progression of the disease, with the appereance of injury in 71% and "failure" in 21% of newborns. In 15% of neonates with verified "injury ", the condition progressed to "renal failure". These findings have shown that by applying the RIFLE classification we can not only identify kidney injury, but also monitor the progression of the disease. Hence the significance of this classification as a solid tool in the diagnosis and follow-up of neonatal AKI in intensive care units [31]. A similar finding is presented in the study by Mohkam et al., in which, according to RIFLE criteria, 43% of newborns with AKI were at risk, 51% at injury and only 6% at failure.[32]. RIFLE classification was also applied to newborns in the non AKI group with no clinical and laboratory signs of kidney injury. The "risk" for AKI was present in 27% of these newborns, while the "injury" in 4% of newborns. We did not record clinical progression of the condition and development of kidney injury in this group of newborns. This finding suggests that in control non AKI group, with verified "risk" and "injury ", we may have overlooked the situation. Namely, in some of these newborns, according to the standard classification, the diagnosis of kidney injury was missed. We hypothesize that treatment with other indications would lead to resolution of kidney injury. This finding suggests that the RIFLE classification could be used as a more sensitive tool than the standard in the diagnosis and monitoring of kidney injury in newborns. The finding of a higher prevalence (8.7%) of AKI in our group, obtained by the RIFLE classification, is a more realistic picture of this disorder in our environment [33,34].

CONCLUSION

By using the RIFLE classification we could not only identify the renal damage, but also monitor the progression of the disease. Hence the significance of this classification as a solid tool in the diagnosis and follow-up of kidney injury in newborns. It would be recommended for critically sick newborns hospitalized in intensive care unit, in order to timely recognizatiot of kidney injury.

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Original scientific paper

EXPRESSION OF FILAMIN A GENE CORRELATE WITH THE GRADE, LYMPH NODE INVASION AND STAGE IN COLORECTAL CANCER

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ABSTRACT

Colorectal cancer is a frequent heterogeneous group of neoplastic diseases with very different anatomic location, progression potential, treatment response and prognosis, depending on the combination of molecular-genetic abnormalities and their characteristic combination in the malignant cells. The main goal of this study was to determine the association between expression of FLNA gene and the differentiation grade, local invasiveness and size of the primary tumor, presence and the number of metastatic lymph nodes, as well as stage in a group of patients with colorectal adenocarcinoma.

The study included 116 patients with verified colorectal cancer and signed consent for inclusion. Detailed clinico-pathologic data was evaluated from each patient. RNA was extracted from the cancer tissue and normal surrounding mucosa of each patient. Gene expression levels were determined by reverse transcription and quantitative real-time amplification (qRT-PCR). The statistical differences were analyzed using Mann-Whitney-U test, Kruskal-Wallis test and Fisher's exact test.

FLNA gene expression was negatively correlated with the histological grade of differentiation. However, the differences in expression levels found between the patients stratified according to the other pathological groups (pT, pN) as well as to the clinico-pathological stage of the disease statistically significant, but not linear.

The results indicate that the expression of FLNA in the patients is consistent with its tumor-suppressor role and supports the potential use of this gene as a marker for diagnostics of colorectal cancer after confirmation on a larger group of patients and data validation.

Key words: Colorectal cancer, gene expression, FLNA

INTRODUCTION

Colorectal cancer (CRC) is the most common malignant transformation concerning the gastrointestinal tract. The cancer originates from the epithelial cells located in the colon or rectum. The etiology of this transformation is multifactorial including the genetic basis, environmental factors, inflammatory bowel syndrome and many other epigenetic factors leading to a several-year process of accumulation of genetic and epigenetic alterations.

CRC is the third most commonly diagnosed cancer (17,2/100 000) worldwide, following the lung and breast cancer. According to data from the Institute of Public Health of the Republic of North Macedonia, the estimated mortality rate for colorectal cancer in the country for 2014 is 21,3 for males and 9,5 for females, standardized per 100 000 population (1). The precancerous lesions that

lead to almost 95% of colorectal cancers are the neoplastic polyps - tubular and villous adenomas. However, it takes 5 to 10 years for development of the malignancy.

Studies have emphasized that sporadic colorectal cancer is a heterogeneous group of neoplasms that can be significantly differentiated according to the molecular profile of the gene disorders. Furthermore, meta-studies have found that molecular-genetic changes functionally affect a relatively small number of intracellular pathways responsible for regulating critical cell processes: division, apoptosis, cell invasion of surrounding tissue, cell motility, and other relevant features for the malignancy (2). Since the dominant malignant clone of the tumor mass contains a unique combination of molecular disorders leading to malfunction of the cells, this combination can be determinant at certain point for the biological characteristics of the neoplasm including the clinical course, therapeutic response and prognosis.

The FLNA gene is located on chromosome Xq28, and encodes for the protein filamine A (FLNA), in literature also referred as ABP 280 (from actin-binding protein 280). This protein is involved in the reorganization of the actin cytoskeleton in cells (3). Abnormal expression of filamin A, under certain conditions has been found in some types of malignant neoplasms, but the levels, timing, duration, and the distribution of the protein product appear to influence in a stimulating or inhibitory manner the cell proliferation. (4). A rare study published in February 2015 has detected reduced levels of expression of the FLNA gene in CRCs (5).

Our study was designed to determine the quantitative expression values of the FLNA in pairs of samples form the cancerous tissue and normal mucosa of the colon or rectum in each individual patient from the study group and compare these values with the clinical and pathological parameters: anatomic location (proximal colon, distal colon and rectum), and grade of differentiation of the tumor. The aim was to determine their statistical association if found and thereby evaluate the potential utility of this gene's expression as a molecular marker for diagnostic and other clinical purposes.

MATERIALS AND METHODS

In this observational, prospective study the relevant clinical-pathological data was gathered in a database for of a group of 116 patients with colorectal adenocarcinoma. The molecular analysis was performed to quantitatively determine the levels of FLNA gene expression in RNA isolates from tissue samples, after which the correlation with the clinical and pathological parameters was calculated. Selection of the patients was performed according to established inclusion criteria (histopathologically proven colon or rectal adenocarcinoma, hand-signed patient consent, availability of appropriate clinical data, etc). For the RNA extraction, after resection from each patient were taken tissue fragments of less than 1 gram of tumor, and a control tissue sample of similar size of the non-malignant mucosa at least 5 cm from the tumor edge. The whole cell RNA was isolated using the commercial Tri reagent following Chomczynski and Sacchi protocol (6). Reverse transcription and complementary DNA synthesis (cDNA) was performed with the Invitrogen SuperScript® III First-Strand Synthesis SuperMix for qRT-PCR kit, according to the manufacturer's instructions. Oligonucleotide primers for PCR amplification of the selected FLNA region as well as the double labeled TaqMan fluorescent probes were from Thermo Fisher Scientific. The sequences of the oligonucleotide primers for amplification are available upon request.

Determination of gene expression was performed by quantitative reverse transcriptase real-time polymerase chain reaction (qRT-PCR) using the relative comparison method. In each sample of tumor and healthy tissue, the RNA expression of the BACT (′ -actin) gene was simultaneously determined, as a referent gene whose expression is balanced in almost all cell types. In the transcript analysis for the FLNA, fluorescent dye SYBR Green (Applied Biosystems) was used. The real-time fluorescence amplification was performed on the StepOne RT-PCR System (Applied Biosystems) and the data was processed with StepOne (Applied Biosistems) software. The specificity of the amplification was checked by post-PCR melting curve analysis (MCA). The mean of the triplicate values was used.

The gene expression values were expressed as normalized to the reference gene. A comparison with a control sample of healthy tissue was used to determine the differences in the tumor tissue. The ΔΔCt calculation by Livak et al. (7), as well as Rao et al. (8) was used. The formula used to compare how many times higher or lower was the expression when normalized to the reference gene and compared to healthy tissue was: $2^{-\Delta\Delta Ct}$. Furthermore, to express the relative concentration (RQ) values we used the formula: $RQ = \log_{10} 2^{-\Delta\Delta Ct}$. Positive RQ values

indicate increased values for expression relative to healthy tissue, while negative values indicate decreased expression of the gene of interest. The unchanged values of RQ or those of healthy tissue, have a value of 1.

Preliminarily, the quantitative values are analyzed with the Shapiro-Wilk test in order to check their normal distribution. The statistical differences between gene expression levels of stratified patient's data were analyzed using Mann-Whitney-U and Kruskal-Wallis tests.

RESULTS

The analysis of the results of our study showed that the FLNA expression was higher in cancers located in the proximal colon and reduced in the distal colon and rectum. The correlation between the expression of the FLNA and the degree of differentiation is inversely proportional, the values decrease as the grade increases and this is statistically highly significant when calculated with different statistical calculations in which the reduced expression of the FLNA is clearly associated with the degree of differentiation. These results support the tumor-suppressor role of this gene in colorectal carcinogenesis.

The comparison of the FLNA gene expression levels with the histological grades of differentiation of CRC is shown in relation to each of the three grades, as shown in Table 1 and Graph 1.

Table 1. Comparison of the FLNA gene expression levels with grades of differentiation of the colorectal cancer G1, G2 and G3

Grade	Mean value	Min. value	Max. value	Standard deviation	Kruskal-Wallis test (two-sided) p
G1	1.87	0.11	3.80	1.25	< 0.0001
G2	-0.35	-1.75	3.02	0.67	
G3	-1.37	-1.96	-0.33	0.51	

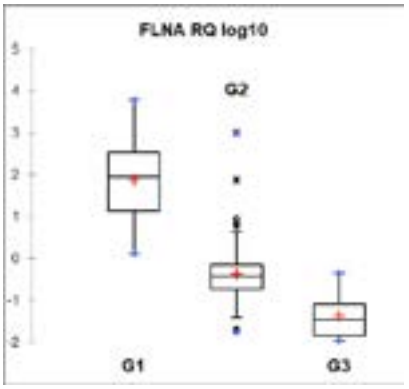

Figure 1. Graphic representation of the FLNA gene expression levels with respect to grades of differentiation of colorectal cancer G1, G2 and G3

According to the results of the statistical analyzes, there is a clear negative correlation between the FLNA gene expression levels and CRC grades of differentiation which is statistically highly significant ($p < 0.01$).

Regarding the pathological TNM classification (pTNM), we compared the FLNA expression levels with the local invasiveness and size of the primary tumor (pT) (Table 2 and Figure 2). As it is obvious from the presented data, although there is a tendency for a moderate negative correlation between the gene expression and the pT groups according to the TNM classification, it is not statistically significant ($p > 0.05$).

Table 2. Comparison of the FLNA gene expression levels with pT stage

Grade	Mean value	Min. value	Max. value	Standard deviation	Kruskal-Wallis test (two-sided) p
pT1	0.62	0.41	0.83	0.30	0.195
pT2	-0.07	-1.75	3.03	1.31	
pT3	-0.31	-1.96	3.02	0.83	
pT4a	-0.13	-1.68	3.80	1.27	
pT4b	-0.77	-1.72	0.64	0.82	

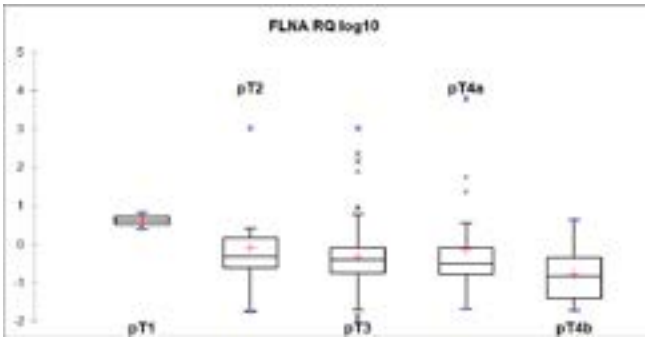

Figure 2. FLNA gene expression levels in relation to the local invasiveness and size of the primary tumor (pT)

Further analysis compared the FLNA gene expression levels with the pathological group describing the presence of metastasis into the regional lymph nodes (pN) as presented in the Table 3 and Figure 3.

Table 3. Comparison of the FLNA gene expression levels with pN

Grade	Mean value	Min. value	Max. value	Standard deviation	Kruskal-Wallis test (two-sided) p
N0	-0.34	-1.96	3.03	0.91	0.039
N1a	-0.32	-0.92	0.41	0.42	
N1b	-0.76	-1.85	0.00	0.60	
N1c	1.18	-0.42	3.02	1.49	
N2a	-0.16	-0.86	2.16	0.73	
N2b	-0.20	-1.85	3.80	1.23	

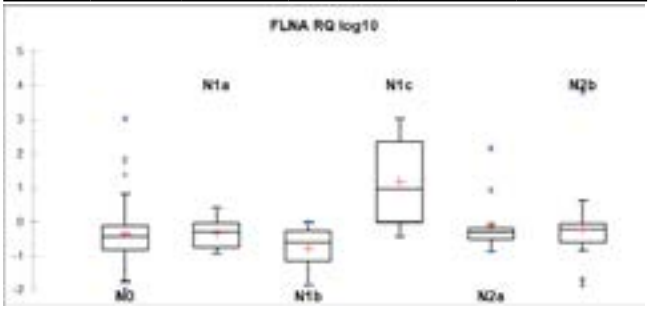

Figure 3. FLNA gene expression levels in relation to the pathologically determined metastasis in the regional lymph nodes (pN)

Although there is no linear correlation between the gene expression and pN groups, the differences among the groups are statistically significant ($p<0.05$).

Finally, we investigated the association between the clinico-pathological stage of the colorectal cancer in the patients with the FLNA gene expression (Table 4 and Figure 4).

Table 4. Comparison of the FLNA gene expression levels with pN

Grade	Mean value	Min. value	Max. value	Standard deviation	Kruskal-Wallis test (two-sided) p
I	0.06	-1.75	3.03	1.34	0.020
IIa	-0.39	-1.96	2.16	0.82	
IIb	0.21	-1.13	1.74	1.12	
IIc	-0.64	-1.33	-0.18	0.60	
IIIa	/	/	/	/	
IIIb	-0.12	-1.85	3.02	0.91	
IIIc	-0.37	-1.85	0.64	0.58	
IVa	-1.58	-1.72	-1.22	0.24	
IVb	-0.21	-1.46	3.80	1.66	

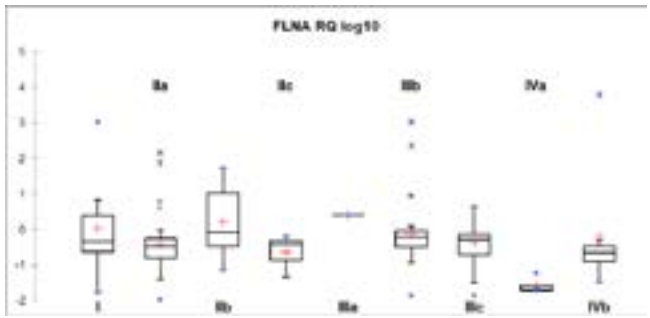

Figure 3. FLNA gene expression levels in relation to the clinico-pathological stage

As it is noticeable from the Table 3, we have no patients categorized as stage IIIa in our study group. Although the stage groups does not follow a linear correlation to the gene expression levels, the inter-group differences are statistically significant ($p<0.05$).

DISCUSSION

The Filamine A is a large cytoskeletal noncontractile protein that binds to actin and stabilizes the delicate three-dimensional actin networks by binding them to the cell membranes (9). The actin cytoskeleton is of an essential importance for the dynamic regulation of the cell morphology, cell movement and migration in response to the external stimuli. The functions associated with the regulation of the cell movement and migration have a potentially direct and indirect role in the process of the metastasis of the malignant cells. The FLNA protein interacts with and binds to a number of other protein molecules, and this complex interaction is still not clarified. Furthermore, FLNA participates in the regulation of cell proliferation and intracellular signal transduction, which plays an important role in the formation and development of neoplasms (10, 11). It was found that in activated cancer cells the FLNA gene is overexpressed together with some oncogenes and growth factors, such as c-MET (12). The biological role of this coexpression of the FLNA and c-MET, may have great significance for tumor biology and potentially lead to the development of new therapeutic approaches for the treatment of human cancers.

There are not many research studies including the expression of the FLNA gene and its role in colorectal carcinogenesis. In a study by Tian et al. (5), the expression of the FLNA gene was determined in 46 tumor and normal tissue samples from the same patients using three parallel methods: immunohistochemistry,

semiquantitative RT-PCR and Western blotting, after which levels of expression were compared in terms of clinical, pathological and prognostic parameters. The immunohistochemical results showed that in colorectal adenocarcinomas, positive expression was detected in 47.83% (22/46) of the samples, of which 26.09% (12/46) with mild positive expression and 21.74% with strong positive expression (10/46). In normal colorectal tissue specimens, the positive expression of filamine A was identified in 91.30% (42/46), of which low expression in 10.87% (5/46) and strong positive expression in 80.43% (37/46). The expression was higher in the normal mucosa compared to the cancerous specimens, and the difference was statistically significant ($p < 0.001$). The semiquantitative RT-PCR method, using the GAPDH gene as a reference gene, showed that the FLNA specific mRNA levels in tumor tissues were lower than in normal tissues (0.24 ± 0.03 vs. 0.95 ± 0.04) , and the differences between the two groups were statistically significant ($p = 0.017$). The GAPDH was also used as an internal reference when quantifying protein-filamin A by Western-blotting. Results showed that filamin A levels in tumor tissues were lower than in normal tissues (0.15 ± 0.02 vs. 0.76 ± 0.04). The difference between the two groups was statistically significant ($p = 0.013$).

In conclusion, we found that the FLNA gene is inversely correlated to the grade of differentiation of colorectal cancer, but the association with the other investigated clinico-pathological parameters is not convincing nor linear. The results of our study indicate the significance of the quantitative change in transcriptional activity of the FLNA gene in colorectal carcinomas, suggesting it has a potential role in the process of colorectal carcinogenesis. Following a larger study and validation, the expression of this gene could play a role as a molecular marker in accordance with the existing clinical and pathological parameters and in order to facilitate the screening, diagnosing, monitoring and planning of the individualized therapeutic strategies.

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Original scientific paper

RETROSPECTIVE ANALYSIS OF WARFARIN CONTROL USING ROSENDAAL METHOD IN PATIENTS WITH ATRIAL FIBRILLATION

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ABSTRACT

Background: Stroke being one of the major causes of Atrial Fibrillation is widely controlled using anticoagulants. Warfarin, a drug with a low therapeutic index and increased risk of bleeding, has found to be under-utilized or ineffective if not monitored frequently. The objective of the study was to determine the quality of control present in patients with Atrial Fibrillation administered with warfarin as the primary anticoagulant. Methods: A retrospective observational study was conducted at Kasturba hospital,

Manipal, from the medical records registry during a period from January 2013 to December 2014. A total of 183 patients' data records was collected during the study. TTR was calculated using the Rosendaal method in comparison with the traditional method. CHA2DS2- VASc for stroke risk analysis.

Results: In the present study, the mean age was found to be 58±14 years. Hypertension (34.43%) was found to be the predominant among the other comorbid conditions, and antihypertensives were the most common concomitant medications (86.34%) prescribed.

The average CHA2DS2-VASc score was 2.74±1.72, with a yearly stroke risk of 3.32±2.71 with five upper gastrointestinal bleeds. Vitamin K was administered as a monotherapy for 17 patients. The mean TTR was concluded to be 17.37±22.67 using the Rosendaal method and 17.59±20.73 using the traditional method. Nine fatalities were identified from the total cases.

Conclusion: The present study suggests that there is a scope for developing standard warfarin dosing protocols in the hospitals, to attain a state of drug utilization that exists between the risk of bleeding and preventing strokes. Individual studies focusing on Indian population should be designed to obtain relevant information on the inter-individual variability by warfarin therapy.

Keywords: Atrial fibrillation, Warfarin, Time in Therapeutic Range, International Normalized Ratio, Bleeding

INTRODUCTION

Atrial fibrillation (AF), being a significant risk cause for stroke, is widely treated using warfarin. An average of 5% of non-rheumatic individuals every year get diagnosed with ischemic stroke, which is 2-7 times the rate in patients without AF. The risk of stroke is not solely attributed to AF, but other cardiovascular diseases as well (1). The attributable risk of stroke from AF is estimated to be 1.5% for those aged 50-59 years, and it approaches 30% for those aged 80-89 years (2). Warfarin is most commonly used as a prophylactic medication to prevent stroke (3). Novel Oral anticoagulants (NOACs) exhibit better clinical outcomes than warfarin, but the right choice of treatment remains questionable in AF patients with multiple comorbidities

(4). The use of NOACs in renal impaired patients with AF remains a concern with the increased risk of bleeding and improper dosing strategies (5). On the other hand, warfarin holds good with lower risks and better efficacy in patients across all strata of kidney diseases (6).

Warfarin has a narrow therapeutic window and a slow onset of action. It requires constant therapeutic monitoring and dose adjustment to achieve an ideal INR value to prevent bleeding complications (7). The importance of genotyping of warfarin in recent times has contributed significantly in achieving the therapeutic outcome in a significant manner and also to prevent the bleeding risks (8). The single nucleotide polymorphisms (SNPs) such as VKORC1 and CYP2C9 have been found to influence the sensitivity of warfarin in various studies. However, the integration of pharmacogenetics in patient management is still not considered as the standard of care (9). The quality of therapy with warfarin can be determined by time in therapeutic range (TTR). The increased TTR (>60%) dramatically affects the safety of the therapy with a decrease in the incidence of bleeding complications in AF patients (10). The TTR is proven to be a useful predictor in clinical and cost outcomes (11). In general, TTR is calculated by three methods for estimating the therapeutic range in patients administered with warfarin. The first is the conventional method, involving the calculation of the fraction of INRs that are in the range, and the second method involves evaluation of the patient's case sheets by cross-section analysis. The third method is termed as the Rosendaal method, which uses a linear interpolation method with a computerized method for calculation (12). The present study helps to identify the factors that influence the individualized effects of warfarin in atrial fibrillation patients.

MATERIALS AND METHODS

A retrospective analysis of warfarin usage and factors influencing the outcomes was conducted. The patients diagnosed with Atrial Fibrillation and prescribed with anticoagulants within the age group of 18 to 70 years were included in the study. The study was approved by the Institutional Ethics Committee (IEC) Kasturba Hospital,

Manipal (IEC No: IEC 434/2015). The patients admitted from January 2013 to December 2014 were collected from the Medical Records Department (MRD) registry using ICD code I48. The data collection form included demographic details, medical and medication history, social history, daily warfarin dosing, INR, Prothrombin Time (PT), and Activated Partial Thromboplastin Time (aPTT). The patients' comorbid conditions, warfarin treatment, bleeding events, and their management was also included for analysis. The CHA2DS2-VASc assessment tool was used to calculate the risk of stroke. The scoring was categorized based on the severity of the risk, 0 was considered as low risk, a score of 1 as low to moderate risk, and a score of 2 or greater was considered as moderate to high risk of stroke. The TTR analysis was carried out using the Rosendaal method in which individual INR was calculated by combining the INR variations and their definite values. It was assumed that changes between subsequent INR variations were linear over time (13). Descriptive statistical methods were used to analyze the data obtained. Continuous data were represented as mean and standard deviation.

RESULTS

3.1 Socio-demographic Characteristics

Out of 183 patients included in the study, 54% were females. Among them, 89% of the patients had no known habits of smoking or alcohol consumption. Most of the cases identified were Unspecified AF (41.53%) followed by 28.96% Atrial Fibrillation with Fast Ventricular Rate (AF-FVR) and 27.32% were diagnosed with Atrial Fibrillation with Controlled Ventricular Rate (AF-CVR). There were three identified cases of paroxysmal AF and one case of Atrial Fibrillation with Sinus Rhythm (AF-SR). The mean dose of warfarin was calculated to be 3.59±1.97. The mean INR was found to be 2.05, which were within the ideal range. The mean PT and aPTT were calculated to be 27.7secs and 38.8secs, respectively. The CHA2DS2-VASc analysis was done for 174 patients, excluding the patients who were dropped out (9). The mean CHA2DS2-VASc score was estimated to be 2.74±1.72, which suggested a high risk of stroke. The calculated yearly risk of stroke (%) was 3.32±2.71.

Rheumatic heart disease (RHD) was the most common condition identified with AF in 41% of patients followed by Hypertension (HTN) in 34%, Congestive Cardiac Failure (CCF) in 30%, and 26% with a history of stroke. Type 2 Diabetes Mellitus (T2DM) was observed in 16% and Ischemic Heart Disease (IHD) in 15% of patients. Peripheral Vascular Disease (PVD) included cases of Deep Vein Thrombosis (DVT), varicose veins, and other conditions in 11% of the patients with AF.

The most common concomitant medication prescribed

was antihypertensives (86.34%), among which furosemide was found to be the choice of drug. Digoxin (60.65%), aspirin (40.98%), amiodarone (41.53%), Statins (34%), and NSAIDs (0.04%) were the other medications which were prescribed. The results of concomitant medications were given in Figure 1. Most of the patients were administered with heparin as bridging therapy before the initiation of warfarin.

The total number of hospitalized days of the patients was found to be 2876, and the INR was monitored for a total period of 1337 days. Out of 1337 days, the INR of <1.0 was maintained for 57 days, followed by 1.0 – 2.0 for 794 days, 2.0 – 3.0 for 297 days, and >3.0 for 189 days. This showed that majority of the patients were under the ideal INR range of 2.0 – 3.0, suggesting a possibility of under-dosing. The highest number of days within range was identified as 14, which was for one patient. Furthermore, the lowest was zero days within range (55.62%) of the patients. The mean number of days within range was calculated as 1.11±1.77. The detailed demographic description is presented in Table

1.

3.2 Assessment of Time in Therapeutic Range (TTR)

Among 183 patients, TTR values of 178 patients were analyzed. The values were calculated using Rosendaal method and compared with the traditional method. According to the Rosendaal method, 40.5% of patients had a TTR value of 0%, and 42.7% of patients had a TTR value ranging from 1–40%. An ideal TTR (>60%) was observed only in 12 patients. The TTR comparison between Rosendaal Method and Traditional Method is illustrated in Figure 1. The mean TTR value was calculated to be 17.37±22.67, according to the Rosendaal Method, and 17.59±20.7 according to the traditional method, which was drastically lower than the ideal TTR.

3.3 Adverse Events and their Reversal Treatment

There were 29 identified cases of adverse events among the 183 patients. Most of them were non-specific (68.96%). The most identified bleeding was found in the Upper GI (17.24%), followed by intra-abdominal (6.90%). One patient was identified with a case of epistaxis following warfarin treatment and another with intracranial bleeding leading to mortality. Figure 3 represents the type of bleedings observed in the patients.

Out of 29 cases, (9.29%) cases were managed by administering 10 mg of Vitamin K for 4-5 days or until the bleeding subsided with continuous INR monitoring. Despite the use of vitamin K, (2.18%) patients were managed solely using Fresh Frozen Plasma, and the remaining (4.37%) patients were given a combination of Vitamin K and Fresh Frozen

Plasma. The management of adverse events during the therapy is specified in Table 2.

DISCUSSION

The occurrence of AF was found to be more in females (54%) compared to males (46%). A study by Charles et al. relating gender and AF, concluded that men are at a higher risk of developing AF than women. However, since the occurrence of AF increases with age and there were more women in the population group of age above 75 years, the number of men and women with AF was found to be equal (14-16). The occurrence of cardiovascular diseases is seen 7 to 10 years late in women than men, due to the increased heart rate and lower body surface being the cause of mortality in women older than 65 years (17).

In the present study, AF due to HTN was found in 34.43% patients, which was substantially higher compared to the other conditions like T2DM, IHD, CCF, PVD, or a history of stroke. Although RHD is a common condition that may lead to AF (18), the findings of the current study had shown that 59% of the patients had no RHD involvement. In an analysis of hypertensive patients conducted by Healey et al. and team, slow atrial conduction velocity, enlargement of the left atria, and left ventricular hypertrophy (LVH) were identified as risk factors of AF and occurrence of thromboembolism (19).

The current study has shown that 25.68% of the patients had a history of stroke. Although the focus is on the prevention of stroke, there was limited data available regarding the prior history of stroke other than the fact that there is an increased risk for a recurrence of the same. Recent studies have shown that the effectiveness of the assessment scores is provided by the CHA2DS2-VASc analysis (20). The CHA2DS2-VASc analysis yielded a mean score of 2.74±1.72, which suggested that most of the patients who were being treated for AF in the hospital had a high risk of developing a stroke. Warfarin was indicated as an anticoagulant therapy, as stated by the risk assessment tool. The risk of stroke was precisely calculated as 3.32±2.71. This has shown that there was a 3% probability of developing stroke within one year.

Time in therapeutic range is a measure of quality for the

efficient use of warfarin. TTR stands as a comparator between the anticoagulants for the daily use in AF patients. The mean TTR was calculated to be 17.37±22.67 in 183 patients. This was well short of the ideal TTR of warfarin estimated to be less than 60% compared with the study conducted by Asarcikli et al. (21). The TTR was below the ideal range due to either under-dosing or overdosing of warfarin. Therefore, frequent monitoring of INR and warfarin dose adjustment is necessary to maintain TTR within the range since, there exists a relationship between TTR, stroke, vascular events, and risk of death (22).

The present study concluded that HTN was the most common condition that was present in 34% of patients. The most common concomitant medication was found to be diuretics, followed by '- blockers. In a study conducted by Edith et al., correlating concomitant drugs in patients with AF, it was found that there was an increased risk of interactions between VKAs and anti-arrhythmic medications whereas, in the current study, amiodarone was the highly interacting drug. The active metabolite of amiodarone (desethylamiodarone) inhibits the metabolism of warfarin by CYP2C9 and increases the anticoagulant effect of warfarin by almost 6%. Analgesics and anti-lipidemic agents were other classes of drugs causing interactions.

In the present study, 29 adverse events were identified, out of which 5 were Upper Gastrointestinal (UGI) bleeding. which had a possibility of being exacerbated with the concomitant usage of NSAIDs. There was one case of intracranial bleeding, which resulted in death. Another patient who presented with UGI bleeding, was administered with warfarin, aspirin, clopidogrel, amiodarone, and diltiazem. The INR was elevated (6.65) before developing UGI bleeding thus, was managed with vitamin K.

A study by Chen et al. concluded that the warfarin therapy carried a similar risk of UGI bleeds in Taiwanese patients as compared with most of the western studies. The old age, the intensity of anticoagulation, known history of UGI bleeds, and advanced liver disease were at high risk of bleeding. Frequent testing of INR values and a strategy of low to moderate intensity of anticoagulation and long-term use of acid suppressants should be considered in these patients. In our study, aspirin was administered as an antiplatelet, but the bleeding was observed in 14 out of the 29 cases. Therefore, the concomitant administration of warfarin and aspirin had a probable chance of accelerating the risk of bleeding (23).

The dropouts in the study were more due to the study design. In the current retrospective study, missing data were high in number which resulted in decreased sample size and incomplete patient outcomes. The regular INR monitoring was not practiced which could be due to the financial constraint or lack of insurance schemes in the study settings.

CONCLUSION

The present study suggests that there is a scope for developing standard warfarin dosing protocols in the hospitals, to attain a state of drug utilization that exists between the risk of bleeding and preventing strokes. The TTR of warfarin was lower than the ideal range in the present study. Setting up of warfarin clinics by a clinical pharmacist can improve the percentage of TTR in the Indian clinical setup. Incorporation of pharmacogenetic guided dosing and medication therapy management can enhance the outcomes and safety of warfarin. Individual studies focusing on Indian population should be designed to obtain relevant information on the inter-individual variability by warfarin therapy.

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TABLES AND FIGURES

Table 1: Socio-demographic Characteristics

Socio-demographic Characteristics	n (%)
Age Mean (SD)	57.92 (13.8)
Gender	
Male	87 (47.28)
Female	96 (52.17)
BMI Mean (SD)	22.71 (5.31)
Smoking	
Yes	13 (7.06)
No	170 (92.39)
Alcohol	
Yes	7 (3.80)
No	176 (95.65)
CHA2DS2-VASc Mean (SD)	2.74 (1.72)
Calculated Yearly Risk of Stroke (%) Mean (SD)	3.32 (2.71)
Mean Dose (SD)	3.59 (1.98)
Mean Days within Range	1.87
INR Mean (SD)	2.05 (1.33)
PT Mean (SD)	27.7 (14.33)
aPTT Mean (SD)	38.81 (9.07)

Comorbidities	
Rheumatic Heart Disease (RHD)	75 (40.98)
Hypertension (HTN)	63 (34.42)
Congestive Heart Failure (CHF)	55 (35.05)
Stroke	47 (25.68)
Type2 Diabetes Mellitus (T2DM)	30 (16.39)
Ischemic Heart Disease (IHD)	27 (14.75)
Peripheral Vascular Disease (PVD)	21 (11.47)
Type of AF	
Unspecified AF	76 (41.53)
AF with CVR	50 (27.32)
AF with FVR	53 (28.96)
Paroxysmal AF	3 (1.64)
AF with SR	1 (0.55)

INR- International Normalized Ration, PT- Prothrombin Time, aPTT – Activated Partial Thromboplastin Time,
AF- Atrial Fibrillation, CVR – Controlled Ventricular Rate, FVR – Fast Ventricular Rate, SR – Sinus Rhythm

Table 2. Management of Adverse events

Management	No. of Patients (n=29)
Vitamin K	17
Fresh Frozen Plasma (FFPs)	4
Vitamin K + Fresh Frozen Plasma	8

Figure 1. Concomitant medications prescribed in the patients

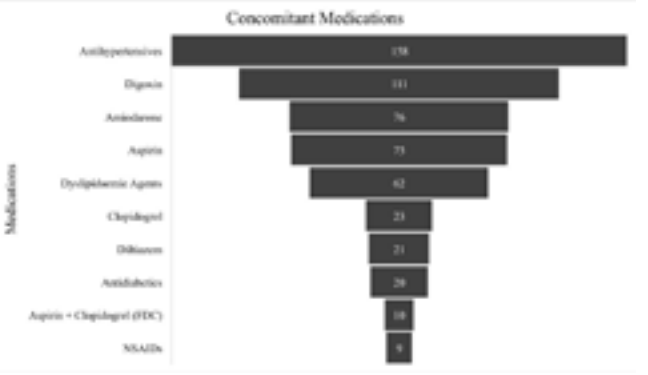


Figure 2. Time in Therapeutic Range (TTR) comparison between Rosendaal Method and Traditional Method

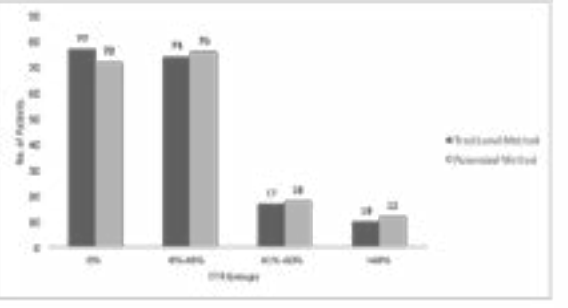
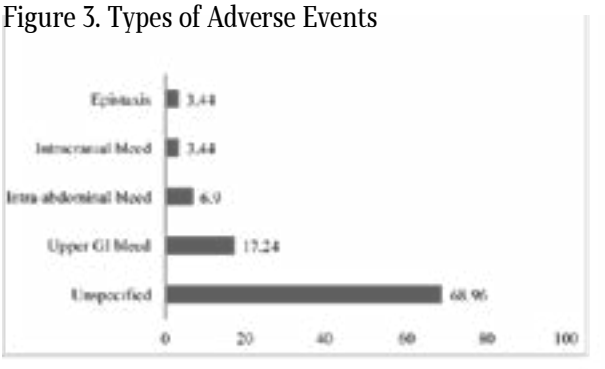


Figure 3. Types of Adverse Events



Profesional paper

SPECTRUM OF HISTOPATHOLOGICAL CHANGES OF THE ENDOMETRIUM IN PATIENTS WITH ABNORMAL UTERINE BLEEDING

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ABSTRACT

Introduction: Abnormal uterine bleeding is a complex gynecological problem, especially in the peri-menopausal and postmenopausal periods. Aetiology may be organic (endometrial polyp, hyperplasia, myoma, endometrial atrophy, carcinoma) or non organic (dysfunctional uterine bleeding)

Objectives: To analyze the histopathological findings of samples of fractionated explorative curettage in patients with abnormal uterine bleeding and to investigate certain risk factors for their occurrence (age, obesity, hypertension, diabetes).

Material and Methods: This is a prospective study on a total of 104 participants. They were divided into two groups: 54 in postmenopausal age and 50 in premenopausal age. The data were collected by interviewing and analyzing the findings from histopathological analyzes of samples obtained by fractional explorative curettage. The following anamnestic data were analyzed: age, history of hypertension and diabetes. The study was performed in the Special Hospital for Gynecology and Obstetrics "Mother Theresa" - Chair.

Results: The mean age of subjects in the postmenopausal group is 57 years and in the premenopausal group 43 years. The average BMI (Body Mass Index) in the postmenopausal group is 33 and in the premenopausal group is 25. The most common pathological finding in both groups is Polypus endometrii (in 39.5% of postmenopausal and 46.9% of premenopausal women. In 4 participants (5.7% of the total), Adenocarcinoma endometrii was diagnosed. The mean value for BMI (Body mass index) is 30, with 33 in the postmenopausal group and 25 in the premenopausal group. Hypertension was found in 64.8% of postmenopausal women. It was detected in 34% of premenopausal women. 13% of postmenopausal women were diagnosed with diabetes. It was detected in 12% of premenopausal women.

Conclusion: To emphasize the importance of diagnostic fractional explorative curettage, for the purpose of prompt and timely diagnosis of premalignant and malignant changes in the female genital tract. We detected Adenocarcinoma endometrii in 7,4% of the postmenopausal patients and in 4% of premenopausal patients with abnormal uterine bleeding. It is especially important to highlight obesity and hypertension as a risk factors for abnormal uterine bleeding and endometrial pathology.

Key words: abnormal bleeding, uterus, fractional explorative curettage

INTRODUCTION

Abnormal uterine bleeding is a complex gynecological problem, especially in the perimenopausal and postmenopausal period in women. It is defined as any bleeding that deviates from the normal menstrual cycle in terms of regularity, volume, frequency or duration, occurring in the absence of pregnancy [1]. The International Federation of Gynecology and Obstetrics (FIGO) has defined a classification system for abnormal uterine bleeding called PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia) . The prevalence is 9-14% during the lifetime and it is the cause of 25% of surgeries performed on women [2, 3]. The etiology may be organic (endometrial polyp, hyperplasia, fibroids, endometrial atrophy, cancer) or non organic (dysfunctional uterine bleeding) [4]. Dysfunctional bleeding is more common in younger patients, while endometrial atrophy and organic lesions are more common in older patients [5]. Endometrial polyps are one of the most common pathologies in patients with abnormal bleeding and occur in both pre- and postmenopausal patients [6]. Endometrial hyperplasia is an abnormal proliferation of the endometrial glands and stroma, and is associated with an increased risk of endometrial cancer [7].

Patients with a history of anovulation, obesity, hypertension, diabetes, and the use of exogenous hormones are at increased risk for endometrial hyperplasia and adenocarcinoma [1].

The endometrium is an easily accessible tissue for sampling for histopathological evaluation. Dilatation and curettage is the standard procedure and method of choice for endometrial sampling [8].

OBJECTIVES

1. To analyze the histopathological findings of the samples from fractionated exploratory curettage in patients with abnormal uterine bleeding and to determine the presence of certain risk factors in the examined groups (age, obesity, hypertension, diabetes).

MATERIAL AND METHODS

This is a prospective study on a total of 104 respondents who underwent fractional exploratory curettage due to abnormal uterine bleeding. The respondents were divided into two groups: 54 in postmenopausal age and 50 in premenopausal age. Data were collected through interviews and analysis of findings from histopathological analyzes of samples obtained by fractional explorative curettage.

Fractional explorative curettage was performed under intravenous anesthesia, with a sample from the endocervix and a sample from the endometrium. Samples were immediately fixed in 10% formalin and sent to a histopathological laboratory.

Analysis of the obtained histopathological findings and their distribution in the two examined groups was performed.

The following anamnestic data were analyzed: age, history of hypertension and diabetes.

Weight and height were measured in all respondents. The Body Mass Index (BMI) is calculated with the following formula: body weight (kg) / body height (m^2) The study was performed at the Special Hospital for Gynecology and Obstetrics “Mother Teresa” - Chair. Histopathological analyzes were performed at the Institute of Pathologic Anatomy at the Medical Faculty - Skopje.

RESULTS

The most common pathological change of the endometrium in both groups is Polypus endometrii (in 38.9% of postmenopausal and 36% of premenopausal respondents). Adenocarcinoma endometrii was diagnosed in 6 respondents (5.8% of the total number). It is more present in the postmenopausal group (in 7.4%) than in the premenopausal group (4%). 27.8% of postmenopausal women were diagnosed with endometrial atrophy, and none in the premenopausal group. Dysfunctional bleeding due to prolonged and inadequate estrogenic action is present in 2 respondents in the postmenopausal group (3.7%) and 8 respondents in the premenopausal group (16%). Endometrial hyperplasia is diagnosed in 13 patients in the premenopausal group (26%) of whom 2 cases (4%) have complex hyperplasia without atypia. In the postmenopausal group, endometrial hyperplasia was detected in 2 cases (5.2%) of which one case was with simple hyperplasia and one with complex hyperplasia without atypia (table 1).

table 1: Distribution of both groups according to histopathological findings

	postmenopausis	premenopausis
Atrophio endometrii	15 (27,8%)	0
Polypus endometrii	21 (38,9%)	18 (36%)
Hyperplasio simplex endometrii non atypica	1 (2,6%)	11 (22%)
prolonged and inadequate estrogenic action	2 (3,7%)	8 (16%)
normal	4 (7,4%)	1 (2%)
Adenocarcinoma endometrii	4 (7,4%)	2 (4%)
Dysplasio epithelii cervicis uteri	2 (3,7%)	0
Polypus cervicalis	3 (5,6%)	5 (10%)
Deficient secretory phase	0	3 (6%)
Hyperplasio simplex et complexa without atypia	1 (2,6%)	2 (4%)
Cervicitis chronica	1 (2,6%)	0
	total 54	total 50

The average age of the respondents is 50 years. In the postmenopausal group the mean age is 57 years, and in the premenopausal group 43 years. The most common age group is 51-55 years (total of 32 respondents or 30.8%).

The mean value for BMI (Body mass index) is 30, with 33 in the postmenopausal group and 25 in the premenopausal group.

table 2: Distribution of both groups according to BMI

BMI	
<25	12 (11,5%)
25-30	34 (32,7%)
30-35	38 (36,5%)
>35	20 (19,2%)
total	104 (100%)

Hypertension was found in 64.8% of postmenopausal women. It was detected in 34% of premenopausal women (table 3).

table 3: Distribution according to the presence of hypertension

hypertension	postmenopausis	premenopausis
yes	35(64,8%)	17(34%)
no	19(35,2%)	33(66%)
total	54	50

13% of postmenopausal women were diagnosed with diabetes. It was detected in 12% of premenopausal women (Table 4).

table 4: Distribution according to the presence of diabetes

Diabetes mellitus	postmenopausis	premenopausis
yes	7 (13%)	6 (12%)
no	47 (87%)	44 (88%)
total	54	50

DISCUSSION

Abnormal uterine bleeding is one of the most common gynecological problems, which can occur at any age, but is most common in the perimenopausal and postmenopausal age. In our study participated 104 respondents, with a mean age of 50 years. The most common age group is 51-55 years (32 respondents or 30.8%). Out of a total of 104 respondents, 39 received a histopathological diagnosis of Polypus endometrii: in 21 (38.9%) of postmenopausal and 18 (36%) of premenopausal respondents. Endometrial polyps are common, and their prevalence increases with age. A screening study of the general female population found that they were more common in postmenopausal women (11.8%) than in premenopausal women (5.8%). Most endometrial polyps are benign. In a meta-analysis of their malignant potential, the risk was found to be highest in postmenopausal women with vaginal bleeding [9]. In a Turkish study, the presence of endometrial polyp was found in 9 out of 45 respondents (20%), and 2 of those 9 showed the presence of simple hyperplasia without atypia [10]. In our study, all polyps were free of hyperplasia. Endometrial hyperplasia is a common cause of abnormal bleeding. It occurs due to prolonged exposure to unopposed estrogen and is a premalignant condition that can lead to the development of endometrial cancer. It is not well known how long it takes for cancer to develop, but a study by Lacey et al. found an average time of 6 years for cancer to develop, in all types of hyperplasia [11]. In our study we detected 15 cases of hyperplasia, of which 13 were in the premenopausal group and 2 in the postmenopausal group. Twelve of them had simplex, and 3 cases with simplex and complex hyperplasia.

Diagnostic curettage should be performed in all postmenopausal patients where a thickened endometrium or endometrial polyp has been detected by ultrasound, due to the possibility of the presence of atypical hyperplasia and cancer at the same time [12]. Endometrial adenocarcinoma is the most common gynecological malignancy. It occurs more often in postmenopausal women. About 40% of cases are associated with obesity

in patients [13].

Endometrial cancer is also associated with excessive estrogen exposure, high blood pressure, and diabetes [14]. In our study we detected Adenocarcinoma endometrii in 6 respondents (5.8% of the total number). It is often in the postmenopausal group (7.4%) than in the premenopausal group (4%).

It is especially important to highlight obesity as a significant risk factor for endometrial pathology. In our study, 38 respondents (36.5% of the total number) are obese, and 20 (19.2% of the total number of respondents) are severely obese (BMI over 35). Hypertension was found in 64.8% of postmenopausal women. It was detected in 34% of premenopausal women. In a study by Giordano et al., It was noted that most of their subjects with malignant endometrial polyps had risk factors such as hypertension, obesity, and unopposed estrogen therapy [15]. In our study, we also analyzed the presence of diabetes mellitus. 13% of postmenopausal women were diagnosed with diabetes. It is detected in 12% of premenopausal women. A meta-analysis by Zhang et al. Found an increased risk of endometrial cancer in patients with diabetes [16].

CONCLUSION

To emphasize the importance of diagnostic fractional explorative curettage, in order to quickly and timely diagnosis of premalignant and malignant changes of the female genital tract. Particular importance is given to the postmenopausal age when no bleeding should occur and when organic causes of abnormal bleeding are more common, especially cancer as the most severe pathology. We detected Adenocarcinoma endometrii in 7,4% of the postmenopausal patients and in 4% of premenopausal patients with abnormal uterine bleeding. It is especially important to highlight obesity and hypertension as a significant risk factors for endometrial pathology. In our study, 38 respondents (36.5% of the total number) are obese, and 20 (19.2% of the total number of respondents) are severely obese (BMI over 35). Hypertension was found in 64.8% of postmenopausal women with abnormal uterine bleeding. It was detected in 34% of premenopausal women.

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Profesional paper

ERYTHEMA MULTIFORME,STEVEN-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS – PEDIATRIC PERSPECTIVES

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ABSTRACT

Pathophysyollogy of Erythema multiforme (EM), Steven-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) is poorly understood, but there are suggestions that it is hypersensitivity reaction triggered by various factors as bacteria, viruses and medications. Drugs often associated with these conditions are sulfonamides, penicillins, barbiturates and phentoins, and infections are those with Herpes simplex virus and Mycoplasma pneumoniae.

We are presenting 6 patients with Erythema multiforme, 1 with Stevens-Johnson syndrome and 2 with Toxic epidermal necrolysis. Three of the patients before the onset of the disease received anticonvulsive therapy phenobarbiton and lamotrygine. Six received antibiotics lincomycine, cefalosporines and 3 antipyretic paracethamol, for minor upper respiratory tract infections. One of the patients with EM major who was on phenobarbiton, lincomycin and paracethamol, had toxic hepatitis and pleuritis with possible etiological factors drugs and infection. Patient with SJS received lincomycin for upper respiratory infection and also had pneumonia with atelectasis and etiology may be infection like Mycoplasma pneumoniae or drug. One of the patients with TEN did not receive any medications, and did not have symptoms of any infection preceding the onset of the disease, but he had elevated titers of antibodies against Varicella- Zoster virus. This patient also is only in the group with long term complications, constrictions of urethra and adhesions of conjuctiva. The other patient with TEN who was positive for Epstain-Barr virus died of septic shock because of out-of-control severe bacterial infection. There was no recurrence of EM and SJS/TEN during 6 months follow up. Important findings of this study is presence of EM in infants and toddlers, suggesting that they can be affected with EM and SJS/TEN, despite of immaturity of the immune system. In our study four patients with EM major and SJS/TEN received intravenouos gammaglobullins (IVIG) as a single dose of 400mg/kg for control of infections. Several authors have reported IVIG as high dose treatment 2gr/kg for these conditions with positive results.

Conclusion: Drugs and infections are possible etiology for EM, SJS and TEN. Infants and toddlers can be affected with EM and SJS/TEN despite the immaturity of the immune system. During the treatment it is important to stop any drug that patient has received before the disease. . High doses of intravenouos gammaglobullins should be considered for the treatment of severe forms.

Key words: Erythema multiforme, Steven-Johnson syndrome, Toxic epidermal necrolysis

INTRODUCTION

Erythema multiforme (EM) is an acute hypersensitivity immunological reaction, which manifests with a typical mucocutaneous eruptions. EM is caused by infections, medications, and other unknown factors. There are two types of erythema multiforme. Erythema multiforme minor characterized by localized, fixed target eruptions of the skin, mainly distributed acrally, with minimal or no mucosal involvement. Erythema multiforme major is the more severe form of EM where one or more mucous membranes are involved and less than 10% of total body surface area (TBSA) may have epidermal detachment. Stevens–Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) are considered to be a single disease entity with different levels of severity. They are characterized with wide-spread cutaneous erythema and blisters, predominant on the trunk and face, epidermolysis and mucosal erosions of the lips, eyes, mouth and genital area. Epidermal detachment is less than 10% of total body surface area for Steven-Johnson syndrome, and Toxic epidermal necrolysis (TEN) with 30% or more of TBSA . Advanced epidermolysis has mobility of the affected epidermis upon healthy skin and epidermal detachment on friction, known as Nikolsky phenomenon (1). There are actually two entities divided into the following: 1. Erythema multiforme consisting of erythema minor and major and 2. Steven –Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) (2). Primary clinical manifestations are fever and malaise, followed by cutaneous eruptions which in the cases of EM major and SJS/TEN can progress into blisters and erosive mucosal lesions of the mouth, lips, eyes and genital area. Cutaneous lesions often occur several days prior to mucosal erosions, but this order may be reversed.

The frequency of erythema multiforme is approximately 1.2-6 cases per million individuals per year. The condition is rare in children younger than 3 years and in adults older than 50 years (3,4,5). The incidence of SJS and TEN is approximately one to two cases per 1 million individuals per year. Reported mortality rates for TEN vary widely, from 20 to 80%. In a German population-based study, SJS had a mortality rate of less than 10%, and that of TEN was about 45% (4).

Many suspected etiologic factors have been reported to cause pediatric erythema multiforme (EM) and Steven-Johnson/Toxic epidermal necrolysis. Main infectious etiological factors include Herpes simplex virus (HSV), Epstein-Barr virus (EBV), Histoplasmosis, Mycoplasma species, viral infections , bacterial infection as well as the virus-drug interactions CMV infection–terbinafine (6).and EBV infection–amoxicillin. (7). More than 50% of cases are related to medication use, but no test reliably proves the link between a single case and a specific drug. Regarding medications, sulfonamides are the most common triggers. The second most commonly involved agents are the anticonvulsants, including barbiturates, carbamazepine, hydantoin, phenytoin, and valproic acid. Causative antibiotics include penicillin, ampicillin, tetracyclines, amoxicillin, cefotaxime, cefaclor, cephalexin, ciprofloxacin, erythromycin, minocycline, sulfonamides, trimethoprim-sulfamethoxazole, and vancomycin. Antipyretic agents as triggers include aspirin and paracethamol. (8,9,10) For SJS/TEN medications, an altered immune response and a genetic susceptibility are predisposing factors as well as infections. However, approximately 50% of cases are idiopathic, with no precipitating factor identified.

Infectious causes are more common in children than in adults.

MATERIAL AND METHODS

This retrospective descriptive study was conducted at the University Pediatric Clinic, a tertiary clinical hospital in Skopje, R.N.Macedonia. Data on all cases of children with a clinical diagnosis of EM minor and major, as well as SJS and TEN, who were hospitalized at our Immunology department during 10 years period were extracted. Dermatologist was consulted for all cases. Only cases consistent with the classification criteria for EM, proposed by Bastuji-Garin et al. (2) were included in this study. The following data were retrieved from patients: epidemiological data like age and gender, illness 2 weeks before the onset of the disease, medications 2 weeks prior to the onset of the disease, possible etiological factors, numbers of days of hospitalization , complications and recurrence 6 during months follow up . Mean values were calculated for quantitative variables, and absolute frequencies for nominal variables.

EM affects mostly young adults, but can also appear in children. The aim of this study was to analyze pediatric EM, SJS/TEN, and to describe some epidemiological data, illness and medications received prior to the onset of the disease which can be possible etiological factors, duration of hospitalization , complications and recurrence 6 during months follow up in our study group.

RESULTS

In our study 6 children were diagnosed with EM, one with SJS and 2 where diagnosed with TEN. Main characteristics of patients with EM, like age, gender, signs of infection 2 weeks prior the onset of the disease, incriminated etiological factors, therapy and outcome are summarized in the Table1.Same parameters for the patients with SJS/ TEN are summarized in the Table2.

In the group with EM, 3 patients had Erythema multiforme minor and 3 had Erythema multiforme major. Age range was from 10 months to 9 years, mean 5,4 years. As for the gender, 4 where females and 2 where mails so the ratio of males to females was 1:2 .Two weeks prior the onset of the disease in the study group 2 patients didn't have any signs of the infection, 3 had upper respiratory tract infection and one had fever. Two week prior to the onset of the disease 3 patients with EM received anticonvulsive therapy : 2 with EM minor received lamotrygine and 1 with EM major received phenobarbiton. Antibiotic therapy (lincomycin, cefixime, ceftriaxone) received 1 patient with EM minor and 3 patients with EM major. Paracethamol received 2 patients with EM major. Mean duration of hospitalization for patients with EM minor was 10,3 days while for EM major mean duration of hospitalization was 24,6 days. Infections and medications prior of the onset of the disease where considered as possible etiological factors, which influenced our therapeuticall decisions. Antipyretic paracethamol was replaced with ibuprofen and previous medications like anticonvulsive and antibiotics were withdrawn from therapy, or replaced with different group of medications. Two patients with EM minor without infection and without complications where treated with corticosteroids and antihistamines while 1 patient with EM minor received antibiotic therapy. All 3 patients with EM major received antibiotics, as well as corticosteroids, antihistamines and treatment for mucosal and skin erosions. Patient with EM major who developed nephritis and acute renal failure, received intravenous gammaglobulins (IVIG) as a single dose of 400 mg/kg. One patient with EM major developed within 3 days of hospitalization pleuritis which is shown on Figure 1, as well as acute hepatitis.

During the study period 1 patient was diagnosed with SJS and two with TEN. One 4 years old mail with SJS, 8 years old female and 6 years old mail with TEN. Mean days of hospitalization for two patients with SJS/TEN were 27,5 days, while 8 years old female patient with TEN died at day 7. Patient with SJS had previous upper respiratory tract infection and received linkomycin prior the onset of SJS, which were regarded as possible etiological factors. Same patient developed pneumonia with atelectasis during hospitalization which were cleared at the time of discharge. As for therapy patient with SJS received antibiotics, corticosteroids, antihistamines, intravenous gammaglobulins and treatment for eyes and skin erosions. Male patient with TEN had no history of previous infection or medications but he has positive serology for Varicella-Zoster immunoglobulin M(IgM) and immunoglobulin G (IgG). This patient received antibiotics, acyclovir, IVIG, antihistamines, plasma and albumen substitution as well as treatment for eyes and skin erosions. After hospitalization he developed adhesions of conjuctiva and urethra which were treated with surgical procedures. Eight years old female with TEN was presented with most severe clinical picture, with large area of skin erosions, severe mucosal involvement and clinical presentation of sepsis. Blood culture come positive for Methicillin resistant staphylococcus aureus (MRSA) and despite intensive skin and mucosal care, antibiotics, substitution with plasma, albumen and IVIG, corticosteroids and antihistamines , patient died with signs of severe septic shock. This patient had fever, tonsillitis and enlarged neck lymph nodes prior to the hospitalization and had high titers for Epstain-Barr virus IgM which was regarded as possible etiological factor as well as antibiotic ceftriaxone and antipyretic paracethamol.

DISCUSSION

In the past decades, EM has been recognized as a separate entity from SJS/TEN, and several studies examining EM and SJS/TEN in the general population have been performed (11, 12). However, until recently, there has not been specific focus on pediatric population. In the last years, several studies focusing on pediatric EM and SJS/ TEN were published.

In our study the mean age of affected children with EM was 5,4 years, ranging from 10 months to 9 years. Results from our study is opposite to the study by Yael Siedner-Weintraub at al. (22) who did not observe EM in infants and toddlers while we had described one infant and one toddler, which is consistent with the findings by Keller et al. (13) and Read Keijzers at al. (14).

The ratio of males to females was 1:2, which is consistent with a slight female predilection found in studies from another authors (15). In our study there were indications for possible infectious etiology in 7 out of 9 children with

EM and SJS/TEN, with a history of a febrile illness in the two weeks prior to the appearance of the disease. In adults, HSV has been implicated as the most common etiology of EM, in up to 70% of cases (16). However, the few studies focusing on pediatric EM report an association with HSV in 0–14% of cases (17, 18, 19).We have identified with serology specific viral pathogens as possible triggers only for two children with TEN , Epstein-Barr virus (EBV),or EBV –Ceftriaxone possible virus-drug interactions as well as Varicella- zoster virus. Association with viral illness in children has been previously reported, but the exact prevalence of the causative viruses is yet unknown. EM and SJS/TEN can be associated with medications in adults, as well as in children (12, 14, 19). Keller et al. (13) performed a 10-year survey of EM in 95 children, which found possible etiological factor to be medications, mainly penicillin in the first year of life, and medications and various infections in children older than one year. In our study, medications were associated with EM, SJS/TEN in 7 of 9 children, probably because of the widespread prescriptions of antibiotics and antipyretics in primary health care system. The culprit medications were, lincomycin, cefixime, cetriaxone and nonspecific anti-inflammatory drug paracethamol, which is in concurrence with the literature (15). Three children where on anticonvulsive drugs lamotrigine and phenobarbiton. This was in addition to drugs that were already known to be highly suspect (20). An immediate reaction to a medication is rare. The typical latency between starting a medication and the onset of an adverse reaction is 4–28 days and is rarely more than 8 weeks .

There was no recurrence of EM and SJS/TEN during 6 months follow up in our children. Recurrence is considered very common in HSV-associated EM in adults. However, the recurrence rate in children is unknown. Mean duration of hospitalization for patients with EM minor in our study was 10,3 days while for EM major mean duration of hospitalization was 24,6 days, which is different from study by Yael Siedner-Weintraub at all (21) where mean duration for the hospitalization was 3.4 days for EM in 30 children age 4-18 years. Mean hospitalization duration for patient with SJS/TEN in our study group was 27,5 days.

Patients were treated with fluids, anti-viral drugs, antibiotics, systemic corticoseroids and anti-histamines, as well as meticulous care of mucous membranes and skin. The use of systemic corticosteroids is puzzling considering the controversy regarding the efficiency of corticosteroids in EM and the self-limiting nature of EM (22–24), but is explained by the severe clinical picture in those with EM major and SJS/TEN. On the other hand corticosteroids given for SJS/TEN had positive results in the study of Jinbo Chen at al.(25) who compere outcome of 82 patients with SJS/TEN divided into 2 groups, one group of 24 were treated with IVIG plus corticosteroids and the other 58 were treated with corticosteroids only. Results indicated that early application of corticosteroids presented beneficial effects on SJS/TEN. In our study four patients with EM major and SJS/TEN received IVIG single dose of 400mg/kg for control of infections. Several authors have reported IVIG as high dose treatment 2gr/kg for these conditions. In the study of Jinbo Chen at al.(25) combination therapy of corticosteroids and IVIG achieved a better therapeutic effect than the administration of corticosteroids alone in doses of 2 g/kg in SJS/TEN patients. Montserrat Molgó et al.(26) in the retrospective study of 15 patients with a diagnosis of Stevens-Johnson or TEN, that received a total dose of 23 +/- 0.6 mg/kg of IVIG over a period of 3 to 4 days, find good response to IVIG . Eighty percent of patients survived, and authors concluded that despite the lack of blind, multicentric and randomized trials, they agree with some international studies that high dose of IVIG is beneficial as a treatment for SJS and TEN.

In our study we observed acute nephritis and acute renal failure in a child with EM major. In the study of Montserrat Molgó et al.(26) who had one patient with SJS/TEN developing acute renal failure it was estimated that reason for the renal failure were administration of IVIG, while acute renal failure in our patient occurs before the treatment with the IVIG as an integral part of the disease. Acute pleuritis and pneumonia with atelectasis was noticed in patients with EM major and SJS respectively. Many author found association of EM and SJS with Mycoplasma pneumoniae infection. Theresa Canavan at all (27) in a systematic review of 202 patients with Mycoplasma pneumoniae-associated mucocutaneous disease had concluded that Mycoplasma pneumoniae infection is associated with extra pulmonary complications, including mucocutaneous eruptions. These eruptions, which have been termed either Stevens-Johnson syndrome or Erythema multiforme in the literature, may differ from drug-induced Stevens-Johnson syndrome or viral-associated Erythema multiforme. Also, Rui Pedro Santos et al.(28) concluded that some patients with Mycoplasma pneumonia have extra -pulmonary complications including mucocutaneous

eruptions resembling EM, SJS and TEN. Recently, a new entity, called M. pneumoniae-induced rash and mucositis (MIRM) was described. The authors present a clinical case difficult to classify attending to the classical classification of epidermolytic syndromes that meets the criteria proposed for the diagnosis of MIRM. The mucocutaneous disease associated with Mycoplasma pneumoniae presents predominant mucositis, with scarce or absent cutaneous involvement. Because of the distinct morphology, pathophysiology and benign clinical course, MIRM should be considered as a new entity, distinct from SJS/TEN and EM. In the case of EM and SJS/TEN it is important for practitioners to consider and look after Mycoplasma infection for proper diagnosis, treatment and prognostic considerations. Acute hepatitis was noticed in another child with EM major, which is consistent with findings of the other authors who describe multiple organ involvement in EM major and SJS/TEN. Conjuctival and urethral adhesions were late complication of TEN (30) , and sepsis with MRSA in a patient with TEN which lead to lethal outcome consistent with the study of Tingting Shi at all (31) who observed complications in three patients like septic shock, respiratory failure and obliterans bronchiolitis and death because of out-of-control severe infection.

CONCLUSION

EM minor and major as well as SJS/TEN are rare but potentially life trethening diseases in childhood, caused by infection, medication or without known causative agent. During the treatment it is important to stop any drug that patient has received before the disease. In this study we found presence of EM in infants and toddlers suggesting , that they can be affected with EM and SJS/TEN, despite of immaturity of the immune system. In patients with marked respiratory tract involvement Mycoplasma pneumonie should be searched, because of the new classification which describes muco-cutaneous involvement during infection as separate entity called M. pneumoniae-induced rash and mucositis (MIRM). High doses of intravenouos gammaglobullins (IVIG) should be considered for the treatment of severe forms of EM, SJS and TEN. Pediatricians and dermatologists should be aware of the diagnostic criteria for EM and the differential diagnosis from SJS/TEN. Larger studies in children are required to better characterize these pediatric conditions.

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Type of EM	Age, gender	Infection 2 weeks prior	Medication 2 week prior	Possible ethiology	Duration of the acute desease	Therapy	Mucosal involvment	Complications
EMminor	8 years F	no	Lamotrigine	Lamotrigine	12 days	Corticosteroids Antihistaminics	no	no
EMminor	7 years M	no	Lamotrigine	Lamotrigine	10 days	Corticosteroids Antihistaminics	no	no
EM minor	10 months M	Upper resp. infection	Amoxicillin Lincomycin	Infection, Amoxicillin Lincomycin	9 days	Cefotaxime Corticosteroids Antihistaminics	no	no
EMmajor	2,5 years F	Upper resp. infection	Cefixime	Infection Cefixime	24 days	Erythromycin Corticosteroids Antihistaminics Mucosal and cutan care	yes	no
EMmajor	9 years F	Upper resp. infection	Ceftriaxone Paracetamol	Infection Ceftriaxone Paracetamol	30 days	IVIG Corticosteroids Antihistamines Cefotaxime Imipenem Mycosal and cutan care	yes	Nephritis,acute renal failure
EMmajor	5 years F	Fever 3 days	Phenobarbiton Lincomycin Paracetamol	Infection Phenobarbiton Lincomycin Paracetamol	20 days	Ceftriaxone Corticosteroids Antihistaminics Mucosal and cutan care	yes	Pleuritis hepatitis

Table 1.Patients with Erythema multiforme minor and major type

Abr: EM minor- Erythema multiforme minor; EM major- Erythema multiforme major

SJS/TEN	Age, gender	Infection 2 weeks prior	Medication 2 week prior	Possible ethiology	Duration of the acute desease	Therapy	Mucosal involvment	Complications
SJS	4 years M	Upper resp. infection	Lincomycin	Infection Lincomycin	25 days	IVIG Corticosteroids Antihistamines Cefotaxime Mycosal and cutan care	yes	Pneumonia, athelectasis
TEN	6 years M	no	no	Infection: (VZV IgM and IgG poz)	30 days	IVIG Plasma, albumines, Acyclovir Cefotaxime Mucosal and cutan care	yes	Late: Conjuctival and urhetral athesions
TEN	8 years F	Pharyngitis Lymphadenitis	Ceftriaxone Paracethamol	Infection: (EBV IgM poz) Ceftriaxone Paracethamol	7 days Egzitus lethalis	IVIG Plasma albumines, Corticosteroids antihystamines Vancomycine Meropenem Mucosal and cutan care	yes	Sepsis (MRSA) Egzitus lethalis

Table 2. Patients with Steven-Johnson syndrome and Toxic epidermal necrolysis

Abr. SJS –Steven –Johnson syndrome;TNT-Toxic ephydermal necrolysis,VZV- varicella-zoster virus,EBV- Epstein Barr virus

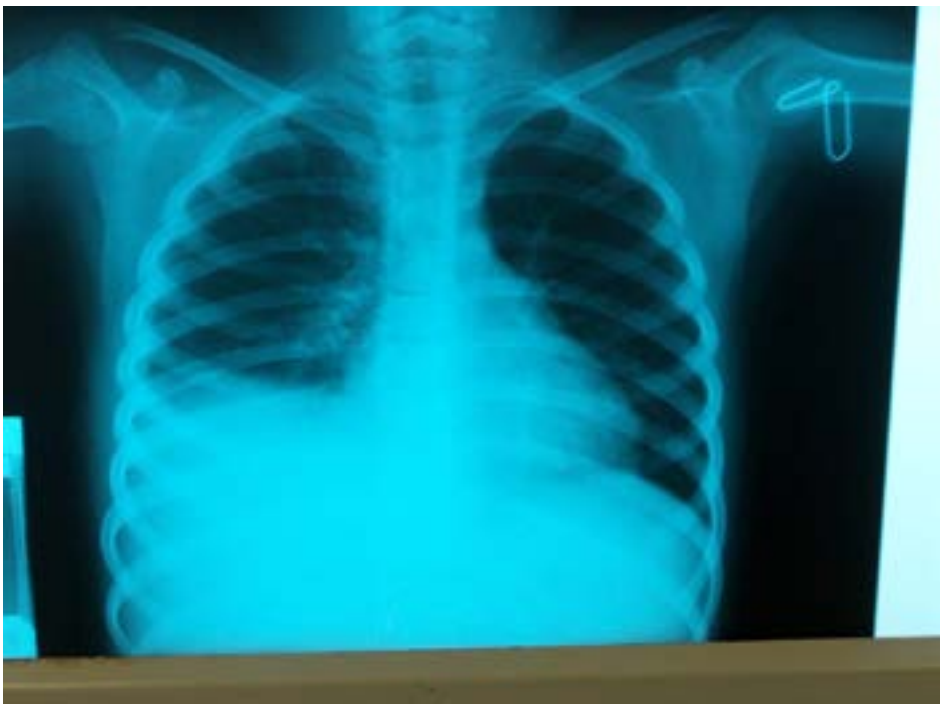

Figure 1. Exudative pleuritis in a patient with Erythema exudativum major

Profesional paper

THE IMPACT OF COGNITIVE FUNCTIONING ON THE QUALITY OF LIFE IN PATIENTS WITH SCHIZOPHRENIA

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ABSTRACT

Introduction: Schizophrenia is an endogenous psychotic disorder with a chronic course. The clinical features of schizophrenia are dominated by positive, negative symptoms, as well as cognitive dysfunction, which affects the quality of life.

Objective: To determine the relationship between cognitive dysfunction and quality of life in patients with first-episode schizophrenia and a chronic course of the disease.

Method: The research involved 37 randomly selected male and female respondents from 18 to 60 years of age who suffer from schizophrenia according to the diagnostic criteria of the International Classification of Diseases - ICD 10. The respondents are divided into two groups. The first group consists of 21 patients with schizophrenia in an acute period of the disease, while the second group consists of 16 patients with chronic schizophrenia treated in the PHI Psychiatric Hospital Skopje-Skopje, the PHI Clinical Hospital Stip and the PHI University Clinic of Psychiatry-Skopje. We used the following measuring instruments: the Positive and Negative Syndrome Scale (PANSS), the Schizophrenia Cognition Rating Scale (SCoRS) and the World Health Organization Quality of Life (WHOQOL)-BREF scale. For the statistical data processing we used the statistical package SPSS version 26 (Statistical Package for the Social Science).

Results: By applying ANOVA we found that the quality of life in acute patients is linearly related with at least one predictor, i.e. $F(21) = 3.570$, sig. $= .036$, $p < .05$. In the regression analysis by means of the t-test we found that there is a significant relationship between the quality of life and the total score of the cognitive functioning obtained by the informer $t(21) = -2.582$, sig.$= 0.019$, $p < .05$; while there is no statistically valid relationship between the quality of life and the total score of cognitive functioning obtained by the patient $t(21) = 1.158$, sig.$= 0.263$, $p > .01$ and between the quality of life and the total score of cognitive functioning obtained by the interviewer $t(21) = 0.096$, sig.$= 0.925$, $p > .01$. Also by using ANOVA, we found that the quality of life in chronic patients is not linearly related to any predictor, i.e. $F(16) = 0.840$, sig. $= .498$, $p > .05$. In the regression analysis by means of the t-test we also found that there is no relationship between the quality of life and the predictors.

Conclusion: In the course of our longitudinal prospective study, we found that cognitive dysfunction in schizophrenia affects a person's quality of life, whereby this is evident in the acute phase of the disease. Rehabilitation is focused on building the required skills for everyday life and work in the community, and is based on the principles of recovery and empowerment, it encourages the patient's autonomy by fostering the ability to work and by reducing incapacity –it improves self-confidence, social functioning and quality of life.

INTRODUCTION

Schizophrenia is an endogenous psychotic disorder with a chronic course which is characterized by dysfunction in multiple domains such as: perceptions, thinking, emotions and cognition. The scientific and clinical public is focused on early detection, treatment and rehabilitation, with a special focus on treatment in the community, however in the last 20 years with the advancement of science, schizophrenia has been studied in the direction of a neurodevelopmental and a neurodegenerative process [1, 2]. In the acute phase, a schizophrenic disorder is manifested by subtle changes in behavior, changes in the neuromotor and cognitive spheres. Due to the heterogeneity of the manifestation of the symptomatology in the early stage of schizophrenia, along with the dominance of positive and negative symptoms, cognitive deficit is also observed, hence early detection and treatment play a major role in reducing difficulties in the person's functioning, therefore the chronic stage of the disease is dominated by negative symptoms and cognitive dysfunction, which of course leaves sequels from a personal and behavioral aspect of the schizophrenic person [3].

Cognitive dysfunction is a basic characteristic of schizophrenia. Deficits are moderate to severe in several domains, including attention, working memory, verbal learning, memory and executive functions. These deficits occur at the beginning of psychosis, however they remain stable throughout the course of the disease in most patients. Studies have shown that cognitive deficits present with variability in severity, persistence of disorders and absence of a cognitive deficit in certain groups of patients up to 25 percent, in whom a neuropsychological deficit has not been identified. A number of studies in the early 1990s found that a cognitive deficit is the best predictor of the functional status in a number of domains of schizophrenia, as well as patient's characteristics, which suggests that the neuropsychological disorder in schizophrenia is stable but over time leads to more severe cognitive impairment [4, 5]. Over the past decade, the focus of cognitive deficit in schizophrenic patients has increased dramatically with the realization that simultaneously it is a predictor of the outcome and the treatment, from both pharmacological and behavioral aspect.

Cognitive dysfunction is present in almost all patients, with varying intensity in different domains, compared to the healthy population, however the most sensitive domain is the one related to information processing speed, memory, attention, executive function, language, motor and spatial abilities. Cognitive dysfunction is basically a constant category with small changes in the manifestation of cognitive functions at different stages of development of the disease and duration of the disease, and there are no important correlations with age, education, socioeconomic status [6, 7]. However, on the other hand, the latest research results suggest that the cognitive functioning of a schizophrenic person affects the person's quality of life [8, 9].

At the same time, on the basis of the research findings, the clinical experiences and the realization that subjective and objective factors are different and sometimes overlap, the subjective quality of life in correlation with objective needs largely affects the outcome in the improvement of the quality of life according to the individual's personality traits, therefore the need of self-assessment in regard to the quality of life of patients with schizophrenia arises [10]. The quality of life in schizophrenic patients has been studied in terms of the severity of the disease, the psychopathology and the prognosis in terms of the available needs and opportunities. Therefore, some authors believe that the quality of life is very subjective and refers to the subjective abilities of the patient that are correlated with the schizoaffective disorder.

A number of studies present the connection between the symptoms of the disease and cognitive dysfunction and the abilities of the functional capacities that are also a product of interaction between environmental factors, social relationships, problem-solving ability, insight, and motivation. At the same time, certain studies have shown that when assessing the quality of life in schizophrenic patients, the highest ranked aspect is social integration, i.e. the contacts and the acceptance of individuals from the narrow and wider social environment.

AIM OF STUDY

- To determine the level of cognitive functioning and the quality of life in patients with schizophrenia;
- To determine the relationship between cognitive dysfunction and quality of life in the first episode of schizophrenia;
- To determine the relationship between cognitive dysfunction and quality of life in patients with chronic schizophrenia.

MATERIAL AND METHODS

The research involves 37 randomly selected male and female respondents from 18 to 60 years of age who suffer from schizophrenia according to the diagnostic criteria of the International Classification of Diseases - ICD 10. The respondents are divided into two groups. The first group consists of 21 patients with schizophrenia in an acute period of the disease, while the second group consists of 16 patients with chronic schizophrenia treated in the Psychiatric Hospital Skopje-Skopje, the Psychiatric department in the Clinical Hospital Stip and the University Clinic of Psychiatry-Skopje diagnosed with schizophrenia according to the diagnostic criteria of the ICD-10 classification. Before the very inclusion in the research, each respondent was informed about the objective of the research, the procedures during the research were explained to the respondent, as well as the advantages and disadvantages of the respondent's participation in the research. The criteria for inclusion of the respondents included: patients (male/female) diagnosed with schizophrenia according to the criteria of ICD-10; patients diagnosed with schizophrenia from 18 to 60 years of age, patients in the acute stage of schizophrenia without prior antipsychotic therapy, and patients with chronic schizophrenia. The criteria for exclusion of the respondents included: patients diagnosed with schizophrenia under the age of 18 and patients diagnosed with schizophrenia and a comorbid psychiatric disorder.

During the research we used the following measuring instruments:

The Positive and Negative Syndrome Scale – PANSS for schizophrenia assessment consists of three subscales [11]. The positive scale contains 7 items (madness, cognitive disorganization, hallucinatory behavior, anxiety, grandness, suspicion and hostility), which same as all the other items in this scale, are scored from 1 (absent) to 7 (extreme). The negative scale also contains 7 items (flat affect, emotional withdrawal, impairment of emotional reasoning, social withdrawal, difficulty in abstract thinking, lack of spontaneity, stereotypical thinking). The maximum score on this scale is 49 points. The General Psychopathology Scale contains 16 items and presents the structure of the clinical presentation. The Cronbach's alpha for 28 of 30 items was .756, which represents a good correlation between items.

The Schizophrenia Cognition Rating Scale - ScoRS is a scale for assessing the cognitive impairment and the extent of its effect on the everyday functioning in patients with schizophrenia [12]. The scale itself consists of 20 items that cover the following cognitive domains: memory (4 items), learning (2 items), attention (3 items), working memory (2 items), reasoning and problem solving (3 items), motor skills (2 items), language (1 item) and social skills (3 items). Each item is ranked from 1 (absent deviation) to 4 (expressed deviation), whereby higher scores reflect a greater degree of disorder. The time frame for the cognitive deficit should not be shorter than two weeks, with retesting performed 3-4 weeks after the commencement of the drug treatment. The statistical validity of the scales expressed with Cronbach is within the range from 0.743 to 0.782.

The WHOQOL - BREF (World Health Organization Quality of Life-BREF) questionnaires a short version of WHOQOL-100 [13]. Namely, 24 questions are selected from the original questionnaire that assesses the quality of life as a whole and the general health, hence the questionnaire basically contains 26 questions. Based on these questions, the quality of life is assessed in 4 domains: physical health, psychological health, social relations and living conditions. The answer to each question is according to the Likert's type from 1 to 5, where 1 means the lowest level of agreement, while 5 means the highest level of agreement with the question. The total score for the quality of life as a whole and the general health is 2-10, for the physical health it is 7-35, for the psychological health it is 6-30, for the social relations it is 3-15 and for the living conditions it is 8-40. The statistical validity of the scale is expressed by Cronbach which was .784.

RESULTS

On the basis of the data from Table 1 it is observable that in patients with an acute course of the disease, the average value of the physical health is M=22.90 with minimum and maximum values from 13 to 34, of the mental health it is M=19.14 with minimum and maximum values from 14 to 27, of the social relations it is M=8.28 with minimum and maximum values from 4 to 12, and of the living conditions it is M=22.90 with minimum and maximum values from 17 to 29. The mean value of ScoRS for a patient is M=47.95, of ScoRS for an informer it is M=50.47 and of ScoRS for an interviewer it is M=53.66.

Table 1. Descriptive statistics of the domains of the quality of life and the total score on the ScoRS scale obtained from a patient, an informer and an interviewer in subjects with an acute course of the disease

Variables	N	Minimum	Maximum	Mean	Std. Deviation	Variance
Physical health	21	13.00	34.00	22.9048	4.91838	24,190.
Mental health	21	14.00	27.00	19.1429	3.66450	13.429
Social relations	21	4,00	12.00	8.2857	1.92725	3.714
Living conditions	21	17.00	29.00	22.9048	3.60423.	12.990
SCoRS_patient	21	32.00	68.00	47.9524	10.63239	113.048
SCoRS_ informer	21	30.00	69.00	50.4762	12.07319	145.762
SCoRS_ interviewer	21	38.00	71.00	53.6667	8.34466	69.633

In order to determine exactly which of the predictors affects the quality of life and its domains in the subjects with acute schizophrenia, we applied linear regression. By means of the corrected R2 (squared coefficient of multiple correlation) we found that the examined variables, i.e. the predictors have an effect on the quality of life of 27.8% in the examined sample (Table 2).

Table 2. Squared coefficient of multiple correlation

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,622a	0,387	0,278	8,88422

a. Predictors: (Constant), SCoRS_interviewer, SCoRS_patient, SCoRS_informer

b. Dependent Variable: Quality of Life

By applying ANOVA we found that the quality of life in acute patients is linearly related to at least one predictor, i.e. F (21) =3.570, sig. =.036, p<.05.

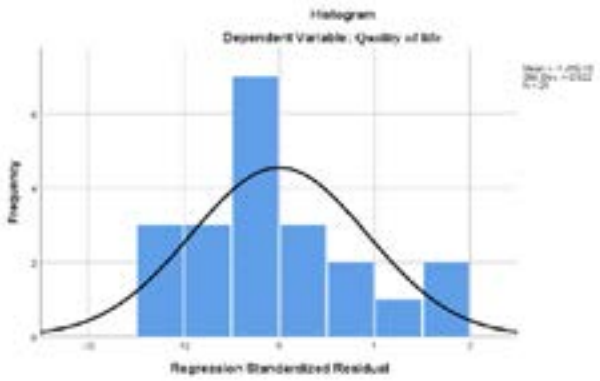
In the regression analysis by means of the t-test we found that there is a significant relationship between quality of life and the total score of cognitive functioning obtained by the informer t(21) = -2.582, sig.=0.019, p<.05; while there is no statistically valid relationship between quality of life and the total score of cognitive functioning obtained by the patient t(21)=1.158, sig.=0.263, p>.01 and between quality of life and the total score of cognitive functioning obtained by the interviewer t(21)=0.096, sig.=0.925, p>.01 (Table 3).

Table 3. Correlation between quality of life and the total score on the ScoRS scale obtained by a patient, an informer and an interviewer

Model B		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		Std. Error	Beta			
1	(Constant)	93.181	13.028		7.152	0.000
	SCoRS_patient	0.411	0.354	0.417	1.158	0.263
	SCoRS_informer	-0.819	0.317	-0.945	-2.582	0.019
	SCoRS_ interviewer	0.030	0.317	0.024	0.096	0.925

a. Dependent Variable: Quality of Life

Graph 1. Shows a histogram of the quality of life in patients with a first episode of schizophrenia.



Graph 1. Histogram of the quality of life in patients with acute schizophrenia.

On the basis of the data from Table 4, it can be seen that in patients with a chronic course of the disease, the mean value of physical health is M=22.81 with minimum and maximum values from 16 to 30, of mental health it is M=18.62 with minimum and maximum values from 13 to 24, of social relations it is M=8.20 with minimum and maximum values from 4 to 11 and of living conditions it is M=22.87 with minimum and maximum values from 10 to 29. The mean value of ScoRS for a patient is M=48.56, of ScoRS for an informer it is M=45.37 and of ScoRS for an interviewer it is M=46.93.

Table 4. Descriptive statistics of the examined clinical and psychological parameters in subjects with chronic schizophrenia

Variables	N	Min	Max	Mean	Std. Deviation	Variance
Physical health	16	16.00	30.00	22.8125	3.29077	10.829
Mental health	16	13.00	24.00	18.6250	2.75379	7.583
Social relations	16	4.00	11.00	8.0000	1.96638	3.867
Living conditions	16	10.00	29.00	22.8750	5.25198	27.583
SCoRS_patient	16	36.00	58.00	48.5625	6.73269	45.329
SCoRS_informer	16	10.00	63.00	45.3750	12.92994	167.183
SCoRS_interviewer	16	12.00	65.00	46.9375	12.90203	166.463

In order to determine exactly which of the predictors affects the quality of life and its domains in the subjects with chronic schizophrenia, we applied linear regression. By means of the corrected R2 (squared coefficient of multiple correlation) we found that the examined variables, i.e. the predictors affect 23.3% on the quality of life in the examined sample (Table 5).

Table 5. Squared coefficient of multiple correlation

Model Summaryb

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,417a	0,174	0,233	9,01238

a. Predictors: (Constant), SCoRS_interviewer, SCoRS_patient, SCoRS_informer

b. Dependent Variable: Quality of Life

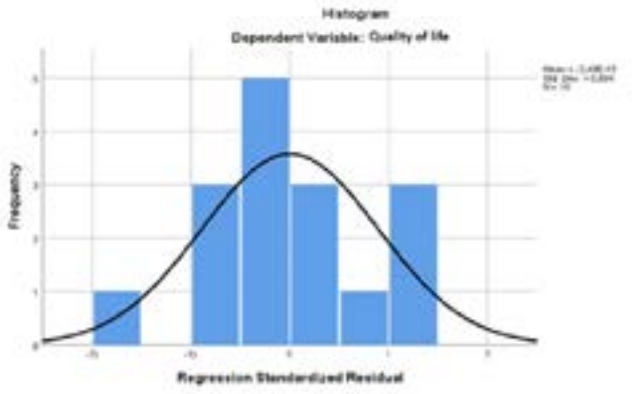
By applying ANOVA we found that the quality of life in chronic patients is not linearly related to any predictor, that is F (16) =0.840, sig. =.498, p>.05. In the regression analysis by means of the t-test we also found that there is no correlation between quality of life and the predictors (Table 6).

Table 6. Correlation between quality of life and the total score on the ScoRS scale obtained by a patient, an informer and an interviewer

Model B	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	Std. Error	Beta			
(Constant)	82.318	17.483		4.709	0.001
SCoRS_patient	-0.439	0.389	-0.333	-1.130	0.281
SCoRS_informer	0.999	1.228	1.457	0.814	0.432
SCoRS_interviewer	-0.725	1.217	-1.054	-0.595	0.563

a. Dependent Variable: Quality of Life

Graph 2. Shows a histogram of the quality of life in patients with chronic schizophrenia.



Graph 2. Histogram of the quality of life in patients with chronic schizophrenia

DISCUSSION

The quality of life in schizophrenic patients has been studied in terms of the severity of the disease, the psychopathology and the prognosis in relation to the available needs and opportunities. It is assumed that the ability of cognitive functioning of the schizophrenic subjects affects their quality of life, hence our objective during this study was to see if cognitive functioning is a predictor of the quality of life in patients with first-episode schizophrenia and a chronic course of the disease [14, 15].

Cognitive deficit in schizophrenia is increasingly accepted as a basic characteristic of the mental disorder and it is an important factor in explaining the dysfunction or

the duration and deficits during clinical remission, but also a risk factor that hinders the processes leading to functional recovery of patients with schizophrenia. Cognitive deficit is considered a basic characteristic of schizophrenia primarily because it is present before the onset of psychosis, i.e. patients with schizophrenia suffer from a wide range of cognitive deficits, which usually occur in a certain period of time, before and after the onset of the disorder, which determines the outcome of the mental condition [16]. In addition, this deficit is usually present during the symptomatic remissions and is relatively stable over time in both patients and persons at high risk for schizophrenia.

Cognitive deficit includes changes in memory, attention, learning, executive function, abstract thinking, and language. It should be noted that 75% of patients with schizophrenia suffer from cognitive symptoms as a result of the disease [17, 18]. The general functionality of schizophrenia is ascribed to cognitive symptoms, even when performing the simplest everyday tasks, the person's ability to cope with certain problems or to perform tasks in an appropriate way is reduced, there are changes in associations, logical comprehension, adequate thinking and acting, problems in using information, decision making and difficulty paying attention, which are reflected in the thought process.

Our hypothesis, that there is a significant relationship between cognitive functioning and quality of life in schizophrenic subjects, is fully confirmed. Thereby cognitive dysfunction affects the quality of life in subjects in the acute phase of the disease compared to chronic subjects. The obtained results support the hypothesis that impaired cognitive functioning leads to social withdrawal, isolation, reduced motivation and ability to perform daily functions in schizophrenic subjects. This coincides with certain studies that suggest that cognitive functioning is an indicator of a more severe and unfavorable course of the disease and poor functioning of the person in the community, i.e. a change in the person's quality of life [19, 20].

Therefore, patients with schizophrenia need to start with antipsychotic therapy and psychosocial therapeutic interventions in time in order to be able to affect the natural course of the disease. Along with the longer period of time that is required to achieve a satisfactory improvement of the patient's mental state, each subsequent deterioration of the psychological condition is continued. At the same time, patients who show a poor response to antipsychotic therapy have residual psychotic symptoms that reduce the person's functional capacity. Therefore, it is believed that timely application of therapy (psychopharmacological, psychosocial and psychotherapeutic interventions) can reduce psychotic symptoms, it can reduce the regressive course of schizophrenia and prevent the development of therapeutic resistance.

CONCLUSION

Modern psychiatry today seeks to integrate the different psychiatric theories and concepts with contemporary neurophysiological findings. All attempts and tendencies to integrate different psychotherapeutic and pharmacotherapeutic interventions rest on this assertion.

It is known that the internal representation of the personal space can be modified with experience. Experience is modified not only through mental experiences, but also through brain functioning and brain architecture. All of this, together with the unique genetic material, establishes the biological basis of the person [21]. The biological basis generates our emotions, experiences and behavior, but also the experience of current brain activities reforms them in the brain structure. Unlike the findings in the past, according to the latest findings it is considered that the brain structures are variable and flexible, and our mind is a complex, biological, historical, cultural and social phenomenon.

Schizophrenia is a chronic mental illness, a clinical syndrome with the presence of specific psychological symptoms, individual variations in terms of the clinical features, the response to therapy and the course of the disease, as well as reduced functional capacities of the person from all aspects - personal, family, work and social. Therefore, our results may be important for the prevention, detection and treatment of schizophrenia. These results can also be applied as an auxiliary means of assistance in the treatment of schizophrenia, in order to prevent or overcome the already negative side effects. With adequate psychiatric and psychological help, in the form of counseling and psychotherapy work, patients can be provided help to more easily accept and overcome the disease. Of course, these results can help the families of patients, but also professionals who deal with the treatment of schizophrenia, through counseling and psychotherapy in the adaptation of the disease, in creating a new way of life, as well as regular use of antipsychotic therapy.

Based on the theoretical analysis and the empirical data we can say that although we have achieved the set goals, this research still leaves space for practical application of the results, but also provides an incentive for further new researches that will provide a better understanding of this complex problem.

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Profesional paper

PATIENTS WITH CEREBROVASCULAR DISEASE WHO HAVE DEVELOPED DEMENTIA AND COMORBIDITIES DIABETES AND HYPERTENSION IN POLYCLINIC BIT PAZAR – SKOPJE DURING THE YEAR 2017-2020

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ABSTRACT

Introduction: Cerebrovascular disease refers to a variety of conditions that affect the supply of blood to the brain and are an important cause of cognitive impairment and dementia in elderly patients.

Aim: is to analyze through it distribution of patients with cerebrovascular insult on the basis of gender and age, to analyze the correlation between age and how many of them have developed dementia, and the presence of comorbidities like diabetes and hypertension.

Methods: 143 patients with cerebrovascular insult ambulate treated in Poliklinik Bit Pazar – Skopje in period of three year who developed dementia and comorbidities hypertension and diabetes. Using statistical methods such as: arithmetic mean and linear correlations.

Results: Cerebrovascular diseases is represented the same in both genders, 18.18 % of them developed dementia. Comorbidities: hypertension is generally presented in 95, 80 % where we can see the importance of it in cerebrovascular diseases. Diabetes is an important risk factor for stroke it is represented in 30 % of cerebrovascular diseases.

Conclusion: Cerebrovascular disease refers to a group of conditions, diseases, and disorders that affect the blood vessels and blood supply to the brain who lead cerebrovascular insults and dementia. Hypertension and diabetes have an impact on the occurrence of cerebrovascular diseases.

Keywords: Dementia, Vascular dementia, cerebrovascular diseases, diabetes, hypertension.

INTRODUCTION

Cerebrovascular disease is an important cause of cognitive impairment and dementia in elderly patients. The link between cerebrovascular disease and dementia has been a controversial topic for decades. At one point, cerebrovascular disease was believed to be the dominant cause of dementia. Then, as recently as a decade ago, it was thought to be exceedingly rare. By 2005, the pendulum has begun to swing back to a larger role for cerebrovascular disease in cognitive disorders. Although recognition of the importance of cerebrovascular disease in dementia is widely accepted, major challenges to the concept remain.(1,2). Dementia is a disorder in which individuals lose independence of daily functioning because of cognitive dysfunction like deterioration in memory, thinking, behavior and the ability to perform everyday activities. Worldwide, around 50 million people have dementia, and there are nearly 10 million new cases every year.

Vascular dementia also known as multi-infarct dementia occurs when vessels that supply blood to the brain become blocked or narrowed. Strokes take place when the supply

of blood carrying oxygen to the brain is suddenly cut off. Symptoms of vascular dementia depend on what part of the brain is affected and to what extent. Like Alzheimer's disease, the symptoms of vascular dementia are often mild for a long time.

In the first few years after a stroke, the rate of dementia is greatly increased.(3) As many as 30% of stroke survivors in one study had dementia by 6 months after their stroke. (4) Another study characterized the risk of dementia as (5)fold compared with individuals of the same age and sex without a new stroke.(6)

PURPOSE

The purpose of the paper is to analyze through it distribution of patients with cerebrovascular insult on the basis of gender and age, to analyze the correlation between age and how many of them have developed dementia, and the presence of comorbitis like diabet and hypertension.

MATERIAL AND METHODS

This study is descriptive, retrospective type. The Material was taken form ambulate treated patients in polyclinic Bit Pazar – Skopje in period of three year from 2017 to 2020. The number of patients in this period diagnosed with cerebrovascular insult was 143 whose age ranges from 52 to 83 years old. In which after neuropsychological test 26 patients were diagnosed with cognitive disorders-dementia. As well as the presence of hypertension and diabetes in these patients. The data are presented by means of tables and graphs. For data processing are used statistical methods such as: arithmetic mean and linear correlations.

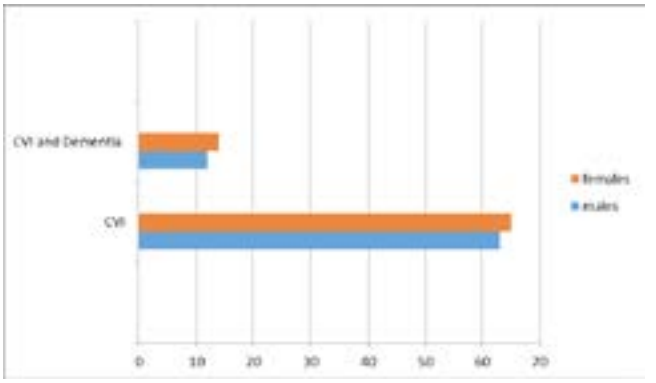
RESULTS

After receiving all data from patients and after their statistical processing, we obtained the results of following

Graph 1. Ratio of male to female patients

Graph 1 shows that out of 143 cases with cerebrovascular insults, 73 of them or 51.04% are female while the rest, 70 or 48.95% are male.

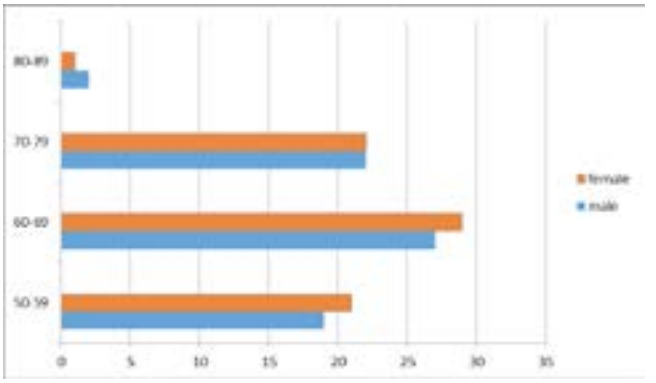
This shows that the presence of cerebrovascular disease is the same in both genders.



Graph 2. Patients with cerebrovascular stroke who have developed dementia

Graph 2 .shows that out of 143 cases with cerebrovascular insults after a neuropsychological test only in 26 or 18.18 % of patients were diagnosed dementia. Were 14 or 9.79 % were females and 12 or 8.39 % were male.

Here we can also conclude that gender does not have any influence on the appearance of dementia.



Graph 4. Distribution of cases by gender across age group

The most attacked age group in both genders is 60-69 years with a total of 56 cases or 39.16 % while the age group 80-89 the same in both genders is less present with total 3 of cases or 2.09%.

Age group	With dementia	%	Without dementia	%
50-59	6	42.85	35	29.91
60-69	8	57.14	48	41.02
70-79	9	64.28	34	29.05
80-89	3	21.42	0	0
Total	14	100	117	100

Table 1. Patients with and without dementia

Table 1 shows that patients with CVI without dementia are mostly found in the age group 60-69, a total of 48 or 41.02%, while those with dementia are found in the age group 70-79 with 9 or 64.28 %.

Age group	Diabetes	%	HTA	%	Total
50-59	23	53.48	36	26.27	40
60-69	10	23.25	54	39.41	56
70-79	7	16.27	44	32.11	44
80-89	3	6.97	3	2.18	3
Total	43	100	137	100	143

Table 2. Patients with diabetes and hypertension

Tab.2 shows that hypertension occurs in all age groups mostly at 60-69 ,54 or 39.41% and diabetes at 50-59 age group 23 or 53.48%

In 143 patients with cerebrovascular disease in 137 or 95.80% we have the presence of hypertension and the presence of diabetes is in 43 or 30 %.

DISCUSSION

The incidence and prevalence of dementia vary from study to study, all population-based epidemiological investigations have shown that vascular demencija increases with advancing age. (7,8)

In addition, Alzheimer Dementia increases with advancing age, so no age-related variations exist in the incidence of the 2 disorders that can be exploited for diagnostic reasons.(9)

Vascular dementia is generally stated to be the second most common cause of dementia in later life in Caucasian populations, although it may be the most common cause in East Asia, and there are few data from other ethnic groups (10, 11).

In our study, out of the total number of patients with dementia symptoms, it is presented to 18.18% of patients, worldwide it is represented 20%. Also does not exist differences in gender.

Chronic hypertension directly affects the structure and function of cerebral blood vessels. But how these cerebrovascular effects lead to cognitive impairment disease pathology is not well understood.

Similar patterns were shown in the Goteborg Longitudinal Population Study, where 70 year olds with elevated blood pressures had more dementia at 79 to 85 years of age, but many also experienced decline in blood pressure in the years more proximal to a dementia diagnosis. (12)

In our study it is clear that HTA occurs in almost all patients with cerebral insult, which shows the importance of hypertension in cerebrovascular disease, including dementia.

Diabetes mellitus increases the risk of stroke. In the study of Tuttolomondo A and collaborators in 102 diabetics and 204 non-diabetic subjects with acute ischemic stroke, matched by sex and age (+/-3 years). Study shows some significant differences in acute ischemic stroke among diabetics in comparison with non-diabetics (higher frequency of hypertension, higher prevalence of lacunar stroke subtype, lower neurological deficit at admission in diabetics). (15)

In the Lausanne Stroke Registry between 1983 and 2002, patients with diabetes had higher relative prevalence of subcortical infarction and lower relative prevalence of intracerebral hemorrhage (ICH). (13). In another study, significant differences were observed in patients with ischemic stroke along with diabetes in comparison with nondiabetics with higher frequency of lacunar infarct and hypertension. (14) Diabetes in our study is represented only 30 % of patients with cerebrovascular insult.

CONCLUSION

Cerebrovascular disease is an important cause of cognitive impairment and dementia in elderly patients, accounting for up to 20% of cases of dementia.

Hypertension is the leading cause of age-related cognitive impairment because it directly affects the structure and function of cerebral blood vessels thus affecting the onset of cerebrovascular disease- strokes and dementia.

Diabetes is an important modifiable risk factor for

cerebro-vascular diseases, especially ischemic stroke or cerebrovascular insults.

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Profesional paper

МАКРОЗОМЕН ПЛОД - ИСХОД КАЈ МАЈКА И ПЛОД

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АБСТРАКТ

Цел: Да се презентираат ризик факторите и исходот на мајките и новороденчињата кај комлицирани бремности со макрозомен плод над 4500 гр во период од три години.

Метода: Оваа студија претставува пресечна ретроспективна анализа спроведена во Специјална Болница за Гинекологија и Акушерство "Мајка Тереза" Скопје во период од три полни години 2017-2019. Во тек на овој период бројот на раѓања бил 11.864.Ние ги следевме новороденчињата со родилна телесна тежина над 4500г, измерени веднаш по породување. Вкупниот број за три години беше 153, односно 1.3 %.Ги анализиравме ризик факторите за макрозомија : застапеноста на повеќеротките,колку од мајките претходно родиле макрозомен плод , средна возраст на мајките и пол на новородените. Беше евалуиран начинот на породување, т.е. колку раѓања завршиле со царски рез . По породување следени се колку од пациентките имале повреди на породилни патишта, видот на повредите и комликации. Кај новороденчињата е следено појава на рамена дистокија, Апгар скор во прва и пета минута, гликемија (средна вредност) во првите 24 часа и повреди - бројот на повреди ,видот и исходот.

Резултати: Со царски рез се породиле 81(53 %), спонтано се породиле 72(47%) пациентки. Од спонтано породените без епизиотомија и други повреди на генитален тракт и без никакви комликации се породиле 12 пациентки, односно само околу 17%,. Како најчеста компликација по раѓање била перинеална лацерација од прв степен,18%.Лацерација од втор степен е регистрирана кај две пациентки (2.8%) две пациентки имале лацерација на цервикс(2.8%) и три пациентки лацерација на вагина(4.1%). Регистрирани се 29 епизиотомии. Пет новородени имале shoulder dystocia.Најнизок Apgar score е виден кај три новородени и тоа 3/5, 4/7, и 5/7, другите беа со Apgar над 7. Гликемија била 3.5+/- 1.2mmol/L. Најниска измерена 2.2 mmol/L. Фрактура на клавикула имале 7 новороденчиња, додека пареза на plexus brachialis 3 новороденчиња.

Заклучок: Фетална макрозомија претставува сериозен проблем во акушерството. Менаџирање на сомнителна макрозомија треба да биде индивидуализирана со цел да се минимизираат мајчините и феталните компликации. Целиот персонал треба да биде запознаен, да биде спремен за очекуваните исходи кај мајка и новородено, да одговори соодветно и да управува со нив.

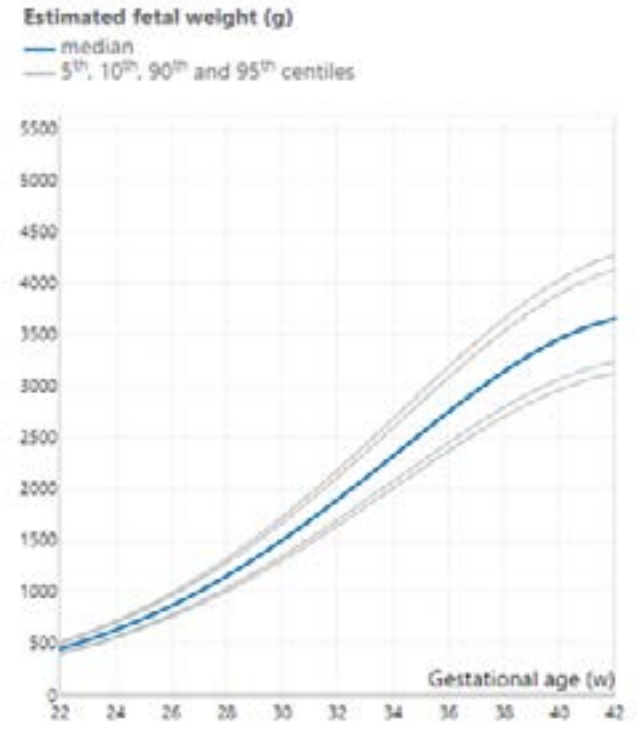
Клучни зборови:макрозомија,царски рез, спонтано породување,исход кај мајка,исход кај новородено

ВОВЕД

Дефиниција: Макрозомен плод подразбира плод кој го користел својот потенцијал за раст над границите за актуелната гестациска старост, односно плод со родилна телесна тежина над 90-та перцентила за гестациската возраст, или во абсолутна бројка - новородено во било која гестациска возраст со тежина над 4500 грами, која кореспондира со 97-ма перцентила.Резултати од долги кохортни студии ја подржуваат втората дефиниција. 1.(14)

Во прилог табела со перцентили за фетална тежина во однос на гестациска старост на плодот во третиот триместар на бременоста (fetalmedicine.org,Fetal medicine foundation -Fetal growth assessmen)(16),

Инциденцата е 1-15% од бременостите зависно од местото,расата,локални фактори и методологијата, на пример во САД 6.9% од новороденчињата имаат телесна тежина 4000-4500г, 1.5% тежат >4500г и 0.1% над 5000г. Нордиски земии имаат најголема преваленца, 20% на новородени над 4000 гр.



Во нашата болница инциденца на макрозомија во периодот 2017-2019 г била 1.3%, сметајќи ги за макрозомни сите новороденчиња со телесна тежина над 4500г.

Како најчести ризик фактори се дијабетес кај мајка (прегестациски или гестациски), претходно родено дете со РТМ над 4000г, повеќеротки, мајки над 35 годишна возраст, постдатизам обезитет, машки пол на новородено. Дијабетесот е веројатно најчестиот и најголем фактор со оглед дека го зголемува ризикот за 10 пати во однос на останатата популација.

Многу е тешко точно да се предвиди телесна тежина на макрозомен плод пред породување. Метода која се употребува за предикција на родилна тежина in-utero е проценка на спомнатите ризик фактори кај мајка, клинички преглед и ултразвук. Двете примарни клинички методи за дијагноза на фетална тежина се Леоплодови маневри и мерење на дистанца фундус-симфиза. Употребата на овие две методи се покажало како слаб предиктор, посебно кај обезни трудници. Ултразвчна фетална биометрија е најсоодветна метода за дијагноза на фетална тежина, но далеку од прецизна со оглед на тоа дека во повеќе од 50% од макрозомните плодови измерената телесна тежина (EFW – estimated fetal weight) отстапува за повеќе од 10% од реалната (15).

Најчести комликации кај мајка се зголемена инциденца на раѓање со царски рез, пролонгирано раѓање со ризик за појава на интрапартална инфекција, повреди на родилни патишта, постпартална хеморагија. Во однос на плодот, најчести и најтешки компликации се рамена дистокија, породилни повреди (фрактура на клавикула, пареза на plexus brachialis), асфиксија, меконијален аспирационен синдром, респираторен дистрес синдром, хипогликемија.

Со оглед на наведените бројни и тешки компликации, обстетричариите имаат склоност да индуцираат раѓање ако се сомневаат на појава на макрозомен плод (“impending macrosomia”), или да ја завшат бременоста со елективен царски рез, или пак со итен царски рез ако раѓањето е веќе започнато. Но, досегашните студии и протоколи не препорачуваат индукција на раѓање кај сомнителен крупен плод, посебно не пред 39 полни гестациски недели.

Вагинално породување не претставува контраиндикација кај плод до 5000г и мајки кои немаат дијабетес, и кај плод до 4500г и мајки кои имаат дијабетес. Ако постои пролонгирање на втора фаза на раѓање, во прилог на фето-пелвична дисропорција - се препорачува завршување на раѓањето со царски рез1′ . (14)

МАТЕРИЈАЛ И МЕТОДИ

Студијата била спроведена во Специјална Болница за Гинекологија и Акушерство "Мајка Тереза" Скопје во период од три полни години 2017-2019. Во тек на овој период бројот на раѓања бил 11 864.

Ние ги следевме новороденчињата со родилна телесна тежина над 4500г, измерени веднаш по породување. Вкупниот број за три години беше 153, односно 1.3 %.

Цел на студијата ни беше да се евалуират ризик факторите кај мајка и начинот на породување, т.е. колку раѓања завршиле со царски рез а колку спонтано. Од спонтаните раѓања ги анализиравме колку од нив биле прворотки а колку повеќеротки. По породување следени се колку од пациентките имале повреди на породилни патишта, видот на повредите и

комликации. Кај новороденчињата е следено појава на рамена дистокија, Апгар скор во прва и пета минута, гликемија првите 24 часа и повреди - бројот на повреди ,видот и исходот.

РЕЗУЛТАТИ

Од вкупниот број 11864 раѓања во тек на три години, 153 новородени биле со родилна телесна тежина над 4500гр. Инциденца на макрозомија била 1.3%.

Околу 77% од пациентките биле мултипари.Само девет од вкупниот број биле прворотки.Претходно родено макрозомен плод имале 62 пациентки или 40%.Средна возраст на мајките во 2017 беше 35 +/- 7.5 год.(range: 19-44 години,median: 35 години), во 2018 беше 34,9 +/- 6 год.(range:26-44 години,median: 34 години) и во 2019 беше 36.3+/- 6год (range:28-44 години, median: 35 години). Во однос на полот на новородените повеќето се од машки пол.Во прилог табела 1 каде е прикажан однос на женски и машки макрозомни новородени по години.

Табела 1.

	2017	2018	2019
женско	12	20	13
машко	37	31	40

Од вкупниот број 153 пациенки, со царски рез се породиле 81, спонтано се породиле 72 пациентки.Во табела 2 е презентиран начин на породување.

Процентот на бремености завршени со царски рез е за околу 60% повеќе од општата стапка на царски рез за тие 3 години. Без епизиотомија и други повреди на генитален тракт и без никакви комликации се породиле 12 пациентки, односно само околу 17 %. Како најчеста компликација по раѓање била перинеална лацерација од прв степен регистрирана кај 13 пациентки. Лацерација од втор степен е регистрирана кај две пациентки, две пациентки имале лацерација на цервикс и три пациентки лацерација на вагина.Сите пациентки биле згрижени веднаш по породување со постпартален уреден тек.

Табела 2.Начин на породување

Година	Вкупен број на раѓања	Макрозомни плодови n (%)	Вагинално породување n (%)	Со царски рез n (%)	Оператив ни вагинални породувања n
2017	3883	49)1.2)	23 (15)	26 (17)	/
2018	4132	51(1.2)	28 (18)	23 (15)	/
2019	3849	53 (1.3)	20 (13)	32 (20)	1

Пет пациентки имале shoulder dystocia. Породилна повреда видена е само кај едно новородено и тоа paresis plexus brachialis. Новородено било родено од мајка прворотка со родилна телесна маса 4550g/54cm и Apgar score 7/8 ,гликемија 3.7mmol/L. На испис новороденото било добро со комлетна регресија повредата и воспоставена функцијата на нервниот сплет. Другите четири новороденчиња немале никакви породилни повреди, беа породени од мајки мултипари кои имале родено претходно макрозомен плод. Apgar score кај две новородени било 8 /9, кај едно 7/9 и кај една четвртоткa со гестациски дијабет новороденото било со тт 4760г и Apgar score 6/7.

Најнизок Apgar score е виден кај три новородени и тоа 3/5, 4/7, и 5/7, другите беа со Apgar над 7.

Гликемија била 3.5+/- 1.2mmol/L. Најниска измерена 2.2 mmol/L.

Фрактура на клавикула имале 7 новороденчиња, додека пареза на plexus brachialis 2 деца.

Најголемо новородено било со РТМ 5180g/54cm родено од мајка петторотка, спонтано, без епизиотомија и повреди на генитален тракт. По породување пациентката имала постпартална хеморагија како последица на хипотонија на утерус - третирана медикаментозно.

ДИСКУСИЈА

Многу студии заклучиле дека антенаталното ултразвучна проценка на фетална макрозомија непотребно ја зголемува стапката на царски рез, и голем процент од тие што се проценети како макрозомни всушност испаѓаат со нормална телесна тежина. Според ACOG, дури и во случај на спонтано започнато раѓање стапката на царски рез е дуплирана ако е проценето телесна тежина на плодот над 4500г, а со тоа значително се зголемува примарниот матернален ризик. Според една студија во САД, кај недијабетични мајки и плод со EFW>4000g треба да се извршат 2345 породувања со царски рез за да се спречи една трајна повреда како последица на спонтано породување.

Од друга страна пак, сериозни компликации како рамена дистокија, фрактура на клавикула и повреда на бранхијалниот нервен сплет се асоцирани со спонтано породување на макрозомен плод, особено ако тоа е асоцирно со мајка со дијабетес (преегзистенцијален или гестациски)4′ . Едно објаснување за оваа е распределбата на поткожното масно ткиво кај макрозомните плодови во предел на вратот и трупот, посебно кај оние со хипергликемија (дијабетични мајки). Ова доведува до зголемување на биакромијалниот дијаметар и абдоминалната циркумференција во однос на циркумференцијата на предлежечкиот дел - главата.

Во нашата студија shoulder dystocia имале пет пациентки, односно 3.2%. Shoulder dystocia претставува ноќна мора за обстетричарите. Иако инциденцата е многу ниска, shoulder dystocia претставува најголем ризик за неонатален и матернален морбидитет и морталитет. Во големи студии стапката на рамена дистокија е 0.6-1.4 % од сите спонтани породувања. Кај макрозомни плодови ризикот за рамена дистокија се зголемува до 10 пати,кај тешка рамена дистокија и до 20 пати(7).Нашиот резултат од 3.2% се должи на тоа што се опфатени само спонтани породувања на макрозомни плодови (над 4500г),1. (14)При рамена дистокија треба да се направи епизиотомија затоа што се отвара повеке место за евентуално внатрешни маневри,иако како примарен проблем при рамена дистокија претставува коскениот дел.8Во наша студија регистриравме 29 епизотомии.

Стапка на перинеални лацерации од прв степен беше 18%, втор степен 2.8%. Лацерација од трет и четврт степен немаше. Лацерација на вагина 4.1 %, цервикална лацерација 2.8%. Перинелните лацерации и постпартална хеморагија се најчести постпартални комликации кај пациентки со макрозомен плод, затоа кај овие пациентки е продолжен престојот во болница за закрепнување.

Постпарталната хеморагија може да е поврзана со дистензија на утерус и зголемената плацентарна маса, како и повреда на меки родилни патишта.

Ризикот за асфиксија и ниски Апгар скорови се зголемува кај макрозомен плод. Тоа е потврдено кај неколку студии. Во нашата болница новороденчињата беа родени во добра кондиција со Апгар скор 7 и над 7 во прва и петта минута освен три новороденчиња кои беа со понизок Апгар скор во прва и петта, а потоа во 10 минута со уредна адаптација и нормални витални параметри.

Фрактура на клавикула е честа и непредвидлива компликација на спонтано нормално породување со инциденца 5-10 на 1000 новородени (14) ,односно процентуално 0.4-0.6 % во однос на вкупниот број на сите раѓања.Кај макрозомен плод ризик за фрактура на клавикула се зголемува за 10 пати. Во наша студија фрактура на клавикула имале 7 новороденчиња односно 4.5%. Нашиот резултат е во однос на вкупниот број на макрозомни плодови. Фрактурите биле дијагностицирани во првите три дена од породувањето. Исходот на фрактурите бил бениген со комлетно закрепнување без неуролошки секвели. Фрактурите на клавикулата се асоцирани со неонаталните соматометрични карактеристики и потешко породување.

Повреда на plexus brachialis е најсериозна комликација. Таа може да биде транзиторна или перманентна. 80-90% од повредите на plexus brachialis заздравуваат во тек на една година. Се јавува кај 1.5 на 1000 новородени, што значи дека 0.1-0.2/1000 новородени ќе имаа трајна повреда на нервниот сплет. Case control студии демонстрираат дека ризикот за повреда на plexus brachialis кај новородени породени вагинално се зголемува 18-21 пати кај новородени со родилна телесна тежина над 4500г со апсолутна стапка помеѓу 2.6%-7%. Но, од друга страна, повреда на plexus brachialis може да се случува и во отсуство на макрозомија и shoulder dystocia или во тек на царски рез. Во наша студија три новороденчиња имале пареза на plexus brachialis, односно 1.9 %. Едното од нив имало и рамена дистокија при раѓање.Од правен аспект, битно е да се нотира кое рамо е предно при породување, бидејќи многу е мала веројатноста да се повреди задното рамо.

ЗАКЛУЧОК

Инциденцата на макрозомија веројатно ќе се зголеми уште повеќе во иднина поради трендот на пораст на стапката на ризик факторите, како што се зголемувањето на возраста на мајката, дебелината и гестацискиот дијабетес. И покрај огромното истражување во оваа област, ограничувања постојат и траат во предвидување и управување со макрозомија и дистоција на рамото. Менаџирање на сомнителна макрозомија треба да биде индивидуализирана со цел да се минимизираат мајчините и феталните компликации. Целиот персонал треба да биде

запознаен, да биде спремен за очекуваните исходи кај мајка и новородено, да одговори соодветно и да управува со нив.

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ПРЕДИКТИВНА ВАЖНОСТ НА НЕИНВАЗИВНИТЕ МАРКЕРИ НА ФИБРОЗА КАЈ ПАЦИЕНТИ СО АЛКОХОЛНИ ЗАБОЛУВАЊА НА ЦРНИОТ ДРОБ

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КУСА СОДРЖИНА

Алкохолнните заболувања на црниот дроб се дефинираат како состојби кои опфаќаат хепатални манифестации како последица на прекумерната консумација на алкохол и вклучуваат реверзибилно замастување на црниот дроб, алкохолен хепатитис, цироза и хепатоцелуларен карцином.

Поради многу висока преваленција на болеста, алкохолните заболувања на црниот дроб остануваат недијагностицирани или нецелосно дефинирани во голем број на случаи. Затоа, цел на многу истражувачи од областа на хепатологијата е да се направат напори за пронаоѓање на средства за не-инвазивна дијагностика.

Последниве години се повеќе се зголемува интересот за откривање и опишување на црнодробните промени со серумски биомаркери, како алтернатива за хепаталната биопсија. Откриени се неколку биомаркери како можни корисни индикатори за црнодробна фиброза.

Серумските биомаркери ги делиме на директни (фрагменти од црнодробниот екстрацелуларен матрикс) и индиректни биомаркери (молекули ослободени во крвта како резултат на промени во хепаталната функција).

Постојат само неколку студии кои ја евалуираат дијагностичката и прогностичката вредност на неинвазивните биомаркери на фиброза кај пациенти со алкохолна црнодробна болест.

Биохемиските биомаркери на фиброза (FibroTest, Fibrometer A и Hepascore) имаат високо ниво на дијагностичка моќ и со нив може да се направи разлика помеѓу напредна фиброза и цироза кај пациенти со алкохолна болест на црниот дроб. Постојат многу други тестови кои се уште не се широко потврдени, но остануваат ветувачки.

Употребата на овие биомаркери може да се користи како скрининг, овозможувајќи на лекарот да го намали бројот на пациенти пред дефинитивно дијагностицирање на црнодробната фиброза со хепатална биопсија.

Клучни зборови: алкохолно заболување на црниот дроб, маркери на црнодробна фиброза.

ВОВЕД

Исконската човечка природа да се побегне од реалноста, да се пронајде еликсир на вечната младост постои уште од дамнешни времиња.

Податоците од историјата на цивилизацијата, покажуваат дека уште пред 7000 години човекот ги открил фармаколошките карактеристики на алкохолот, опишувајќи го како стедство за опуштање и еуфорија. Алкохлните пијалоци се добивале по пат на природна ферментација, се до 8-миот век кога арапските лекари ја откриле дестилацијата и добиениот дестилат го нарекле ''al- kohol''.

Зборот алкохол потекнува од арапскиот збор al-khwl и најчесто се однесува на етанол, познат и како зрнест алкохол (направен од житни растенија), или, пак, на било кој пијалок кој содржи етанол. Во хемијата, алкохол е поопшт термин, кој се применува за секоја органска супстанца во која хидроксилната (-OH) група е поврзана со јаглероден атом, кој, од друга страна, е поврзан со други водородни и/или јаглеродни атоми.

Етанолот е бистра, безбојна и лесно запалива течност со хемиски состав CH3-CH2-OH. (1)

Хроничната консумација на алкохол доведува до оштетување на многу органи и системи. Алкохолните заболувања на црниот дроб предизвикуваат промени во структурата и функцијата на црниот дроб, и се дефинираат како спектар на состојби кои се движат од реверзибилно замастување на црниот дроб, алкохолен хепатитис, цироза и хепатоцелуларен карцином. Познато е дека количината и времетраењето на консумираниот алкохол е главен предиспонирачки фактор за развој на сериозни оштетувања на црниот дроб вклучувајќи ги и факторите на животната средина и факторот домаќин. (2,3)

Поради многу висока преваленција на болеста, алкохолните заболувања на црниот дроб остануваат недијагностицирани или нецелосно дефинирани во голем број на случаи. Затоа, цел на многу истражувачи од областа на хепатологијата е да се направат напори за пронаоѓање на средства за неинвазивна дијагностика.

Последниве години се повеќе се зголемува интересот за откривање и опишување на црнодробните промени со серумски биомаркери, како алтернатива за хепаталната биопсија. Откриени се неколку биомаркери како можни корисни индикатори за црнодробна фиброза, поделени во две групи: директни (фрагменти од црнодробниот екстрацелуларен матрикс) и индиректни биомаркери (молекули ослободени во крвта како резултат на промени во хепаталната функција).(4)

Целта на овој преглед е да се презентираат најчесто користените индиректни маркери на фиброза објавени во литературата, и нивната предиктивна важност за утврдувањето на стадиумот на алкохолната црнодробна лезија, односно можноста за диференцијација меѓу едноставната стеатоза, стеатофиброза и цироза.

Во сите случаи не- инвазивните маркери на фиброза се споредувани со хистопатолошкиот наод добиен со биопсија на црниот дроб, кој сеуште представува дијагностички ' златен стандард' .

Користењето на не-нинвазивните индиректни маркери на фиброза може да биде корисна метода за рана детекција на алкохолните црнодробни заболувања во општата популација во Р.Македонија за ' screening' и диференцијацијата помеѓу замастен и фибротично променет црн дроб и во голема мера ќе ја намали потребата од црнодробна биопсија која како и секоја инванзивна процедура носи извесен ризик за пациентот, а од економски аспект и во голема мера ја зголемува цената на дијагностичката процедура.

Патофизиологија

Алкохолот се апсорбира во желудникот и тенкото црево. Во над 90% се метболизира во црниот дроб со процес на оксидација. Прв меѓупроизвод е ацеталдехидот, кој настанува под дејство на три ензими: алкохолна дехидрогеназа (одговорна за 80% метаболизам), цитохром- P–450 2E1 (CYP2E1) и каталаза.

Митохондријалната алдехид деходрогеназа, ацеталдехидот го претвора во ацетат. Хроничен алкохолен абузус го зголемува создавањето на ацетатите и доведува до насобирање на водородните јони кои го претвораат nikotinamid–adenin dinukleotid (NAD) во негов редуциран облик (NADH), со што се зголемува вкупниот редокс потенцијал во црниот дроб. Ова доведува до намалување на искористеноста на масните киселини за создавање на енергија, се намалува оксидацијата на масните киселини и доаѓа до насобирање на триглицеридите во црниот дроб и хиперлипидемија. Вишокот на водородни јони го претвораат пируватот во лактат со што се намалува создавањето на гликоза (хипогликемија), настанува ренална ацидоза, се смалува излачувањето на урати, што има за последица развој на хиперурикемија и гихт.

Долготрајната алкохолна консумација доведува до зголемена кислородна потрошувачка, што се должи на зголемената ре-оксидација на NADH. Хиперметаболната состојба во црниот дроб има за последица хипоксија на хепатоцитите и нивна консекутивна некроза, оштетување на клетките со посредство на слободните радикали и квантитативна редукција на антиоксидансите (глутатион, витамин Е, А) .

Екцесот на ацеталдехид е одговорен за појава на воспаление и фиброза кај пациентите со алкохолен хепатитис. Ацеталдехидот го стимулира претворањето на sвездестите клетки кои ги обложуваат црнодробните крвни садови (синсоиди) во фибробласти кои создаваат миоконтрактилни елементи и активно произведуваат колаген. Синосоидите се опструираат со што се намалува транспортот на крв . Цревните ендотоксини неможе да се метаболизираат поради оштетениот црн дроб и доведуваат до создавање на воспалителни цитокини. Ацеталдехидот и продуктите на липидната пероксидација ги активираат леукоцитите што резултира со уште поголемо создавање на цитокини.

Тоа доведува до насанување на circulus viciosus, фиброза и изумирање на хепатоцитите.

Мастите се акумулираат во хепатоцитите (зголемен прелив од периферните масни ткива), се зголемува синтезата на триглицериди, се намалува оксидацијата на липиди , и се намалува создавањето на липопротеини што од друга страна доведува до смалување на можноста за излегување на мастите од црниот дроб. (5,6,7)

Патологија

Алкохолната болест на црниот дроб може да се презентира како: замастен црн дроб (стеатоза) , алкохолен хепатитис (стеатохепатитис) и цироза.

Замастен црн дроб (стеатоза) се јавува како последица на прекумерна консумација на алкохол. Потенцијално е реверзибилна. Се дефинира како нсобирање на макровезикуларни масти во облик на големи капики триглицериди кои ги дисоцираат јадрата на хепаталните клетки. Поретко, мастите може да се јават во микровезикуларен облик кој не го дисоцира јадрото. Клиничките манифестации се минимални . Лабораториските тетсови обично се нормални освен лесно покачен AST (aspartate transaminase), ALT (alanine transaminase) и GGT (′ -glutamyl transferase) . Прогнозата е добра.

Алкохолен хепатитис (стеатохепатитис) се дефинира како комбинација на замастен црн дроб, дифузно воспаление и некроза (обично фокална) . Оштетените хепатоцити се набрекнати со зрнаста цитоплазма (балонска дегенерација) , или може да содржат фибриларни протеини во цитоплазмата (алкохолни хијалини тела- Малориеви). Таложење на колаген и фиброзата во терминалните хепатални венули ја компромитираат перфузијата и доведуваат до појава на портална хипертензија. Клиничката слика варира од асимптоматски облици па до фатална инсуфициенција на црниот дроб. Периодот на рековалесценција е долг .

Цироза (Laennaecova цироза), се дефинира како дифузен процес на фиброза (последица на хепатоцелуларна некроза и колапс на лобулусите) следена со компензаторно создавање на нодули. Нодулите може да бидат мали(микронодули) кои ги зафаќаат скоро сите лобулуси, или големи(макронодули) кои се среќаваат и нормални лобулуси. Микронодуларната цироза со тек на време може да се претвори во макронодуларна. Клиничката слика на алкохолната цироза е идентична како кај цирозата од друга етиологија и има лоша прогноза со 5 годишно преживување под 50 %. (8,9,10)

Епидемиологија

Околу 2 милијарди луѓе во светот консумираат алкохолни пијалаци , а од нив над 76 милиони имаат органски пореметувања предизвикани од консумација на алкохол. СЗО проценува дека користењето на алкохол е одговорно за околу 2,3 милиони прерани смртни случаи на годишно ниво во целиот свет (3,7% од глобалниот морталитет).(11)

Според податоците од Светска здравствена организација , во 2000г.во Македонија, на популација од 100.000 жители, морталитетот од алкохолна цироза на црниот дроб изнесувала 12.3.% кај машка, и 3.3.% кај женска популација.(12)

Алкохолот има негативен ефект и врз социо-економскиот живот, цената на прекумерните социјални пиења се 1% или повеќе од бруто домашниот производ во земјите со висок приход.(13,14)

Епидемиолошките податоци зборуваат дека постојат регионални и национални разлики во количината на консумација на алкохол, а актуелните трендови укажуваат дека достапноста и консумирањето на алкохол ќе продолже да расте во иднина.

Најголема консумација на алкохол на годишно ниво по глава на жител (15,7 L по лице) има во Источна Европа има , додека во Северна Африка и Блискиот Исток таа е најниска (1.0 L по лице).(15)

Моратлитетот од алкохолна цироза во 16 земји на Европската унија покажува тренд на опаѓање,така што вредноста од 15.6% во 1980г. е намалена на 10.6% во 2000г. Овој тренд е во корелација со промените во навиките на алкохолната консумација. (16)

Фактори на ризик

Факторите на ризик кои доведуваат до развој на алкохолна болест на црниот дроб може да се поделат на надворешни (животна средина) и внатрешни (домаќин) ризик фактори.

Надворешни фактори

Постои линеарна корелација помеѓу количината и траењето (повеќе од 8г) на алкохолната злоупотреба и развојот на хепаталната болест.

Консумација на 20 гр. алкохол кај жена и 60 гр. кај маж може да доведат до тешки оштетувања на црниот

дроб доколку секојдневно се конзумираат во тек на неколку години. Внес на повеќе од 60 гр/ден во тек на 2-4 недели кај здрав маж доведува до масна промена на хепарот во; 80 гр/ден може да доведе до алкохолен хепатитис; а на повеќе од 160 гр/ден во пек на десетолетие доведува до цироза. Количеството на алкохол се проценува така да количеството на пијалок во мл. се множи со процентот на алкохол. Отприлика во 40 мл 40% алкохолен пијалок се наоѓа 16 мл.алкохол. Секој мл.алкохолен пијалок содржи приближно 0.79гр. алкохол. (17,18,19)

Внатрешни фактори

Возраст: Способноста да се метаболизира алкохолот се намалува со возраста, бидејќи стареењето предизвикува намалување на големината и протокот на крвта во црниот дроб а истовремено се намалува и активноста на ензимите кои го метаболизираат алкохолот, како алкохолната дехидрогеназа, ацеталдехид дехидрогеназата и цитохромот 4502Е1. (20,21)

Црниот дроб кај постарите лица станува посебно осетлив на токсичното дејство на алкохолот. Повеќето студии кој го обработуваат овој проблем објавуваат дека постои позитивна корелација помеѓу возраста на пациентот и напредната фаза на фиброза или цирозата на црниот дроб. Една студија од САД покажа дека возраста на пациентите кои биле хоспитализирани поради болсети поврзани со алкохолното заболување на црниот дроб се движела просечно помеѓу 45 и 69 години.(22,23,24)

Стареењето на човечката популација во светот, најверојатно ќе има влијание и врз прогресијата на алкохолната црноцробна болест (АЦБ).

Пол: Ризикот за развој на болести на црниот дроб поврзани со консумацијата на алкохол значително се зголемува со консумација на 7-13 пијалоци неделно за жени и 14-27 пијалоци неделно за мажи.(25)

Жените се изложени на поголем ризик за развој на цироза отколку мажите а оваа полова разлика се должи на неколку фактори како што се разликите во нивото на гастричната алкохолна дехидрогеназа (желудечната слузница кај жена има помалку алкохолна дехидрогеназа што има за последица помала оксидација на алкохолот при првото метаболизирање) (26,27), како и поголемиот процент на масти во телото на жената. (28,29)

Според студија на Bellentani и сор. соодносот мажжена кај пациенти со алкохолна цироза на црниот дроб се движи во однос 9: 1.(30)

Во една голема национална студија изведена во периодот од 1988 до 2004 во САД, во која се опфатени хоспитални пациенти испишани од болница со дијагноза на алкохолното заболување на црниот дроб, покажа дека 4,5 на 100.000 лица имале акутен алкохолен хепатитис, со сооднос мажи наспроти жени од 1,83:1, а 13,7 на 100.000 лица имале хроничен алкохолен хепатитис со цироза, со сооднос мажи наспроти жени од 2,64: 1.(31)

Нутритивен статус: Повеќето пациенти со алкохолен хепатитис покажуваат знаци на малнутриција , а ризикот од смрт е во тесна корелација со степенот на неухранетост. (32) Смртноста се приближува до 80% кај пациенти со тешка малнутриција . (33) Витаминскиот дефицит исто така, потенцијално може да ја влоши болеста.(34)

Метаболни фактори: Дебелината е предиспонирачки фактор за развој на алкохолна црнодробна болест (АЦБ). Повисок индекс на телесна маса (БМИ) е значително поврзан со зголемување на фиброзата кај пациенти со АЦБ. Инсулинската резистенција (ИР) е клучен фактор во развојот на метаболниот синдром и во голема мера е одговорен за развој на дијабетес тип 2. Постои тесна врска помеѓу АЦБ и ИР, што укажува дека метаболениот синдроми и тип 2 дијабетес се поврзани со развојот на АЦБ. (35,36)

Генетските фактори: Се прават значителни напори за да се идентификуваат генетските фактори кои придонесуваат за патогенезата на АЦБ.(37,38)

Постои повисока појава на алкохолизам кај посвоените деца на родители алкохоличари и кај монозиготните близнаци во споредба со дизиготни близнаци. Полиморфизми на гените кои го кодираат цитохром Р-450 ензим, се поврзани со почеста појава на АЦБ.(39)

Пронајдена е тесна врска помеѓу единечениот нуклеотиден полиморфизам (SNPs Single Nucleotide Polymorphism) - еден нуклеотид – А (adenine, T(thymine), C(cytosine) или G (guanine) - во геномот, се разликува помеѓу членовите на еден биолошки спациес или во пар хромозоми) во DNK (Deoxyribonucleic acid) и подложност за појава на многу болести. (40)

Податоците сугерираат дека некои од единечениот нуклеотиден полиморфизам (SNPs), освен PNPLA 3

(Enzyme Activites of Human Patatin-Related Protein - новооткриени гени кои имаат улога во кодирањето на протеини (ензими) кои имаат важна улога во регулација на метаболизмот на липидите.), може да бидат поврзан со патогенезата на АЦБ. Откриен е и близок сооднос помеѓу единечениот нуклеотиден полиморфизам SNPs (rs361525) на тумор некрозирачки фактор (aTNFA) и АЦБ. Постои повисока фреквенција на CD14-159 C / T (гени кои ги кодираат протеините кои се составен дел на вродениот имунолошки систем) кај пациенти со алкохолна цироза отколку кај оние без оваа болест .(41)

Единечениот нуклеотиден полиморфизам(SNP) е во силна корелација со содржината на масти во хепатоцитите (пациенти со GG генотип имаат 73% повеќе масти отколку оние со CC генотипот) и прогресијата на болеста (луѓе со ORs на GG vs , CC генотип, имаат за 3,25% поголема некроинфламација а кај 3,26% се развила фиброза). Имено, овие наоди биле конзистентни во сите етнички групи. Слични резултати се добиени кај пациенти со АЦБ.(42)

Неколку публикации објавени во последниве години го опишуваат вилијанието на човечките пататини (PNPLAs- Enzyme Activites of Human Patatin-Related Protein - новооткриени гени кои учествуваат во кодирањето на протеини (ензими) кои имаат важна улога во регулација на метаболизмот на липидите.) во регулација на диференцијацијата на адипоцитите, протеин за кој се смета дека игра важна улога во метаболизмот на липидите, како што е хидролизата на триацилглицеридите.(43,44,45)

Мултиваријантна анализа открила дека човечките пататини (PNPLA3) и единечениот нуклеотиден полиморфизам (SNP) се почесто се наоѓа кај пациенти со АЦБ отколку во контролната група (OR odds ratio- коефициент на сооднос изнесува 2.08) и дека единечениот нуклеотиден полиморфизам (SNP) е најсилниот независен показател за прогресијата на алкохолнната цироза на црниот дроб(OR odds ratio-коефициент на сооднос изнесува 2.08).(46)

Неинвазивни индирекни маркери на фиброза

Серумските маркери на црнодробна фиброза треба да се нудат како ефикасна алтернатива на хепаталната биопсија. Овие методи се неинвазивни, практично нема компликации, мали грешки и мали варијабилности , мерењата може да се вршат во неколку наврати, со што се овозможува динамичка контрола на фиброзата.

Идеалниот биомаркер за црнодробна фиброза треба да ги има следниве карактеристики: да биде високо сензитивен и специфичен, лесно достапен, безбеден, евтин и репродуктивен, да се користи за следење на прогресијата или регресијата на болсета и да не прикажува лажно позитивни резултати. Иако не постои единствен идеален маркер, биле откриени неколку маркери како можни корисни индикатори за фиброза, посебно кога се комбинираат едни со други. Поделени се на директни и индиректни маркери . (47)

Директен маркери на фиброза се фрагменти на црнодробниот матрикс т.е компоненти произведени од страна на црнодробните sвездести клетки за време на процесот на ремоделирање на екстрацелуларниот матрикс. Може да се користи самостојно или да се комбинираат едни со други. Најчесто користени се: Procollagen type I carboxy terminal peptide (PICP) и Procollagen type III amino-terminal peptide (PIIINP), Metalloproteinases (MMPs), ткивни инхибитори на матрикс металопротеинази (TIMPs), Transforming growth factor-β1 (TGF-β1), хијалуронска киселина, YKL-40 (chondrex), Laminin, Connective tissue growth factor (CTGF), Paraoxonase 1 (PON-1), Microfibril-associated glycoprotein 4 (MFAP-4).

Индиректни маркери на фиброза се дефинираат како молекули кои се ослободуваат во крвта како резултат на воспаление на црниот дроб , молекули кои се синтетизираат или излачуваат од црниот дроб и маркери кои се појавуваат како резултат на нарушената црнодробна функција, како што е инсулинска резистенција. (48)

Најчесто користени неинвазивни лабораториски тестови кај пациенти со АЦБ се: хијалуронска киселина, FibroTest, FibrometerA, Hepascore, Forns и APRI индекс, FIB4- комбинација на протромбин индекс (ПИ), α-2 макроглобулин и хијалуронска киселина.

Поголемиот дел од овие тестови како од приложената литература (Fibrotest, Fibrometer A и Hepascore) покажале одлична дијагностичка точност во идентификување на напредната фиброза и цироза.

Ефикасноста на тестовите е изразена со AUROC (the area under the receiver operating characteristic),а за предвидување на фиброза и цироза на црниот дроб се пресметувани: сензитивност, специфичност, позитивната предиктивна вредност (PPV) и негативна предиктивна вредност (HCB) .

HepaScore- Комбинација на возраст, пол, билирубин, γ-глутамил трансфераза, хијалуронска киселина и γ2-макроглобулин. Во студијата која обработи 512 хронични HCV пациенти, HepaScores тестот покажал добри предиктивни перформанси за значајна фиброза (AUROC со дијагностичка точност од 0,88), тешка фиброза (AUROC = 0,82), и цироза на црниот дроб (AUROC со дијагностичка точност од 0,88). HepaScore тестот може да биде автоматизиран со еден единствен анализатор.(49)

FibroMeter е комбинација на бројот на тромбоцити, протромбинскиот индекс, AST, ′2 макроглобулин, хијалуронат, серумска уреа и возраста. Добрите перформанси и применливоста на FibroMeter била потврдена кај голем број на хронични заболувања на црниот дроб, вклучувајќи хроничен вирусен хепатитис Б или Ц, алкохолни заболување на црниот дроб (АЦБ) и неалкохолен масен црн дроб (НАМЦБ). Важна карактеристика на FibroMeter е тоа што се внесува износот на црнодробна фиброза како процент од фиброзно ткиво во црниот дроб. Друга значајна карактеристика на FibroMeter е дека ги потврдува резултатите преку експертски систем кој детектира грешни резултати. FibroMeter има две главни дијагностички цели – фиброзана фаза која одговара на хистолошката, Metavir системот и вредноста на фиброза која одговара на морфометричките определби на фиброзното ткиво .(50)

FibroTest и FibroSure се идентични тестови под различни имиња во Европа и Америка за процена на фиброзата и некроинфламаторната активност. Резултатите од FibroTest се пресметуваат со математички дефинирани формули кој го пресметуваат процентот на фиброза врз основа на резултатите добиени од следниве параметри: возраст, пол, серумски хаптоглобин, α2 -макроглобулин , аполипопротеин A1, γ - glutamyltransferase и билирубин .(51)

Таа ги генерира резултатите кои се во корелација со степенот на оштетување на црниот дроб кај луѓе со различни болести на црниот дроб . Дијагностичката точност на AUROC е 0,69 и 0,91 за дијагноза на значајни фиброза (F ≥ 2) и цироза на црниот дроб кај 74 пациенти од кои 36 се со ХЦВ , 10 со ХБВ а 28 со примарната билијарна цироза.Сензитивноста и специфичноста на FibroTest во откривањето на тешка фиброза е пронајдена кај 75 % и 85 %. (52)

Постојат само неколку студии кои даваат оценка на дијагностичката и прогностичката вредности на неинвазивните биомаркери на фиброза кај пациенти со алкохолно заболување на црниот дроб.

Во студија на Naveau и сор, поголемиот дел од пациентите со алкохолно заболување на црниот дроб (93%) имале фиброза; 69,5% имале клинички значајна фиброза (F2 или повисока), 31% имале цироза, а 29% имале алкохолен хепатитис. AUROC на FibroTest за откривање на умерена до тешка фиброза (F2-F4) била повисока кај FibroTest, Fibrometer A и Hepascore, отколку кај Forns, APRI и FIB4. Постоела значајна корелација помеѓу фазите на фиброза и FibroTest (R = 0,71), FibrometerA (R = 0,72) и Hepascore (R = 0,71). Сите три тестови (Fibrotest, FibrometerA, Hepascore) покажале одлична дијагностичка точност во идентификување на напредната фиброза и цироза.(53, 54)

Во студијата на Calès и сор, 46,3% од пациентите имале фиброза, 41,1% имале цироза, а 29% имале алкохолен хепатитис. AUROC за клинички значајна фиброза (F2 или повисока) во тестот со комбинирање на протромбинско време, α-2 макроглобулин, хијалуронска киселина и возраста била повисока од онаа на FibroTest . Дијагностичката значајност на овие тестови за предвидување на клинички значајна фиброза била: 91,8% за сензитивност, 92,6% за специфичност, 96,6% за PPV и 83,3% за NPV. Преформансите на хијалуронската киселина, PIIINP и TIMP-1, е споредувана со патохистолошкиот стадиум. (55)

Во студијата на Poynard сор, минимална фиброза била присутна кај 63% од пациентите а цироза кај 31% од пациентите. Резултатите укажале дека FibroTest има највисока сензитивност за откривање на цироза, бидејќи резултатите од FibroTest кај сите циротични пациенти бил ≥ 0.3 (сензитивност и NPV = 100%).За напредната фиброза (F2-F4) резултатите од FibroTest ≥ 0,3 имле пониски чувствителност (84%) и NPV (70%). Затоа, пациентите со резултат <0.3 имале мала можност за цироза. Кога резултатот се зголемиил над 0,7, сензитивност и NPV за дијагноза на напредна фиброза и цироза се намалил, но специфичноста и PPV се зголемила. 91% од пациентите со FibroTest со резултат > 0.7 имале цироза. Постоела и значителна усогласеност помеѓу FibroTest и биопсијата со коефициент на корелација = 0,961 за Ф4 и 0,899 за Ф1. Причините за дискоординанца помеѓу FibroTest и биопсијата на црниот дроб се припишува на грешки во интерпретацијата биопсија. (56) Дијагностичката

вредност на Fibrometer A и Hepascore не се разликува од онаа на FibroTest за напредната фиброза и цироза. Немало разлика помеѓу дијагностичката точност на FibroTest и хијалуронската киселина. Овие резултати потврдија дека серумската хијалуронска киселина има добара дијагностичка вредност за дијагноза на цироза. (57)

ЗАКЛУЧОК

Потребата да се пронајде соодветен неинвазивен биомаркер за црнодробна фиброза станува еден од најголемите предизвици во хепатологија. Биохемиските биомаркери на фиброза (FibroTest, Fibrometer A и Hepascore) имаат високо ниво на дијагностичка моќ и со нив може да се направи разлика помеѓу напредна фиброза и цироза кај пациентите со алкохолна болест на црниот дроб. Постојат многу други тестови кои се уште не се широко потврдени, но остануваат ветувачки. Затоа, употребата на овие биомаркери може да се користи како скрининг, овозможувајќи на лекарот да го намали бројот на пациенти пред дефинитивно дијагностицирање на црнодробната фиброза со хепатална биопсија.

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CONGENITAL NEPHROLITIASIS WITH COMPLICATIONS, XANTHOGRANULOMATOUS PYELONEPHRITIS AND STENOSIS URETER

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ABSTRACT

Introduction: Xanthogranulomatous pyelonephritis (XGP) is a rare form of chronic pyelonephritis and represents a chronic granulomatous disease resulting in a non-functioning kidney. Radiographic features are usually specific.

Case reports: A 19-year-old patient with pain in right flank and anamnesis of renal calculus in the right kidney diagnosed when she was 2 years old. Complete medical documentation is available. Ultrasonographical it was noticed that the right kidney is bigger with signs of hydronephrosis grade IV. In the lower part, the calluses are enlarged with impaired integrity. Also, there is presence of internal echoes which points to the presence of empyem. The cortex is visibly thinner almost invisible. Two smaller calculus (4mm and 5mm) sideways and one average of 10 mm at the level of pyelourethral segment. Laboratory urinalysis and CTM recommended. Proceeded by palliative surgery: lumbar percutaneous nephrostomy and placing of J-J catheter with the suggestion for surgical solution of the stenosis.

Taking into consideration the renogram and analysing the ultrasonography with CTM it was differentiated focal xanthogranulomatous pyelonephritis stage I on the right kidney with secondary stenosis the right ureter.

Keywords: chronic pyelonephritis, nephrolithiasis,ureteral stenosis.

INTRODUCTION

Xanthogranulomatous pyelonephritis is, as the name suggests, a chronic granulomatous process believed to be the result of subacute/chronic infection, inciting a chronic but incomplete immune reaction. Various bacteria are isolated, however, the most commonly isolated species are Escherichia coli and Proteus mirabilis.

XGP is seen essentially in all age groups, but most frequently in middle - aged to elderly patients. There is a 2:1 female predilection, presumably relating to an increased incidence of urinary tract infections and thus struvite (staghorn) calculus. Clinical presentation is typically vague, consisting of constitutional symptoms such as malaise, weight loss and low-grade fever. Haematuria and flank pain are sometimes encountered. Despite often absent urinary tract symptoms, pyuria and positive urinary cultures are present in the majority of cases (95 and 60% respectively).

The kidney is eventually replaced by a mass of reactive tissue, surrounding the usually present (90%) inciting staghorn calculus with associated hydronephrosis of a greater

or lesser degree. Foamy (lipid-laden) macrophages predominate.

The inflammatory process eventually extends into the perinephric tissues and even adjacent organs.

Staging:

One method of staging is based on the degree of involvement of the adjacent tissues:

stage I: the disease is confined to the renal parenchyma only

stage II: involves renal parenchyma as well as an extension to perirenal fat

stage III: disease extends into the perirenal and pararenal spaces or diffuse retroperitoneum

Radiographic features

Two forms of the disease are recognised both macroscopically and on imaging:

a) Diffuse (90%)

b) Focal / tumefactive form (10%):

- Sometimes a truly focal process in a normal kidney

- In other instances, this represents diffuse XGP of one moiety of a duplex system

CASE REPORT

A 19 year old patient with pain in right flank and anamnesis of renal calculus in the right kidney diagnosed when she was 2 years old. Complete medical documentation is available. Ultrasonographic, right kidney is bigger with signs of hydronephrosis grade IV. In the lower part, the calluses are enlarged with impaired integrity. Also, there is presence of internal echoes which points to the presence of empyem. The cortex is visibly thinner almost invisible. Two smaller calculus (4mm and 5mm) sideways and one average of 10 mm at the level of pyelourethral segment. Laboratory and CTM recommended. Proceeded by palliative surgery: lumbar percutaneous nephrostomy and placing of J-J catheter with the suggestion for surgical solution of the stenosis.

Figure 1a - (longitudinal ultrasonography of the right kidney, empyema lower part); 1b – (longitudinal ultrasonography of the right kidney, hydronephrosis. grade IV); 2 - (longitudinal ultrasonography of the right kidney, calculus).

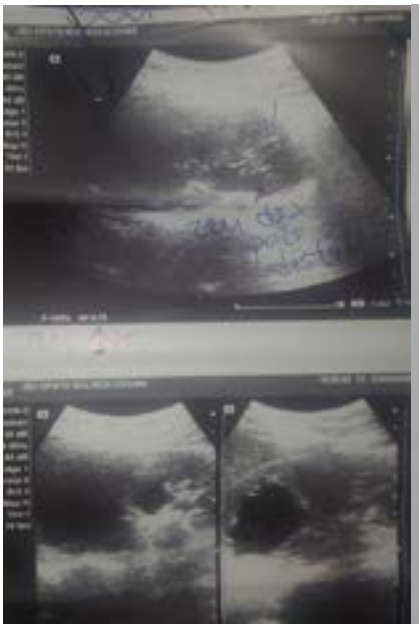

Fig. 1(a, b) ;

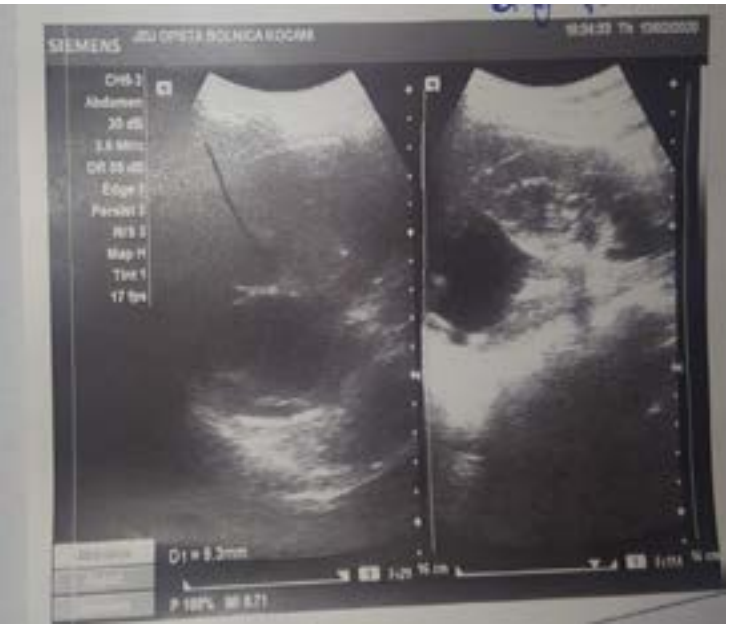

Fig. 2

DISCUSSION

Renogram analysis made in childhood indicated reduction in the excretion in the right kidney. After the application of diuretic, the curves of the two kidneys were equalized which points to the existence of functional (dilatation, hypotonic) obstruction and the mechanical obstruction (obstructive uropathy) was excluded.

Figure 2 a (before application of diuretic) ; 2 b (after application of diuretic).

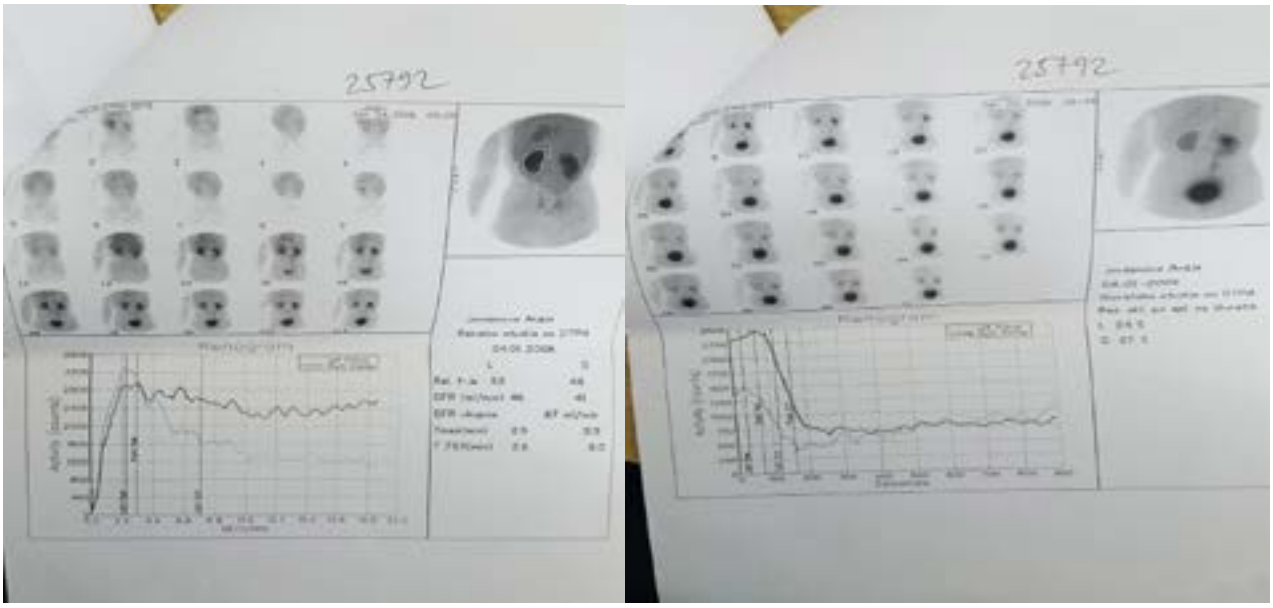

Fig. 2a, 2b.

The ultrasonography together with the CTM give us the whole picture of the case. Ultrasonographically: enlarged right kidney with stagnant changes and deformation of the calluses of the lower group as well as presence of empyema in distant part of the canal system of the kidney. In the arterial phase of the CTM there is early stage imbibition of the parenchyma of both kidneys with clear distinction and border -cortex - renal capsule - perirenal and pararenal lodge. It has to be pointed out that in the lower part of the kidney the cortex is almost inexistent at one segment but there is a clear border capsule - perirenal area. In the late phase of CTM, a bigger accumulation of contrast in the canal system (calluses and pyelon) is concluded, without visible overflow of the contrast perirenal and pararenal (especially in the lower part of the kidney) and with excretion of contrast in both ureters .

Figure 3a (-arterial phase) 3b, 3c (-late phase).

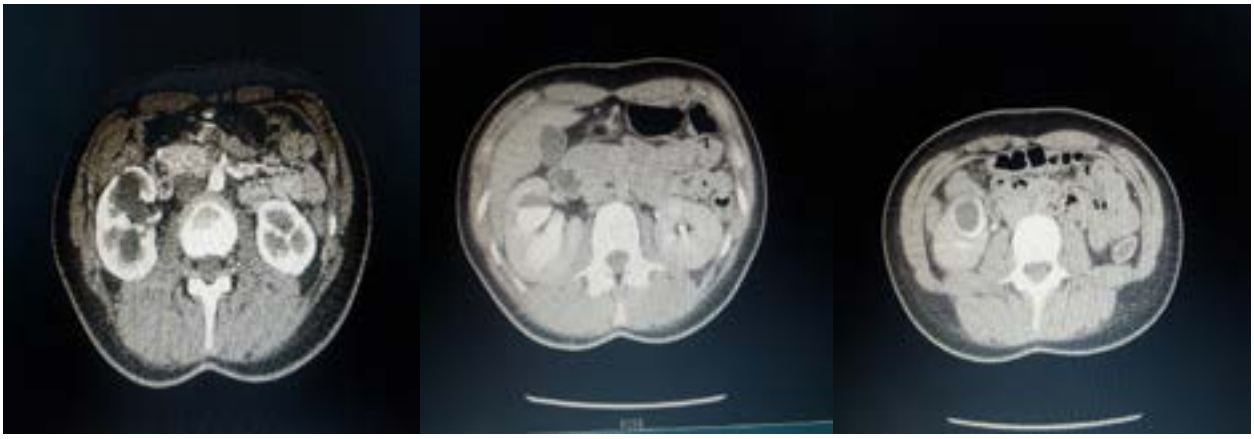

Fig. 3a, 3b, 3c.

CONCLUSION

From all of the above, we can conclude and differentiate focal xanthogranulomatous pyelonephritis of the right kidney, stadium I with secondary created stenosis (stricture) of the right ureter .

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DILEMMAS IN THE DIAGNOSIS OF DORSALLY SEQUESTERED DISC IN THE THORACIC SPINE AS A RARE CONDITION

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ABSTRACT

Posterior migration of sequestered disc of thoracic spine is an extremely rare case and can mimics spinal lesions like tumor, abcess, disc space infection or another space-occupying lesions. Our case is about 54 years old patient, female, who was admitted to the Neurosurgery Clinic due to severe paraparesis of the lower extremities with preserved sensitivity. MRI was very effective for the diagnosis of this rare pathological condition. Peripheral rim enhancement around the nonenhancing disc fragment is typical appearance on contrast MRI for disc fragment. Using the DWI sequence, we showed that there is no restriction of diffusion, which once again confirmed that it is not about an inflammation, not a tumor lesion. So, MRI as a diagnostic procedure offers opportunities to eliminate dilemmas regarding diagnosis in one fell swoop, which is necessary for the timely resolution of the patient's condition.

Key words: sequestered disc, thoracic spine, MRI, DWI sequence

INTRODUCTION

Posterior migration of sequestered disc of thoracic spine is an extremely rare case and can mimics spinal lesions like tumor, abcess, disc space infection or another space-occupying lesions.Disc sequestration is the migration of a herniated disc fragment into the epidural space. The fragment is completely separated from the parent disk. (1) Imaging modality for the diagnosis of sequestered disc, or the gold standard is MRI, which is recommended as a diagnostic method in all diseases of the spine. (2)

AIM

The aim of this case study is to present a rare case of thoracic spine disc sequestration, for which only a few cases have been reported in the literature so far.

Disc sequestration is more common in the lumbar spine, while intervertebral disc sequestration in the thoracic spine is extremely rare (3) These levels of disc herniation are 0. 25 – 0.75%.(4) They occur most commonly at the Th11-Th12 level, but can occur from Th8 to Th12 levels. (5) This is due to the biomechanics of the thoracic spine and its endurance in the lower segment. The clinical presentation is variable depending on the level at which sequestration occurred pain, sensory and/or motor deficits in one or both legs, paraparesis, paraplegia (6)

CASE DESCRIPTION

Our case is 54 years old patient, female, who was admitted to the Neurosurgery Clinic due to severe paraparesis of the lower extremities with preserved sensitivity. An MRI of the thoracolumbar spine was performed from Th8 - 10, whered an oval longitudinal lesion was noted with a diameter of about 3 cm in the longitudinal direction and about 1 cm in the transverse direction. With the largest diameter, transversely was localized at the level Th9, extramedullary, in the spinal canal posterolaterally to the left. Adjacent discs at the levels of Th8-9 and Th9-10 are significantly degenerated with the presence of significant disc herniation, dorsocentral bilateral, acceptuated to the right at the level of Th9-10. There was a discrete bone oedema of the Th9 corpus and the medulla itself at the level of T9 was significantly compressed with compression edema. Discrete staining of the foramen at the level of Th9-10 on the left was also followed. Additional sequences were made with DWI where no restriction of diffusion was noted, so the changes did not support an abscess. Laminectomy was performed ad the level T8-9. Pathohistological examination was degeneratio fibrohyaloidea of the disc

DISCUSSION

As written started at the beginning, disc sequestration is essentially the completely separate of the disc fragment and its migration in the epidural space. It is usually associated with trauma. (7) In our case, the pacient had no history of trauma. She had paraparesis, but the sensitivity was preserved. MRI was very effective for the diagnosis of this rare pathological condition. Atypical sequestrated disc herniations we usually seen as heterogeneously hypointense to isointense on T1- weighted sequences and hypointense or hyperintense on T2-weighted MR images. Location of sequestar may be intra or extradural. (8) In our case, the location of sequestrated disc was extramedullary, in the spinal canal, posterolaterally to the left. Because of the differential diagnosis, which include neoplastic lesion, we use contrast medium with whom we differentiate sequestrated herniated disc from tumors and other epidural lesions. Herniated disc fragment rarely may include central enhancement, attributed to vascular granulation tissue infiltrating the fragment, but is never associated with enhancement of the spinal meninges, early landmark finding in neoplastic lesions such as lymphoma, neurofibroma, neuroblastoma, mesothelioma etc.(9) Gadolinium is also useful to differentiate a herniated disc from a disc space infection, abscess. Peripheral rim enhancement around the nonenhancing disc fragment is typical appearance on contrast MRI for disc fragment . Using the DWI sequence, we showed that there is no restriction of diffusion, which once again confirmed that it is not about an inflammation, not a tumor lesion.

Malignancies typically show homogeneous or heterogeneous uptake, and rarely ring enhancement. Chondrosarcomas may show moderate peripheral enhancement, but have lobulate architecture, differing from the disc fragment. Metastases commonly affect the adjacent bones and have a wide variety of signals. Nerve sheath tumors are isointense on T1W and hyperintense on T2W, with enhancement after contrast infusion, resembling the sequestered fragment, however, are primarily intra-dural,situation that occurs very rarely in disc herniations.(10) Extradural hematomas may also provide contrast enhancement, but have trauma history associated.

CONCLUSION

Low incidence and absence of characteristic clinical and radiological features make diagnosis of posteriorly sequestered thoracic disc migration is very rare, that's why is very interesting. MRI is the most important imaging technique for diagnosing and timely surgical treatment of this condition, which offers possibilities for solving the dilemma, imposed by the differential diagnosis. MRI as a diagnostic procedure offers opportunities to eliminate dilemmas regarding diagnosis in one fell swoop, which is necessary for the timely resolution of the patient's condition.

Figure 1. Thoracic disc herniation, an oval longitudinal lesion, isointense on T1- weighted sequences (Fig.1(a) Sagital T1) and hypointense on T2-weighted MR images (Fig.1(b) Sagital T2). Peripheral rim enhancement around the nonenhancing disc fragment (Fig.1(c) Axial T1 C+)

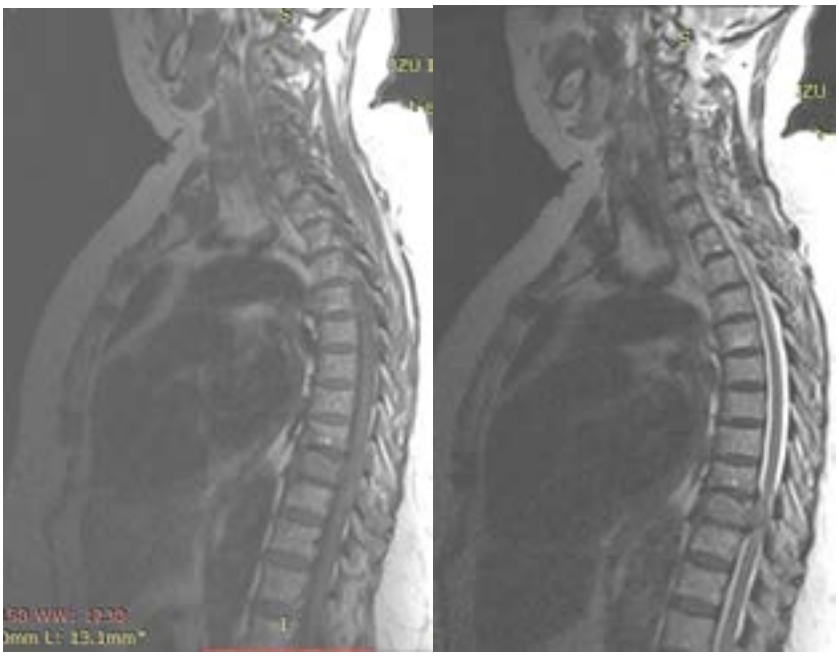

Fig. 1 (a,b)

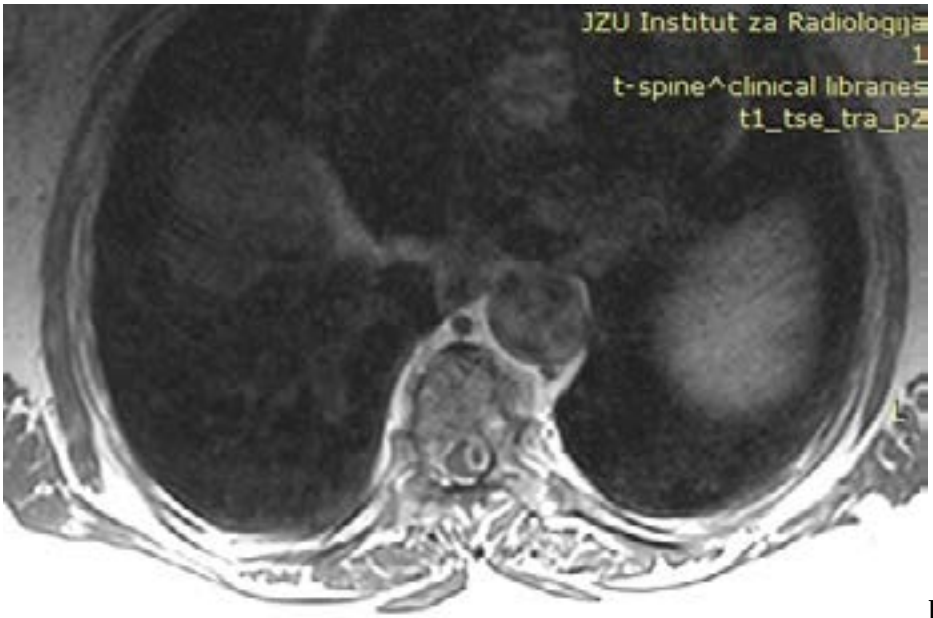

Fig.1 (c)

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CASE OF OVARIAN ENDOSALPINGIOSIS AS A RARE ENTITY

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INTRODUCTION

Endosalpingiosis is the presence of ectopic, cystic glands outside the fallopian tube that are lined with fallopian tube-type ciliated epithelium(1). Endosalpingiosis may occur in pelvic organs, including ovaries, fallopian tube serosa, uterine serosa, myometrium, or pelvic peritoneum. It may also occur in the bladder or in a retroperitoneal or axillary lymph node (2). Endosalpingiosis is not well-studied, and the clinical features remain uncertain. It has been reported to be associated with pelvic pain, infertility, pelvic mass, and/or urinary symptoms(3-6). However, the diagnosis is made only after surgical biopsy. A key challenge regarding this condition is to differentiate it clinically from endometriosis. Another notable feature of endosalpingiosis is its histologic relationship to pelvic serous neoplasms (eg, lesions of low malignant potential, low-grade pelvic serous carcinoma).

However, the role of endosalpingiosis as a risk factor or as part of the pathogenesis of these conditions is unknown (7).

HISTOPATHOLOGY AND PATHOGENESIS

Endosalpingiosis is the presence at ectopic sites of ciliated cells, secretory cells, and intercalated cells similar to those seen in the normal fallopian tube epithelium(8). Endosalpingiosis lesions and normal fallopian tube epithelium express similar biomarkers (8). As noted above, endosalpingiosis may occur in female reproductive organs, including ovaries, fallopian tube serosa, uterine serosa, myometrium, or pelvic peritoneum. Similar to endometriosis, endosalpingiosis is thought to arise in ectopic locations either through metaplasia or ectopic transport. In addition, transplantation of ciliated fallopian tube cells to peritoneal surfaces may occur as a result of surgical intervention on the tubes or ovary (5) . Endosalpingiosis differs from endometriosis in that it has ciliated glandular elements and no endometrial stroma. Small vesicles of endometriosis and endosalpingiosis can have a similar surgical appearance, presenting as small vesicular cystic lesions that are clear, white, or tan in color (9).

PRESENTATION OF THE CASE

We describe a case of a 54 years old woman which was hospitalized in our Clinic with pelvic pain in the right side and a vaginal bleeding for 9 days. The personal history included menarche at 14 years old, finished reproduction, two births with Cesarean Section, and a menopause two years ago. After the admission we did to the patient all the laboratory and clinical researches. The tumor markers and the full blood test were in referent values. Also the

hormonal status (estradiol and FSH) were in referent values for the patient which as we sad was in menopause for 2 years. Transvaginal ultrasound 2D and color Doppler revealed cystic adnexal mass with 44mm on the right side. There was no fluid in the Douglas pouch, also the uterus and the left ovary were in normal references. Third Laparotomy with transversal Pfanennstiel section was indicated, total hysterectomy with bilateral adnexectomy was performed. Intraoperative there were many adhesions from the two Cesarean sections, that's why an adhesiolysis was performed. Also was taken an abdominal fluid for cytologic examnation, biopsy of the parietal peritoneum and the big omentum. Patient recovery was quick after the surgery. Hystopathological examination of the Operative material revealed Endosalpingiosis of the bilateral ovaries. And the cytopatological examination was from the I-st Classification Group.

DISCUSSION

Endosalpingiosis first was described by Sampson in 1930; he found epithelium resembling the fallopian tube in ectopic locations in women who had undergone previous salpingectomies or tubal sterilization. Endosalpingiosis can present with chronic pelvic pain, dysmenorrhea, menorrhagia, and infertility or can be asymptomatic. A retrospective studies showed that no significant association was found between endosalpingiosis and chronic pelvic pain, neither between endosalpingiosis and infertility, as against endometriosis, which is proven to be associated with these presentation (10). Some retrospective studies say that the rate of previous gynecologic and abdominal surgery and a history of tubal disease was documented in most of the patients with endosalpingiosis, which raises the possibility that peritoneal implantation may be a factor in the etiology of endosalpingiosis. The patient in our study also had previous 2 cesarean sections before this surgery. Also the hormone dependence theory of endosalpingiosis should be re-evaluated, because most of the patients with endosalpingiosis in all retrospective studies were postmenopausal. Also our patient is in posmenopausa for two years(11). Gross appearance of endosalpingiosis may mimic a primary peritoneal tumor or papillary carcinoma of ovary, but the absence of mitotic activity or atypia on histopathology contradicts the diagnosis of carcinoma. Endosalpingiosis is mostly asymptomatic. Asymptomatic endosalpingiosis does not require any treatment. It may become symptomatic by mechanical irritation of abdominal organs. Surgical removal of the cystic structures may effectively abolish the symptoms(12).

CONCLUSION

Endosalpingiosis is a rare benign entity, masquerading peritoneal or ovarian malignancy. Endosalpingiosis has been associated with pelvic pain, infertility, and urinary symptoms. It is not clear if endosalpingiosis causes these symptoms or is an incidental histologic finding in women with these symptoms. Rarely, endosalpingiosis presents as a cystic pelvic mass. Endosalpingiosis is never a preoperative diagnosis. It is a histologic diagnosis based upon tissue biopsies obtained during surgery for pelvic pain, infertility, or the evaluation of a pelvic cystic lesion identified on an imaging study. The differential diagnosis of endosalpingiosis includes primarily endometriosis, but also other conditions associated with pelvic pain, infertility, urinary symptoms, or pelvic mass. This includes vesicles or tumor-like lesions of the peritoneum including endometriosis, peritoneal inclusion cysts, peritoneal borderline serous tumors, and low-grade serous ovarian tumors. In spite of the benign nature, the patients need to be kept on follow-up because of significant association between endosalpingiosis and gynecological malignancies, specially the premenopausal patients.

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SEZARY SYNDROM-CASE REPORT

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ABSTRACT

Sezary syndrome is a leukemic variant of pimary CTCL (cutaneous T cell lymphoma) manifested with clinical triade consisting of erythroderma, peripheral lymphadenopathy and atypical mononuclear cells(Sezary cells).[8]

We present a case of 45 years old female, with non-specific primary skin lesions which fastly progressed in erythrodermia. Skin biopsy, immunohistochemical investigations, biopsy from bone marrow and detectable Sezary cells>5% in periphery blood were inclusive for cutaneous limphoproliferative disease(Sezary syndrome). Lymph node punction showed atypical lymphocytes. RTG pulmo and ultrasound of abdomen without abnormalities. CHOP therapy was started.

We present a case with Sezary syndrome, clinically classified T4N2M0(stage IV A).

Keywords: primary cutaneous T cell lymphomas, Sezary syndrome, Sezary cells, CHOP therapy

INTRODUCTION

Se´zary syndrome (SS) was named after the French dermatologist, Albert Se´zary, who first described a patient with generalized erythroderma with monster cells (or now known as Se´zary/Lutzner cells) in the skin and blood in 1938. The term 'Se´zary' was first linked to the clinical presentation of SS in 1953 [1]. SS is a rare leukemic variant of cutaneous T-cell lymphomas (CTCLs) and comprises 3 -- 10% of CTCLs [2,3]. Historically, SS was defined as generalized erythroderma, lymphadenopathy and > 20% of atypical T-cells in the peripheral blood [4]. Patients with SS usually present with erythroderma, recently more specifically defined as confluent pink or red skin with or without scaling, involving at least 80% of the body surface area.With the advent of multicolor flow cytometry, it is now possible to quantitate SS cells more specifically using antibodies allowing the differentiation between erythrodermic mycosis fungoides (MF) and SS [5]. SS is defined as B2 blood involvement, which is defined as presence of a dominant T-cell clone plus one of the following: an absolute Se´zary cell count of 1000 cells/mm3 or higher, expanded CD3+ or CD4+ cells with a CD4/CD8 ratio of 10 or higher, or expanded CD4+ T cells with abnormal immunophenotype including loss of CD7 or CD26 [5,6]. A dominant T-cell clone is identified via polymerase chain reaction or Southern blotting, which would show a dominant T-cell receptor gene rearrangement in the blood [6]. The tumor-node-

mestasis-blood staging system is used for both MF and SS with staging depending on skin stage, tumor, lymph nodes, blood involvement and visceral disease. In 2018, an updated version of World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) consensus classification was published and the staging system was revised. SS is staged as IVA based on the revised staging guidelines in 2018 [7].

Therapy in SS should be based on stage of disease. The current consensus is that patients with early stage disease should receive skin directed therapies (topical chemotherapy - nitrogen mustard(mechlorethamine), carmustine (BCNU), Targretin(bexaroten), PUVA (photochemotherapy), radiotherapy and total body electron beam therapy). Systemic therapies (Immunotherapy, retinoids-Bexaroten, chemotherapy-CHOP, extracorporeal photopheresis, toxin therapy-Denileukin diftitox, fully humanized anti-CD4 antibody (Zanolimumab), histone deacetylase (HDAC) inhibitors) are reserved for those with early stage disease resistant to skin directed therapy or advanced disease. [9-14]

CASE PRESENTATION

We present a case of 45 years old female, dentist asistent, without anything special in personal and family history. She doesn't take any suspect medicaments, supplements and herbal products.

The problem appeared like pruritic erythema on photoexposed skin. She was treated from family dermatologist as photodermatosis. Dermatological examination showed diffuse erythema with 80% BSA (body surface area); and small area of healthy skin on the back (fig.1) and flexures (fig.2).

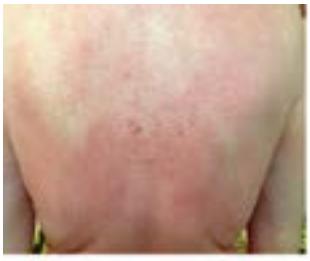

Fig.1

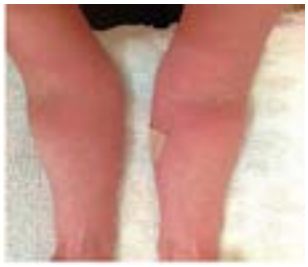

Fig.2

There were grouped small papules with lichenoid aspect on the trunk and face (fig.3). On the thigh papules were distributed follicular(fig.4). There was discreet pitiriasiform descvamation on some parts of the trunk and edema on the calf. Face, mucosa, nails and capilitium were not affected. There wasn't any sign of deffluvium also.

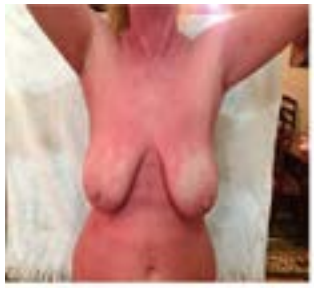

Fig.3

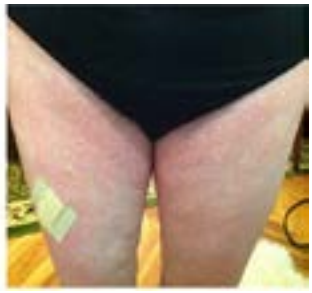

Fig.4

On admission there were no signs for organomegal only enlarged bilateral supraclavicular lymph nodes, mobile and without pain.

Clinical diagnosis: erythrodermic Lichen Ruber Planus and Pityriasis rubra pilaris.

Table 1 shows laboratory concessions, other parameters were in normal ranges

Table 1. Laboratory results (September) and last one before chemotherapy (December):

	September	December
Le $10^3/mm^3$	$8x10^3/mm^3$	$13,1 \times 10^3/mm^3$
Ly $x10^3/mm^3$	$3,1x10^3/mm^3$	$7,4x10^3/mm^3$
Cholesterol mmol/l	6,68mmol/l	6,19mmol/l
LDH U/L	203 U/L	288U/L

Skin biopsy was made from two specific skin changes (first from the calf- infiltrative erythema and second from forearm - lichenoid papule). Histological findings showed chronic inflammation(inclusive for erythrodermia and exclusive for lichen), because of the type and distribution of mononuclear infiltrate, absence of epidermotropisam, cutaneous limphoproliferative disease was suspected. Next step was imunohistochemistry made on Institute of pathology in Skopje and the results were: predomination of cell infiltrate with CD3(+), CD4(+), CD8(+), CD5(+), CD20 (-), CD30 (+), CD68(-), CD57(-). Biopsy from bone marrow made on University Clinic of chematology with non-specific signs, but in the periphery blood there were detectable Sezary cells >5%. Lymph node punction showed atypical lymphocytes. RTG pulmo and ultrasound of abdomen without abnormalities. CHOP therapy (Cyclophosphamide, Hydroxydaunorubicin or adriamycin,

Oncovin-vincristine, Prednisone or prednisolone), was started in decembar. Until today there were conducted 5 therapy cycles with reduction of pruritus and regression of skin lesions. Adverse effects from chemotherapy nausea and vomitus.

DISCUSSION

The early lesions of CTCL mimic psoriasis, chronic eczema, atopic dermatitis, lichenoid pityriasis, pityriasis rubra pilaris. The differential diagnosis of SS includes other causes of erythroderma and non-SS leukemias with cutaneous involvement. Because the clinical features of erythroderma are often invariable regardless of cause and because the histopathology may not be specific, history and evaluation of the blood are often necessary to distinguish SS from the conditions discussed below.

In our case differential diagnosis were erythrodermic Lichen Ruber Planus and Pityriasis Rubra Pilaris. Classical adult onset Pityriasis Rubra Pilaris (PRP) is an uncommon cause of erythroderma; PRP may reveal palmoplantar keratoderma identical to SS but may be distinguished by history of preceding localized involvement and cephalocaudal progression.

Erythrodermic form of lichen ruber planus is very rare and in that cases there is always involvement of mucosa (oral or genital), which wasn't in our case.

Histology and immunohistochemistry were significant for diagnosis. Detectable Sezary cells>5% in periphery blood were of great value for making definitive diagnosis. According to staging guidelines made from ISCL and EORTC our patient was in stage IVA(T4N2M0). The current consensus for therapy based on staging proposed first line therapy for cases like that is chemotherapy and electron beam therapy. CHOP therapy was started and gives good results, with minor adverse effects.

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ПАРАЛИТИЧЕН СТРАБИЗАМ – АФЕКЦИЈА НА N.ABDUCENS (VI)

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АПСТРАКТ

Вовед: Паралитичен страбизам е вид на неконкомитантна кривогледност која настанува како резултат на пареза или парализа на еден или повеќе екстраокуларни мускули.Резултат е на афекција на три околумоторни нерви (n.oculomotorius (III), n.trochlearis(IV), n.abducens(VI).

Во трудот прикажуваме жена на 65 годишна возраст со паралитичен страбизам со афекција на n.abducens, која се жали на кривење на десно око кон внатре, ограничено движење на булбусот кон надвор,појава на дупли слики и намалена видна острина.

Цел на трудот е преку приказ на случај да се презентира дека 45% припаѓа на афекција на овој нерв и да се потенцираат современите модалитети на третман.

Заклучок: Лекувањето на паралитичниот страбизам е долготраен процес, кој првенствено опфаќа симптоматска и каузална терапија, аплицирање на фолија призма во тек на 6 месеци, па потоа хируршки третман. Во однос на хемоденервација со ботулински токсин В во третман на страбизам се состои од ретроспективни студии, кохортни студии или прегледи на случаи. Овие даваат корисни информации, но потребно е појаснување за ефективната употреба на ботулински токсин како независен модалитет на третман. При повеќе рандомизирани контролни испитувања се покажале различни резултати почнувајќи од недостаток како профилактички третман при акутна парализа на n.abducens, до слаб одговор, и кај пациенти кои побарале повторен третман. Стапката на компликации во овие студии се движела од 24% до 55%.

Клучни зборови: паралитичен страбизам, диплопии, n.abducens, фолија призма, ботулински токсин В.

ВОВЕД

Страбизмот за прв пат се појавува во списите на Хипократ (460-377 п.н.е.), и прв ја истакнал наследната компонента на страбизмот.(1). Паралитичен страбизам е вид на неконкомитатна кривогледност која настанува како резултат на пареза или парализа на еден или повеќе екстраокуларни мускули. Постојат 6 екстраокуларни мускули, 4-ри прави и 2 коси мускули. Овие мускули се инервирани од три околумоторни нерви (N.ocolumotorius III, N trochlearis IV, N abducens VI). Афекција на овие нерви поединечно или во комбинација доведува до пареза или парализа на екстраокуларните мускули. Парализа на n.ocolumotorius и n.trochlearis повеќе е застапена во детската популација а парализа на n.abducens кај возрасна популација.(2), (3), (4), (8).

Етиологијата може да биде неврогена, миогена, и како резултат на афекција на невромускулен спој. Главни причини кои може да доведат до афекција на овие нерви се васкуларни болести (diabetes mellitus,покачен крвен притисок, атеросклероза), инфламаторни лезии (енцефалит, менингит), неопластични лезии (тумори на мозок), трауматски лезии (повреди на главата), демиенилизирачки лезии (Sclerosis multiplex), невромускулни лезии (Myastenia gravis).(3), (4).

30% од паралитичен страбизам е резултат на афекција на n.ocolumotorius, 11% е резултат на афекција на n.trochlearis, 45% е резултат на афекција на n.abducens воедно и најчеста афекција на овој нерв во општата популација.(1)

Во зависност кој нерв е афектиран се појавуваат

соодветни знаци и симптоми од страна на афектираниот нерв (примарна девијација на афектираното око, рестрикција на окуларен мотилитет, компензаторна положба на главата, намалена видна острина доколку окото не може да фиксира, појава на дупли слики).

Дијагнозата се заснова врз основа на анамнеза, клинички испитувања,имицинг техники.(4), (5).

ПРИКАЗ НА СЛУЧАЈ

Жена,пензионерка на 65 годишна возраст препратена од Универзитетска клиника за Неврологија –Скопје при Универзитетска клиника за Очни болести –Скопје поради кривење на десно око кон внатре, ограничено движење на очниот булбус кон надвор, појава на дупли слики,намалена видна острина, изгубен стереоскопски вид (перцепција на длабочина), поставена работна дијагноза пареза на n.abducens со појава на диплопии. (1).

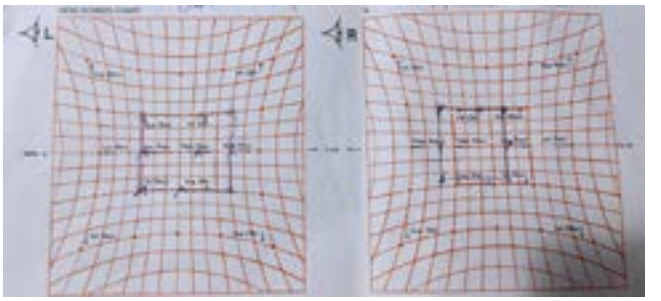
По комплетниот офталмолошки преглед и извршените имицинг иследувања МРИ (наод на васкуларопатски промени лево вентрално од преден рог на лева лателарна комора) како и во корелација со системските заболувања се постави дијагноза паралитичен страбизам со афекција на n.abducens.

На клиничкиот преглед се потврди дека пациенткта има видна острина намалена на десно око VOD:0.6 с.с., на лево око VOS:0.9 с.с.,кривење на десно око кон внатре, ограничен мотилитет кон надвор (дефицит на абдукција), појава на хоризонтални дупли слики, абнормална позиција на главата (главата е свртена кон афектирана страна – појава на torticolis), отсутен стереоскопски вид.(1), (3).

Се доби податок за лична позитивна анамнеза за Diabetes mellitus тип II на таблетарна и инсулинска терапија, покачен артериски крвен притисок соодветно регулиран со антихипертензивна терапија, hypertrigliceridemija соодветно регулирана со терапија. Исто така се доби позитивна лична анамнеза за покачен крвен притисок 220/100mmHg и покачена гликемија 15mmol/L една недела пред појава на дуплите слики и кривењето на десно око.

Од направениот офталмолошки преглед се заклучи дека има ограничен мотилитет кон надвор бидејќи парализа на m.rectus lat. кој е инервиран од n. abducens предизвикува доминација на неговиот антагонист m.rectus med, компензаторна положба на главата, намалена видна острина, изгубен стереоскопски вид, појава на дупли слики, и направен Hess-ов тест.

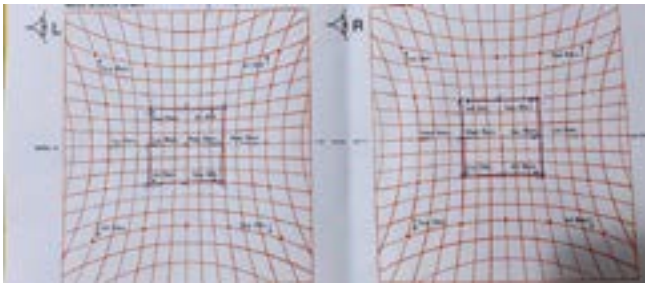
По направениот Hess-ов тест Сл.1. се дијагностицира намалена десна шема и проширена лева шема, десна шема покажува значајно намалена активност на m.rectus lateralis и благо зголемена акција на m.rectus medialis, лева шема покажува зголемена акција на m. rectus medialis.(1).



Сл.1. HESS – ов тест покажува намалена десна шема и проширена лева шема, десна шема покажува значајно намалена активност на m.rectus lateralis и благо зголемена акција на m.rectus medialis, лева шема покажува зголемена акција на m.rectus medialis

Лекувањето е каузално вклучувајќи симптоматска терапија, витамини од групата B, вазодилататори,третман на диплопија (со оклузивни лепенки или призма),и како крајна цел хируршки третман.(3), (5), (7).

После 6 месечна терапија со призма се направи повторно Hess-ов тест Сл.2. каде се дијагностицира нормален наод, подобрување на видната острина Vod:0.9 с.с, Vos:0.9 с.с., нормална положба на главата, исчезнување на хоризонталните дупли слики, нормален окуларен мотилитет и ортофорија.



Сл.2. HESS – ов тест (После 6 месечна терапија со фолија призма на десно око овој тест оди во прилог на нормален наод)

ДИСКУСИЈА

Страбизам или разрокост е неправилна положба на очите.Постојат девет дијагностички положби на погледот, тоа се шест главни положби, примарна положба, елевација и депресија.(1).

Паралитичен страбизам е вид на неконкомитатна кривогледност која настанува како резултат на пареза или парализа на еден или повеќе екстраокуларни мускули.Постојат 6 екстраокуларни мускули, 4-ри прави и 2 коси мускули. Овие мускули се инервирани од три околумоторни нерви (N.ocolumotorius III, N trochlearis IV, N abducens VI). Афекција на овие нерви поединечно или во комбинација доведува до пареза или парализа на екстраокуларните мускули. Паралитичниот страбизам почест е кај возрасната популација 44%, за разлика од детската популација 7%. (8). Постојат одредени карактеристики кои го карактеризираат паралитичниот страбизам од непаралитичниот страбизам (3), кои овозможуваат подобра и навремена дијагноза и лекување.(Табела бр.1)

КАРАКТЕРИСТИКИ	ПАРАЛИТИЧЕН СТРАБИЗАМ	НЕ-ПАРАЛИТИЧЕН СТРАБИЗАМ
Почеток	Наеднаш	Бавно
Диплопии	Присутни	Отсутни
Окуларни движења	Ограничени	Целосни
Положба на главата	Ограничено	Нормална
Наузеа и вртоглавица	Присутна	Отсутна
Секундарна девијација	Поголема од примарната	Еднаква на примарната
Во постари случаеви патолошки секвели во мускули	Присутни	Отсутни

Табела бр.1.Разлика помеѓу паралитичен и не-паралитичен страбизам

Главни причини кои може да доведат до афекција на овие нерви се васкуларни болести (diabetes mellitus,покачен крвен притисок, атеросклероза), инфламаторни лезии (енцефалит, менингит), неопластични лезии (тумори на мозок), трауматски лезии (повреди на главата), демиенилизирачки лезии (Sclerosis multiplex), невромускулни лезии (Myastenia gravis). (3), (4). Најголем процент од паралитичен страбизам 45% припаѓа на афекција на n.abducens (VI), како во нашиот случај.Овој нерв го инервира внатрешниот прав мускул и негова функција е абдукција.Кога овој мускул е афектиран се намалува неговата функција и се зголемува функцијата на неговит антагонист m.rectus medialis. (1).

Во зависност кој нерв е афектиран се појавуваат соодветни знаци и симптоми од страна на афектираниот нерв и мускул. Во нашиот случај поради афекција на n.abducens се појави кривење на десно око кон внатре, ограничено движење на очниот булбус кон надвор, појава на дупли слики, намалена видна острина, изгубен стереоскопски вид (перцепција на длабочина).(1), (2), (3), (4),(7).

Дијагнозата се поставува врз основа на анамнеза, клинички карактеристики, клинички испитувања (тест на покривање - Cover-тест, тест на откривање - Uncover-тест, алтернирачки Cover-тест, призма Cover-тест кој прецизно го мери аголот на девијација, испитување на мотилитет, испитување на диплопии), и имицинг техники.(1).

Лекувањето е каузално, бидејќи често причината останува непозната, се употребуваат витамини од групата В, вазодилататори, термо и електротерапија. Во тек на 6 месеци доаѓа до реверзибилност на оштетениот мускул. Диплопиите се третираат со оклузивни лепенки или фолија призма која дава најдобри резултати.Хируршките интервенции при парализа на шестиот кранијален нерв треба да се разгледаат само доколку е јасно дека нема да дојде до подобрување од претходните третмани.Тоа е после 6 месеци. Хируршко лекување носи ризик од постоперативен развој на исхемија на преден сегмент на окото, но за да се избегне оваа компликација ретропозицијата на надворешниот прав мускул може да се замени со хемоденервација со ботулински токсин В, (1), (6), меѓутоа потребно е да се процени ризикот од постоперативни диплопии, што во најдобар случај се решаваат со ставање на корективна призма.

ЗАКЛУЧОК

Лекувањето на паралитичниот страбизам е долготраен процес, кој првенствено опфаќа симптоматска и каузална терапија, аплицирање на фолија призма во тек на 6 месеци, па потоа хируршки третман. Во однос на хемоденервација со ботулински токсин В во третман на страбизам се состои од ретроспективни студии, кохортни студии или прегледи на случаи.(1),(6). Овие даваат корисни информации, но потребно е појаснување за ефективната употреба на ботулински токсин како независен модалитет на третман. При повеќе рандомизирани контролни испитувања

се покажале различни резултати почнувајќи од недостаток како профилактички третман при акутна парализа на n.abducens, до слаб одговор, и кај пациенти кои побарале повторен третман. Стапката на компликации во овие студии се движела од 24% до 55%.(1),(6).

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CANDIDA INTERTRIGO IN A PATIENT ON ICU POSITIVE TO COVID19

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ABSTRACT

Intretigo is a common dermatological manifestation caused by occlusive conditions in skin folds increasing local heat and moisture and skin-on-skin friction. We present a 58-year-old woman with intertrigo hospitalized in Intensive Care Unit (ICU) due to severe COVID-19 infection. Intertrigo was localized on large areas on the body, mostly genitocrural area, axillary area and sub-mammary folds, but also on the trunk, arms and legs. During COVID-19 treatment mechanical ventilation was applied; nasogastric tube was placed and the patient was treated with intensive COVID-19 therapy. Intravenous Fluconasole 200 mg helped improving the skin condition. While most of intertigo is benign disease and it is not difficult to treat it is important to be aware of the dermatologic manifestations and complications during COVID- 19 patients and properly treat complications.

Keywords: COVID-19, Intertrigo, Pneumonia, SARS-CoV-2, Skin

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the underlying cause of the novel coronavirus disease of 2019 (COVID-19), which has resulted in over 3.8 million infected patients worldwide [4]. Literature has described involvement of other organ systems, including the cardiovascular, gastrointestinal, renal, and neurologic systems. Recently, there has been increasing recognition of the dermatologic complications of COVID-19. [5] Intertrigo is a superficial inflammatory skin condition of the skin's flexural surfaces, prompted or irritated by warm temperatures, friction, moisture, maceration, and poor ventilation [1]. It is believed that this condition is more common in obese people and patients with diabetes mellitus [2]. Intertrigo commonly becomes secondarily infected, notably with Candida; however, other viral or bacterial etiologies may play a factor in its pathogenesis [1]. Intertrigo is found primarily in the sub-mammary, inguinal, abdominal and perianal skin folds. [3]. The increased likelihood of a naive or reduced immune system, lack of mobility, and urinary/bowel incontinence contribute to the skin manifestations like redness in mirror format and moist skin, followed by sensations of itching, burning, pain and odor . [3, 4]

CASE PRESENTATION

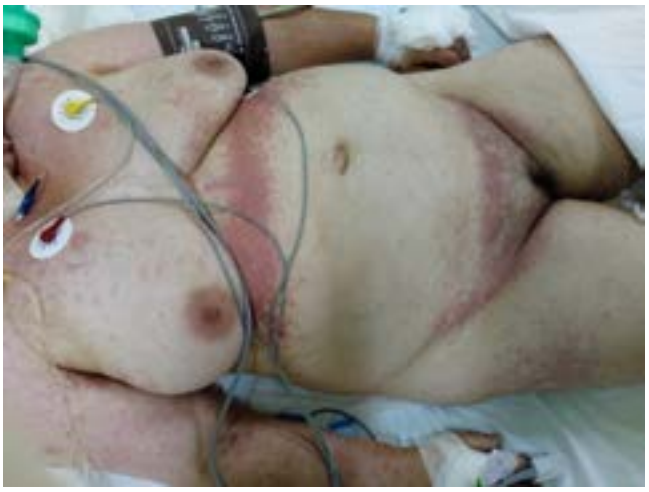
We present 58- year old woman that was hospitalized in ICU because of bilateral pneumonia. The main symptoms she presented were fever, cough, fatigue, dyspnea. The patient was confirmed positive by nasopharyngeal Polymerase Chain Reaction (PCR) for SARS-CoV-2. In her medical history, noted hypertension was under therapy. The patient's initial vital signs were blood pressure of 140/78 mmHg, heart rate of 85 beats per minute, oxygen saturation of 40% on room air, with a body temperature up to 40 degrees Celsius. Chest X-Ray and CT images showed

parenchymal abnormalities with massive peripheral consolidations with bilateral involvement predominantly right.

Laboratory test revealed: WBC White Blood Cells - ↑ increase 16.2 109 /L- Normal Range (3.5 - 10109 /L),PLT Platelet Cells - normal275 109/L- Normal Range (100 - 400 109/L), Glucose - high↑ 8 mmol/L- Normal Range (3.6 - 6.4 mmol/L), BUN Blood Urea Nitrogen - high ↑ 13.4mmol/L- Normal Range (2.8 - 7.2 mmol/L), CRE Creatinine - normal 77umol/L- Normal Range (49 - 115umol/L), NaSodium - normal 145mmol/L- Normal Range (136 - 145mmol/L), K Potassium - normal 4.5mmol/L - Normal Range (3.5 - 5.1mmol/L), Ca Calcium - low ↓ 2.06mmol/L- Normal Range (2.10 - 2.55mmol/L), AST Aspartate Aminotransferase - normal 20 U/L- Normal Range (5 - 34U/L), ALT Alanine Aminotransferase - normal 33 U/L- Normal Range (6 - 55U/L), ALB Albumin - low ↓ 21.7 g/L- Normal Range (34 - 50g/L), CRP C Reactive Protein - high ↑ 431 mg/L- Normal Range (0 - 10mg/L) , PT Prothrombin Time - normal 11.6 sec- Normal Range (10.3 - 13.0 sec), INR International Normalized Ratio - normal 1 - Normal Range (< 1.1), aPTT Activated Partial Thromboplastin Time - reduced ↓ 21.5 sec - Normal Range (25 – 35 sec), D-Dimers - increase ↑ 2.19 mg/L - Normal Range (< 0.55mg/L), LDH Lactate dehydrogenase- high ↑ 327 U/L - Normal Range (81 - 234 U/L), TBI Total Bilirubin - low ↓ 4.3 umol/dL- Normal Range (5 - 21 umol/dL)

Admitted to the ICU the patient was started off-label antiviral therapy with lopinavir/ ritonavir and double antibiotic therapy: third generation cephalosporin (ceftriaxine) and macrolide (azirtomicin). Other drugs administered during hospitalization were: subcutaneous low molecular weight heparin, systemic corticosteroid therapy (dexamethasone), paracetamol. During COVID-19 treatment mechanical ventilation was applied from day one in ICU. She received liquid nasogastric tube feeding.

Mild erythema presented as red plaques localized on large areas on the body, mostly genitocrural area, axillary area and sub-mammary folds were noticed on the 7th day of the ICU stay. After two days the rush became more intense with maceration and fissuring. Small maculo-papular rush disseminating on trunk and upper and lower extremities followed. The majority of the lesions were localized on the trunk and the hands and feet were spared. The intensive skin rush was the reason the dermatologists were consulted. (figure 1)



(figure 1)

Even though COVID19 disease is mostly new and cutaneous manifestations do occur, we believe that in this case, the reasons for the rush were prolonged double antibiotic therapy, intensive corticosteroid therapy, reduced immune system, prolonged high body temperature, and also prolonged high glycemic blood levels. No biopsy was obtained. We suggested intravenous antimycotic therapy (Fluconasole 200 ml) once a day, for 7 days. In the subsequent days gradual improvement of the skin lesions started to appear. We could not document the skin improvement because of the exitus letalis of the patient form the COVID-19 complications.

DISCUSSION

Various cutaneous manifestations have been observed in patients with COVID-19 infection. [6] . A rash associated with COVID-19 can involve various body regions, most commonly the trunk, but extremity involvement may also occur [3].

Gottlieb M et all. [6] summarized multiple reports of patients presenting with a maculopapular rash, characterized by erythematous macules covered with small papules, or with large plaques. They have summarized that other dermatologic findings may include urticaria, petechia, purpura, chilblains, livedo racemosa, and distal ischemia [6].

Sachdeva M, et all [7] reported that the most common cutaneous manifestation of COVID-19 was found to be maculopapular exanthem (morbilliform), presenting in 36.1% (26/72) patients. The other cutaneous manifestations included: a papulovesicular rash (34.7%, 25/72), urticaria (9.7%, 7/72), painful acral red purple papules (15.3%, 11/72)

of patients, livedo reticularis lesions (2.8%, 2/72) and petechiae (1.4%, 1/72). Majority of lesions were localized on the trunk (66.7%, 50/72), however, 19.4% (14/72) of patients experienced cutaneous manifestations in the hands and feet.

While most of intertigo is benign disease and the treatment is rapidly effective it is important to be aware of the dermatologic manifestations and complications during COVID- 19 patients and properly treat complications of the disease .

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PLACENTA PREVIA INCRETA: CASE REPORT ЗА УСПЕШЕН МЕНАЏМЕНТ И ОПЕРАТИВЕН ТРЕТМАН НА УРГЕНТНА ОБСТЕТРИЧКА ОПЕРАЦИЈА

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АБСТРАКТ

Placenta previa increta е ретка компликација во бременоста, која е асоцирана со големо интра и постпартално крварење и најчесто по породување завршува со отстранување на матката- хистеректомија. Како што расте бројот на царски резови, така се зголемува и инциденцата на оваа состојба, која игра значајна улога во мајчиниот и неонаталниот морталитет.

Ова е клиничка презентација на редок случај на ризична бременост, со Placenta previa increta кај 33 годишна трудница, со лошо акушерско минато (гравида 3, пара 1). Пациентката е примена како итен случај за завршување на породувањето во 33,1 г.н. од бременоста со породилни контракции, претходно контролирана во друга болница. Ултразвукот покажа дека се работи за тотална плацента превиа која го инвадираше зидот на матката и цервиксот, што се прикажа со Doppler ултразвук. Состојба на плодот беше уредна во карлична презентација. Беше добиен податок дека два дена претходно, било спроведено зреење за матурација на плодот со Флостерон во две дози. Пациентката беше итно примена, и предоперативно се направија итни клинички и лабораториски иследувања. Се вклучи токолиза со Атосибан, но контракциите не престанаа и се одлучи породувањето да се заврши со итен царски рез. По добивање на лабораториските анализи и обезбедување на крвни деривати, пациентката се внесе во операциона сала и во општа анестезија се отвори абдомен, со инфраумбиликален рез и породувањето се изврши со корпорален рез на матката. Беше породено здраво женско новородено со тежина 2060 гр., добиено во добра кондиција со АПГАР скор 6/7. Поради обилно и континуирано крварење, кое доаѓаше од долниот сегмент на матката каде беше врасната постелката, а кое го загрозуваше животот на мајката се одлучи да се направи тотална хистетректомија и да се отстрани матката. Истата се направи со тотално отстранување на матката, без аднексектомија, поради возраста на пациентката. Интраоперативно пациентката прими 4 единици декантирани еритроцити и 4 плазми. Постоперативниот тек на родилката беше стабилен, со супституција со крвни деривати, двојна антибиотска терапија, тромбопрофилактична терапија и ја напушти болницата после 5 дена од породувањето и оперцијата, без дополнителни компликации. Резултатот од хисто-патолошката анализа на изваденият препарат, покажа дека се работи за Placenta previa increta, со пробив на хорионските ресички и трофобластот низ целиот зид на долниот сегмент на матката и цервиксот до параметрата. Најчесто ваквите случаи во светот завршуваат со оперативно отстранување на матката и смртноста за мајката и новороденото може да биде голема. Ваквите случаи треба внимателно да се менаџираат и кога ке се откријат во тек на бременоста, да бидат постојано под лекарски надзор или хоспитализација и со навремено завршување на породувањето, за сведување на минимум на компликациите по мајката и новороденото.

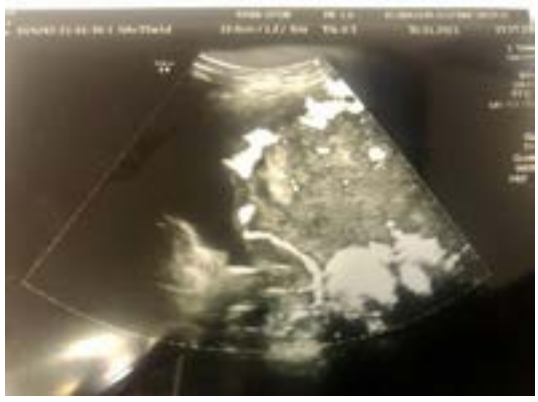
Водечки зборови: Placenta previa increta, царски рез, хистеректомија, ризична бременост, крварење, новородено

ВОВЕД

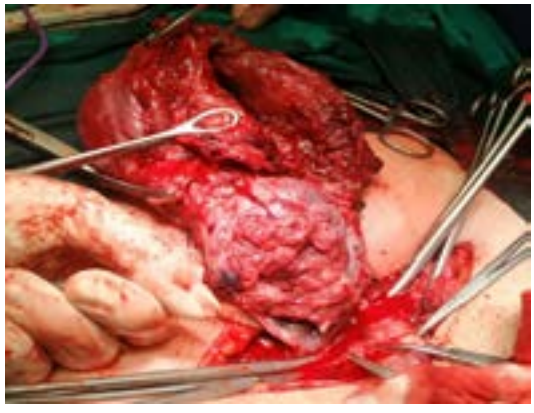
Сите состојби на патолошка плацентација како Placenta previa и Placenta (accreta, increta, percreta) во текот на бременоста се со многу голем ризик за мајката и плодот, проследени со обилни крварења во текот на бременоста и породувањето [1]. Тие се резултат на патолошка абнормална инвазија на трофобластот, кога дел од постелката или целата постелка може да врасне во зидот на матката, па и во околните структури. Кај Placenta accreta хорионските ресички инвадираат во миометриумот. Кај Placenta increta- хорионските ресички враснуваат длабоко во миометриумот. Кај Placenta percreta- хорионските ресички го пробиваат миометриумот и може да враснат и во околните органи и структури околу матката [1]. Инциденцата на овие состојби се зголемува последните години, поради зголемен број на царски резови и враснување на постелката на претходен рез или лузна на матката. Се дијагностицираат во тек на бременоста со ултразвук, Doppler ултразвук и со MRI [2] [3]. Пропратени се со обилни крварења во тек на бременоста и породувањето и со голем ризик за здравјето и преживувањето на мајката и новороденото [4]. Поради обилните крварења може да резултираат и со интраваскуларни коагулопатии, електролитен дизбаланс и акутна бубрежна инсуфициенција. Крвозагубата кај овие случаи е голема и се движи од 3000-5000 мл. и мора активно да се субституираат за време на интервенцијата и потоа [5]. Смртноста кај овие состојби е исто така голема во светски рамки и во некои делови на светот надминува и 50%.

CASE REPORT

33 годишна пациентка (гравида 3, пара 1), со породилни контракции и без надворешно крварење, со изразена анемија беше примена во болницата Аџибадем-Систина, во 33,1 г.н. од бременоста со дијагноза Placenta previa totalis. Во анамнезата беше добиен податок дека пациентката пет години претходно имала една вонматерична бременост, оперирана лапароскопски. Истата година потоа поради голем цервикален миом кај пациентката, со операција е отсранет најголем дел од грлото на матката- трахелектомија (цервиксектомија), при што во истиот акт е поставен и интра- абдоминален церклаж, како превенција за понатамошно идно забременување и породување. Две години подоцна во 2017 г. пациентката забременува и поради мртов плод во 34 г.н. од бременоста и претходно реализиран интра- абдоминален церклаж, е породена со царски рез. Пациентката една година подоцна во 2018 година, имала уште една неуспешна бременост која завршила со абортус во 8 г.н. од бременоста. Нема живо дете. На преглед со ултразвук на приемот, се детектира вијабилен плод во карлична презентација, кој одговараше по растот за 33 г.н., со доволно околуплодова вода. Со трансабдоминален и вагинален ултразвук се детектира постелка лоцирана комплетно ниско, во долен сегмент на утерус при што со Doppler ултразвук се визуелизира васкуларизација и пробив на трофобластот во зидот на матката. Пациентката даде податок дека два дена претходно е завршена фетална матурација со Флостерон во две дози по 14 мг. Веднаш се направи хоспитализација, се земаа лабораториски анализи и се вклучи Атосибан како токолитик, меѓутоа контракциите не престанаа. По добивањето на лабораториските анализи кои покажаа анемија со Hb- 86 g/l и Hematocrit 25 % , Trombociti 105-109/ l, уроанализа без присуство на крв во урината, уредна хемостаза, се обезбедија крвни деривати и се одлучи дека породувањето мора веднаш да се заврши со царски рез.



Doppler ултразвук- Placenta increta



Интраоперативен приказ

Поради можни компликации беа повикани и абдоминален хирург и уролог, да присуствуваат на операцијата. По внесување во операциона сала, во општа анестезија се отвори абдомен со инфраумбиликален рез и породувањето се изврши преку корпорален рез на матката. Беше породено здраво женско новородено со тежина 2060 гр., добиено во добра кондиција со АПГАР скор 6/7. По породувањето на плодот се јави обилно и континуирано крварење, кое доаѓаше од долниот сегмент на матката каде беше врасната постелката, а кое го загрозуваше животот на мајката и се одлучи да се направи тотална хистетректомија и да се отстрани матката. Се поставија хемостатски шавови на корпоралниот рез на матката и се прејде на нејзино отстранување со тотална абдоминална хистеректомија, без аднексектомија, поради возраста на пациентката. Во текот на операцијата имаше средно обилно крварење и поради претходно изразена анемија кај пациентката, интраоперативно беа ординирани 4 единици декантирани еритроцити и 4 плазми, а по отстранување на препаратот, проверка и корекција на хемостазата, се постави абдоминален дрен. Постоперативниот тек на породената беше стабилен, со супституција со уште една единица декантирани еритроцити, двојна антибиотска терапија, аналгетска терапија, тромбопрофилактична терапија и многу мала дренажа на абдоминален дрен од само 50 мл., кој беше изваден два дена по операцијата. Мајката беше физички активирана од вториот ден по операцијата, со уредни витални параметри и ја напушти болницата заедно со бебето после 5 дена од породувањето и операцијата, во добра општа состојба и без дополнителни компликации. На првата контрола и еден месец по породувањето, мајката и новороденото беа во одлична здравствена состојба. Резултатот од хистопатолошката анализа на изваденият препарат, покажа дека се работи за Placenta previa increta со пробив на хорионските ресички и трофобластот низ целиот зид на долниот сегмент на матката и резидуалниот дел од цервиксот до параметра.

ДИСКУСИЈА

Инциденцата на абнормалната плацентација и инвазија на плацентата во зидот на матката Placenta previa (accreta, increta, percreta) и со околните структури и органи, се јавува во 2-9 случаи на 1000 породувања [1] [6]. Оваа инциденца се зголемува последните години во литературата, поради се поголемиот број на завршувања на породувањата со претходен царски рез [7]. Останати ризик фактори за нејзино јавување се претходни интервенции на матката и ендометриумот, малформации на матката и мултипаритет. Инциденцата најмногу се зголемува кај претходни породувања со царски рез [6]. Антенаталната и препартална дијагноза на овие состојби е пресудна за менаџментот и породувањето на овие мајки и новородени и влијае на зголемување на смртноста од овие состојби. Ултразвукот, Doppler ултразвукот и MRI, може да бидат искористени во препарталната дијагноза кај овие бремености [2] [3]. Сите завршуваат со породување со царски рез и најчесто во истиот акт и со отстранување на матката, поради обилните крварења [4] [5]. Во некои случаи доколку по породување на плодот, нема обилно крварење од местото на инсерцијата на постелката, може да се остави постелката и потоа да се третира најчесто со Methotrexate [6] [7]. Во нашиот случај, комбинацијата на Placenta previa increta, претходен царски рез и операција со субтотално отстранување на грлото на матката и пласиран интра- абдоминален церклаж, проследено со обилно крварење за време на породувањето и операцијата, заврши со комплетно отстранување на матката. Се доби здраво новородено и жива мајка без дополнителни компликации по нивното здравје.

ЗАКЛУЧОК

Кај потенцијално животозагрозувачки состојби за мајката и новороденото за време на бременоста, како што е Placenta previa increta, раната дијагноза на состојбата, менаџментот на бременоста и терминирањето на завршување на бременоста се од исклучително значење. Обилноста на крварењето во тек на породувањето со царски рез кај овие породувања, интра-оперативно ја одредува одлуката дали ќе се направи и хистеректомија или ке се остави постелката и матката, доколку нема крварење и потоа ке се третира со Methotrexate.

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THORACOLUMBAR FRACTURES IN PATIENTS WITH ANKYLOSING SPONDYLITIS (BECHTEREV DISEASE). PRESENTATION OF TREATMENT RISK AND COMPLEXITY THROUGH A COMPLICATION.

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ABSTRACT

Introduction: Ankylosing spondylitis (AS) as a chronic inflammatory disease primarily affects the spine and paraspinal soft tissue. Patients suffering from this disease tend to have spinal fractures and injuries due to limited mobility enhanced further by serious cases of osteoporosis. This paper aims to report the clinical effect and problems of early operative treatment via posterior spinal fixation and the occurrence of a complication in a patient with L1 fracture and ankylosing spondylitis. Case presentation: Patient with 3-year-long history of ankylosing spondylitis sustained L1 spine fracture due to trauma with an impact directly on the back. The patient had back pain and paraplegia. After preoperative preparation, the patient underwent the first surgical treatment with short-segment posterior spinal fixation. Postoperatively neurologic status improved. 2 months postoperatively there was hardware failure without neurologic compromise. Second surgery with posterior long segment spinal fixation and cement augmentation was performed, which lead to fracture healing.

Conclusion: Spine fracture treatment in patients with ankylosing spondylitis represents a challenge because of the altered biomechanical characteristics of the „bamboo spine“, which behaves like a long bone. In this type of injury, long-segment fixation is necessary to obtain construct stability and fracture healing.

Keywords: Ankylosing spondylitis, Posterior spinal fixation, Postoperative complications.

INTRODUCTION

Ankylosing spondylitis (AS) also known as Morbus Bechterew is one of the most common seronegative (HLA-27 associated) spondyloarthritis subtypes. It's a chronic inflammatory disease that primarily affects the spine and paraspinal soft tissue. This chronic inflammation leads to pathological remodeling and new bone formation of the spine.1 End stages include the "bamboo spine phenomenon" where bone structures and ligament calcifications fuse the vertebral bodies. This remodeled spine is osteopenic, less active, and less elastic. Neck or back pain, loss of flexibility, and inability to walk upright without a horizontal line of vision make these patients susceptible to falls and trauma. AS patients have more than 10-fold increased risk for spinal fracture and increased incidence of associated neurologic deficit compared to the healthy population.2

AS patients have an increased risk for pulmonary and cardiac complications, which lead to greater perioperative morbidity and mortality, compared to the healthy population.3,4 However, studies show that conservative treatment including bed rest, bracing, or traction is associated with pseudoarthrosis and neurologic complications development in these patients.5,6 Unfavorable outcome of conservative treatment along with advances in surgical techniques cause a shift towards surgical treatment for thoracolumbar spinal fractures in patients with AS.3

CASE PRESENTATION

We present a case of L1 fracture in a 62-year-old man with AS.

The patient was involved in a motorcycle accident, in which he crashed with low velocity in a static object. He was admitted with paraparesis and back pain. Anal sphincter tone was preserved. American Spinal Injury Association (ASIA) impairment score (AIS) was grade C.7 He had no other injuries. X-rays and CT scans showed hyperextension injury of L1.

The patient was diagnosed with AS (HLA-B27 positive) 3 years before the injury. 2 years before AS diagnosis he sustained C7 vertebral fracture without neurologic deficit, which was treated conservatively and healed uneventfully. Other significant comorbidities include arterial hypertension, benign prostatic hyperplasia, and metabolic syndrome.

The patient was treated with posterior pedicle screw fixation surgery. The patient was placed in a prone position with careful padding. Th12-L1-L2 fixation with polyaxial screws and rod was performed. Due to fracture configuration, the fractured vertebra was fixed as well. (Figure 1)

Figure 1.

Postoperatively neurologic deficit withdrew. The patient was able to weight bear and had sphincter control (AIS grade D), but due to fracture instability was fitted with a brace and instructed to stay in bed, which he closely followed.

Figure 2.

Two months post initial surgery, the patient started having intense back pain without any deterioration of neurologic deficit. Control X-rays and CT showed pedicle screws loosening and pull-out. There was marked lucency zone corresponding to circumferential osteolysis surrounding the screws in the Th12 and to smaller extent L2 vertebral bodies on transverce CT slices. Also, comparison of X-rays and CT in different positions (standing vs. supine) demonstrates implant mobility. (Figure 2) Revision surgery was performed, in which fixation of Th10-L3 spine with cement augmentation was used. Pedicle screws in the fractured vertebra had no cement augmentation. Straight rods without attempts for deformity correction were applied. (Figure 3)

Figure 3.

The patient stayed in bed for 3 weeks and was verticalized with a brace and crutches. 6 months postoperatively patient is able to weight bear without crutches. He uses a cane for security and support. He has residual hip adductor muscle weakness and no other neurologic deficit. He has not returned to pre-injury level of activity.

DISCUSSION

The incidence of thoracolumbar fractures in patients with AS is unclear. Between 30% and 50% incidence can be found in the literature. 8,9 Most frequent mechanism is low energy trauma, such as fall from sitting/standing position and some patients do not recollect any trauma at all. Fractures can be located through the vertebral body or the intervertebral disc, due to its calcification and ossification. Most acute spinal fractures in the AS population occur in the cervical spine (81.2%). 4,8 We believe the C7 fracture in this patient was also related to the ankylosed spine, although at that time diagnosis of AS was not made yet.

The neurologic deficit is frequent in patients with AS. A meta-analysis by Westerveld et al. including studies with 345 AS patients with spinal fractures showed a 67.2% incidence of a neurologic deficit on admission. Secondary deterioration of neurological status was observed in 48 patients (13.9%). In the majority of cases, the definitive treatment did not influence the outcome of neurological status, but operatively treated patients had fewer complications and more frequent neurologic recovery.4 Patients with traumatic fractures of the ankylosed spine are susceptible to secondary spinal cord injury (SCI) due to highly unstable fracture configurations between the fused segments. A study by Teunissen et al. that included patients with ankylosing spine disorders that sustained traumatic spine injuries showed a 34.1% incidence of SCI.

Of the patients with SCI, 11 (19.3%) had delayed SCI and 6 patients (10.5%) had SCI as a direct result of surgical intervention for their fracture when unstable fractures displaced during positioning of the patient. Patients with SCI had a significantly higher rate of complications and had a lower probability of survival. 10

Careful patient positioning with proper preoperative fracture reduction is the first step of surgery for thoracolumbar fractures in patients with AS. Posterior spinal fixation is a treatment of choice for thoracolumbar fractures in patients with AS.3,6,11 Surgical decompression can also be performed via posterior approach when needed. Isolated anterior approach is not preferred in these patients, due to lesser stability of anterior constructs in kyphotic osteopenic spine. A combined antero-posterior approach is needed when large anterior gaps in hyperextension injuries cause risk for pseudoarthrosis and implant failure. In such cases, expandable cage systems and stable anterior plating are recommended. 6

In posterior spinal fixation, implant loosening with a need for revision is a major issue occurring in up to 15% of patients.12 Therefore, long constructs extending 3 levels above and below the fracture are preferred by several authors. 8,13 Long stabilizing systems are usually combined with postoperative bracing to reinforce stabilization. In a study by Tezeren and Kuru, the final outcome regarding local kyphosis, sagittal index, and anterior body compression is better in the long segment instrumentation group than in the short segment instrumentation group.14 Serin et al. showed that four levels posterior fixation is superior to two levels posterior fixation and a four levels fixation plus offset hook is the most stable.15 The Spine Section of the German Society for Orthopaedics and Trauma recommends that a minimum of two levels above or below the fracture are fixed. If osteopenia or osteoporosis is present, the load should be distributed to more screws and/or combined with cement augmentation. 6

Biomechanically, monoaxial pedicle screw systems are preferred for achieving greater construct stability. 6computed tomography (CT Stiff rods are used for the same reason. However, Lindtner et al. propose a reduction of rigidity of instrumentation to decrease the strain at the bone-metal interface and to allow for postoperative fracture reduction with early postoperative mobilization with a similar mechanism as dynamic constructs in long bone fixation. They propose increasing the working distance of the rods by leaving at least one vertebral body adjacent to the fracture site without pedicle screws for the same reasons. In their study comparing open treatment with a rigid construct and percutaneous treatment with a less rigid construct, they had a higher rate of complications, including implant loosening in the rigid construct group.

Patients with AS treated surgically for a thoracolumbar fracture have significantly increased rates of surgical site infection, transfusion, respiratory failure, pneumonia, and acute renal failure postoperatively compared with patients without AS.18 They are also at increased risk for aortic dissection or pseudoaneurysm.19 Considering the large number of postoperative complications and comorbidities in AS patients, there is a tendency for an increased number of minimally invasive procedures. Many studies show that percutaneous techniques have lower rates of blood loss, lower surgical site infection rates, shorter hospital stay while achieving good stabilization with comparable union rates to open fixation and high patient satisfaction.

In our case, we achieved a marked improvement in neurologic status after the first intervention. However, fixation of a single level above and below the injured vertebra for this fracture pattern in this patient proved to be insufficient. Hardware failure occurred despite limited loading of the spine and construct. A second intervention with long-segment fixation and cement augmentation was necessary to achieve stability of the construct. Pedicles of the fractured vertebra were intact and this allowed for intermediate screw fixation, but the cement was not used in order not to interfere with fracture healing. We did not consider an anterior approach necessary for closing the fracture gap, because this was not the primary reason for construct failure.

CONCLUSION

Thoracolumbar fractures in patients with AS are more frequently associated with SCI compared to identical fracture patterns in the healthy population and are associated with greater morbidity and mortality. Their treatment represents a challenge because of the altered biomechanical characteristics of the „bamboo spine“ which behaves like a long bone. In this type of injury, long-segment fixation is necessary to obtain construct stability and fracture healing, even if it requires longer operating time and greater blood loss.

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FIGURES

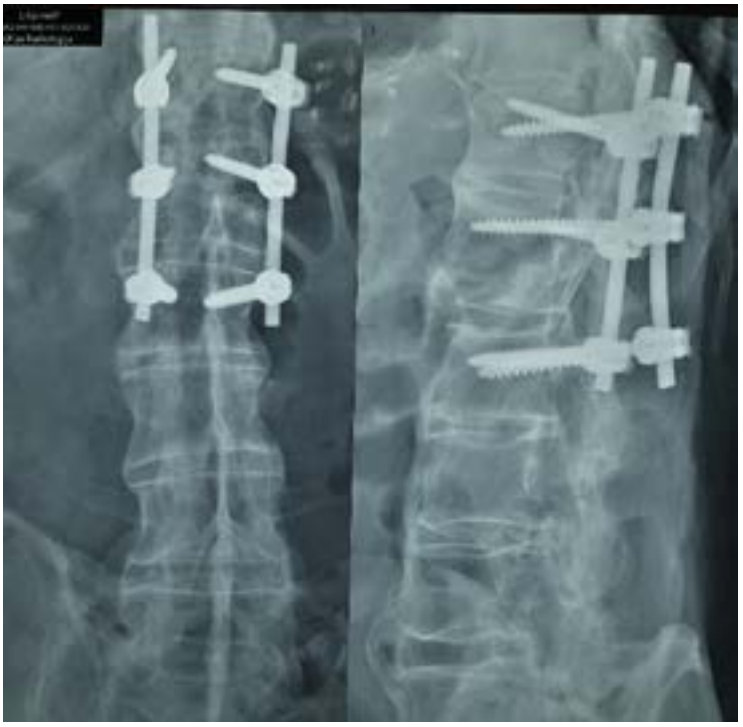

Figure 1. Postoperative X-ray of thoracolumbar spine.

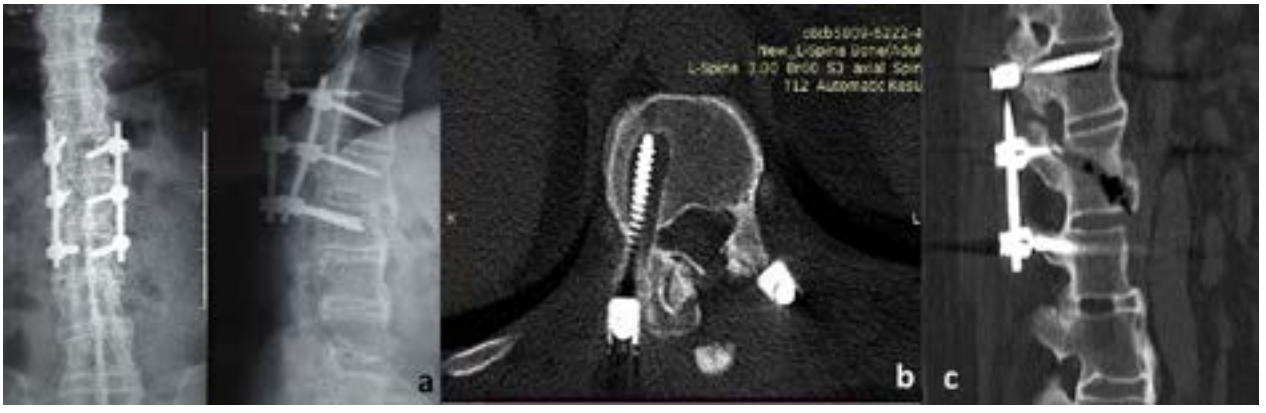

Figure 2. Imaging studies 2 months post initial surgery demonstrating loosening of implants. A. X-ray of thoracolumbar spine. B. CT slice through Th12. C. Sagittal reconstruction of CT showing pattern of injury.

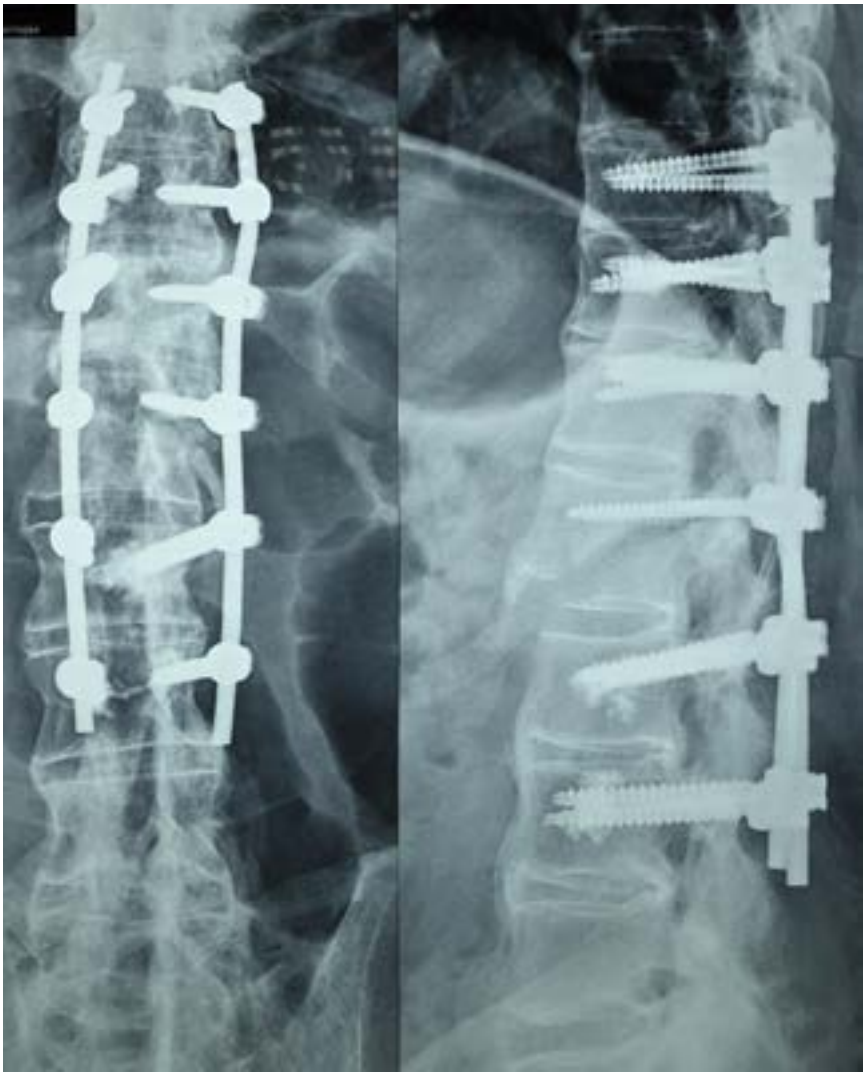

Figure 3. X-ray of thoracolumbar spine demonstrating long-segment fixation from Th11 to L4 with cement augmentation.

КАВЕРНОЗЕН АНГИОМ ВО СЕЛАРНА РЕГИЈА

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АПСТРАКТ

Васкуларните малформации во селарната регија се многу ретки. Нивната локализација и "mass" ефектот што го предизвикуваат на околните ткива често пати имитира макроаденом на хипофиза. Претставуваме случај на интра и супраселарен кавернозен ангиом кој радиолошки одговара на макроаденом на хипофиза, а клинички се презентира со промени во видното поле и секундарна аменореја како последица на хиперпролактинемија. Направената МРИ на хипофиза во прилог на ексцентрично лоциран макроаденом со силна пропагација во десно, со инволвирање на десниот синус кавернозус, кој се шири и параселарно десно а целосно ја исполнува и супраселарната цистерна. Пациентката оперативно третирана во два наврати , во тек на првиот зафат е спроведена декомпресија на десниот оптички нерв со фронтално - латерална краниотомија без екцизија на лезијата заради обилно крварење. Во постоперативниот период направена и дополителна дијагностика со која се исклучи постоење на аневризма и се направи соодветна подготовка за да се спречи обилно крварење при ресекција на туморот. Во тек на втората операција после 3 месеци се направи целосна ресекција на туморот со невронавигација и подготовка на десната каротидна артерија во десниот цервикален дел.

Клучни зборови: кавернозен ангиом, макроаденом, хипофиза, магнетна резонанца.

ВОВЕД

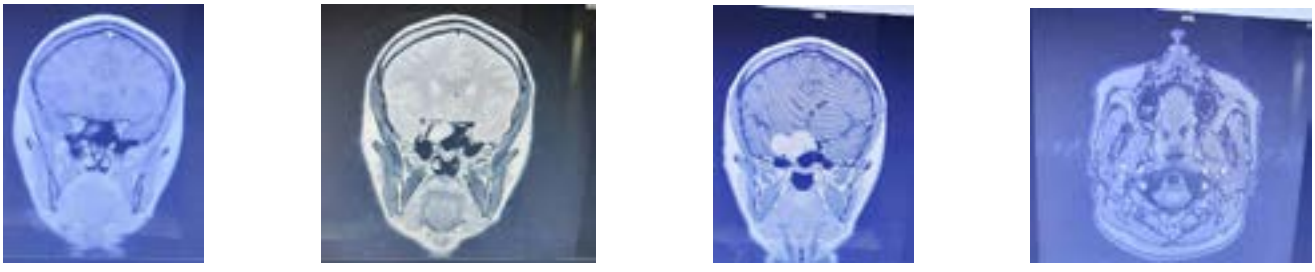
Интраселарните кавернозни ангиоми се ретки васкуларни лезии , и заради тоа се најчесто погрешно дијагностицирани и третирани како макроаденоми на хипофиза. Кавернозните ангиоми опфаќаат 5 до 13 % од сите васкуларни малформации, и се јавуваат кај 0, 5 до 1 % од населението. Во нашиот случај се работи за пациент кој првично предоперативно радиолошки и клинички беше евалуиран како макроаденом на хипофиза , но ретроспективно и постоперативно добивме патохистолошки наод во прилог на кавернозен ангиом.

ПРЕЗЕНТАЦИЈА НА СЛУЧАЈ

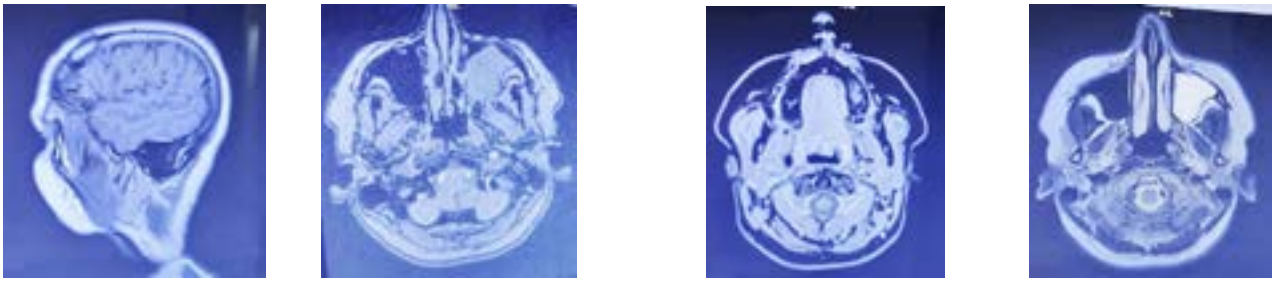
Пациентка на 41 година консултира заради главоболка во предниот десен дел на челото која датира од пред 7 години, пратена со болка во десното око со заматување на видот месец дена пред прегледот . Мајка на две деца, спонтано забременила и се породила по природен пат. За прв пат измерени високи вредности на пролактин во 2018 година (600-800 mU/mL) и ординирана терапија со Tbl.Cabergoline а 0.5 mg ½ неделно кога се намалил до 400 mU/м/L. Поради секундарна аменореа, со хормонска терапија предизвикано менструално крварење и направени хормонски иследувања: Prolactin 8.72 ng/ml (1100 mU/ml), TSH 1.68 mU/ml, fT4 14.1 Pmol/l, FPG 4.9 mmol/l, Cortisol 530.0

nmol/L, ACTH 16.82 Pg/ml, FSH 4.17 mU/mL, LH 0.900 mU/ml, STH <0.05 ng/mL, IGF-1 71.0 ng/mL, Na 141 mmol/l, K 4.4 mmol/l, Ca 2.4 mmol/l, jCa 1.20 mmol/l, Cloridi 108 mmol/l, специфична тежина на урина 1.030. На направената МРИ на хипофиза на 18.12.19 година се гледа ексцентрично лоциран макроаденом на хипофиза со силна пропагација во десно , со инволвирање на десниот синус кавернозус, кој се шири и параселарно десно и целосно ја исполнува и супраселарната цистерна од десната страна и ја компромитира и дислоцира хијазмата кон кранијално со димензии 5x3.5 см. На постконтрасната серија се гледа прилично обемно но нехомогено сигнално зголемување, а на направената МРИ артериографија TOF се гледа дека завршниот сегмент на десната a.carotis e истегнат и потиснат кон латерално а двете каротиди се оддалечени една од друга. Постои истегнување и на обете aa.cerebri anterior кон кранијално. Периметрија (25.12.19 година) со наод на минимални парацентрални релативни мали скотоми на видно поле. Од страна на Ендокринолог ординирана терапија со Tbl.Cabergoline a 0.5 mg 2x1/2 неделно. На 17.02.20 направена контролна периметрија и се гледа минимално влошување во споредба со предходнота периметрија. На 13.03.20 периметрија со уреден наод на лево око, а на десно око наод на релативно многу мали скотоми, но без никакво влошување споредбено со видното поле од пред 1 месец. На 05.05.21 година направен контролен МРИ на хипофиза кој во корелација со предходниот наод има минимална регресија. Хормонските иследувања покажуваат нормална функција на хипоталамо-хипофизна, тироидна и адреналната оска, со МРИ докажан макроаденом. Пациентката е хируршки третирана при што е спроведена декомпресија на десниот оптички нерв преку остеопластика на десната страна со фронто-латерална краниотомија со невронавигација, со зголемување на оптичкиот прозорец без екцизија на лезијата поради обилно крварење. Постоперативно направена дополнителна дијагностика - ДСА ангиографија со која се исклучи присуство на аневризма и МРИ на хипофиза која покажа хетерогено задржување на контрастот атипично за макроаденом на хипофиза. Постоперативно пациентката без друг фокален невролошки дефицит, освен со окуломоторна пареза на десната страна, со пад на очниот капак, мидријаза и отежнато движење на десното око. Постоперативните хормонски анализи со наод на хипопитуитаризам со испади на тироидна и адренална оска, поставена на заместителна терапија со Хидрокортизон и Левотирохин.

После три месеци пациентката реоперирана со направена целосна ресекција на туморот , преку предходна остеопластична краниотомија од десниот страничен дел на черепот (десно фронтално-латерално), со невронавигација и подготовка на десна каротидна артерија во десниот цервикален дел. Патохистолошкиот наод – кавернозен ангиом.



Слика 1, предоперативен нативен и постконтрастен МР преглед, ексцентрично лоциран макроаденом на хипофиза со силна пропагација во десно,со инволвирање на десниот кавернозен синус. Димензии 5x3,5cm.



Слика 2, постоперативен нативен и постконтрастен МР преглед, целосна редукција на експанзивниот супстрат во селарната регија со наод на атрофични промени со глиоза на десниот темпорален лобус со секундарна

дилатација на десниот темпорален рог. Голема цистична промена во лев максиларен синус.

ДИСКУСИЈА

Интраселарните кавернозни ангиоми се ретки васкуларни лезии, и заради тоа се најчесто дијагностицирани и третирани како макроаденоми на хипофиза. Дијагнозата и менацирањето на мозочен кавернозен хемангиом не се секогаш едноставни и најдобри резултати се постигнуваат со мултидисциплинарен пристап.

Васкуларните малформации може да се појават во било кој орган, и се групираат во следниве четири типа според нивниот раст и хистопатолошки карактеристики:

- Капиларни малформации (или телеангиектазии)
- Кавернозни малформации (кавернозни ангиоми / хемангиоми)
- Венски малформации
- Артериовенски малформации на шантирање.

Нашиот преглед во литературата идентификуваше 8 случаи на интраселарен кавернозен хемангиом (табела 1). Сите се потврдени со хистопатологија, а во само 2 од 8 случаи лезијата беше целосно лоцирана во села турцика, додека другите се протегаа во супраселарната цистерна и кавернозниот синус и ја опфаќаа внатрешната каротида. Првиот случај бил дијагностициран со обдукциски наод, а по 2000та година, сите пациенти се оперирани преку трансфеноидалниот пристап.

Табела 1. Резиме на клинички профил на претходно пријавени случаи на интраселарен кавернозен хемангиом

ГОДИНА	ВОЗРАСТ/ПОЛ	ЛОКАЦИЈА	СИМПТОМИ	ХИРУРГИЈА	РЕЗУЛТАТ
1980	72/Ж	Селарен и лев, латероселарен простор	Транзиторна диплопија	Обдукциски наод	Без резултат
1984	42/Ж	Селарен, супраселарен и лев латероселарен простор	Главоболка, напади	краниотомија	Целосно отстранување
1991	45/Ж	Десна страна на села	Губиток на вид, главоболка	краниотомија	Субтотално отстранување
2001	41/М	Десна страна на села	Без симптоми	Трансфеноидален пристап	Целосно отстранување
2006	62/Ж	Селарен и десно латероселарен простор	Птоза на око	Трансфеноидален пристап	Субтотално отстранување
2008	50/М	Селарен и лев латероселарен простор	вртоглавица, главоболка	Ендоскопски траснфеноидален пристап	Тотално отстранување
2010	77/Ж	Селарен, супраселарен и лев латероселарен простор	Траума на глава	Трансфеноидален пристап	Субтотално отстранување
2014	нема	Селарен и лев латероселарен простор	Губиток на вид, главоболка	Ендоскопски трансфеноидален пристап	Без резултат

ЗАКЛУЧОК

Селарните кавернозни ангиоми се ретка васкуларна малформација, кои треба да бидат вклучени во диференцијалната дијагноза на хипофизните туморски промени. Употребата на интра оперативни невронагициски техники овозможуваат ресекција на лезии кои се длабоко лоцирани со минимални постоперативни невролошки испади и ниски стапки на морталитет и морбидитет. Стереотактичката радиохирургија зема значително место во ефикасно лекување на неоперативни каверноми.

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СЛУЧАЈ НА ГАСТРИЧЕН МЕТАСТАТСКИ МЕЛАНОМ 2 ГОДИНИ ПО ПОЧЕТНА ДИЈАГНОЗА НА КОЖЕН МЕЛАНОМ

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АПСТРАКТ

Меланомот е најчестиот карцином кој метастазира во гастроинтестиналниот тракт, сепак, метастазите во желудникот е ретка појава. Ние го претставуваме случајот на пациентка со повеќе коморбидитети, дијагностицирана а потоа оперирана од бенка во дел на левото рамо 2 години пред презентацијата на неспецифични гастроинтерстинални симптоми и редукција на крвната слика. На горно дигестивна ендоскопија најдени се нејасно ограничени полипозни формации со васкуларна структура, кои хистопатолошки се потврдени за метастатски меланом во желудникот. Често неспецифични гастроинтестинални симптоми се причина за одложување на дијагностицирање на овој вид тумор, или воопшто не се дијагностицира ниту по обдукција[2.3].

Заради ова, секој неспецифичен гастроинтестинален симптом заслужува една горно дигестивна ендоскопија во најкраток временски период, со цел рано дијагностицирање, спречување на напредување на болеста а по можност и навреме преземање на соодветен третман.

ВОВЕД

Меланомот е вид на рак на кожата, кој брзо се шири и има лоша прогноза. Се јавува кога меланоцитите, односно клетките кои продуцираат пигмент мутираат и почнуваат неконтролирано да се делат. Како главни ризик фактори за меланом се лица со светла кожа, прекумерно изложување на сонце, како и фамилијарна анамнеза за меланом. Одредување на стадиумот на ширење на туморот помага во одлучување за соодветна терапија и прогноза на болеста. Во моментот кога се шири болеста, познато е како метастатски меланом. Обично може да се појави за време на III или IV фаза и најчесто ги опфаќа: лимфните жлезди, белите дробови, црниот дроб, мозокот и коските [1].

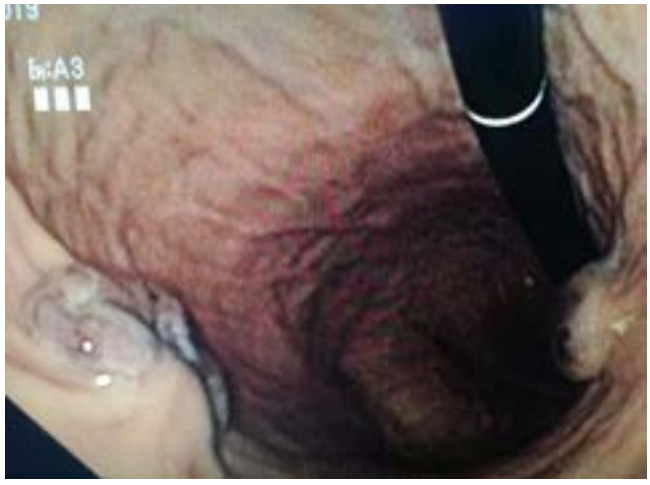
Метастатскиот меланом во желудникот е ретка појава и претставува лоша прогноза со просечно преживување од 4 до 6 месеци [2]. Дијагнозата ретко се поставува без ендоскопија или операција, бидејќи придружните симптоми се неспецифични(замор, гадење, повраќање, грчеви или болка во стомакот, губење на телесна тежина, мелена и анемија) и се манифестираат само кај 1-4 % од пациентите со метастази [1-5]. Најголем број на пациенти се асимптоматски се додека болеста не напредува што доведува до одложување на дијагнозата или целосно пропуштање до обдукција. Доколку постои сомневање за метастаза во желудникот, треба да се направи езофагогастродуоденоскопија (ЕГД), и биопсија на промената доколку се открие истата. Сензитивноста на КТ при откривање на метастази е 60-70%, затоа треба да се направат дополнителни испитувања кај пациентите со уреден КТ наод [2,4] Поголем број на гастрични метастази се јавуваат во телото и фундусот на желудникот, а најчесто на големата кривина на желудникот[12,13]. Ендоскопскиот изглед на туморот може да се класифицира во три вида: 1. Улцерирани меланотични нодули во нормалната вјуга. 2. Субмукозни маси со улцерации. 3. Масовни лезии со некроза и меланоза[10]. Хистопатолошкиот наод од биопсијата ја потврдува дијагнозата.

Важно е да се направи разлика помеѓу примарниот меланом на мукозниот гастроинтестинален тракт и метастатскиот меланом. Кај пациентите со примарен меланом во желудникот или во другиот дел на гастроинтестиналниот тракт нема доказ за истовремен меланом или атипична меланоцитна лезија на кожата, нема екстраинтестинално метастатско ширење на меланом и присатни се интрамукозни лезии во епителот на желудник или на другиот дел на гастроинтестиналниот тракт. Опциите за третман за метастази во желудникот вклучуваат: хируршка ресекција, хемотерапија и радиотерапија[3].

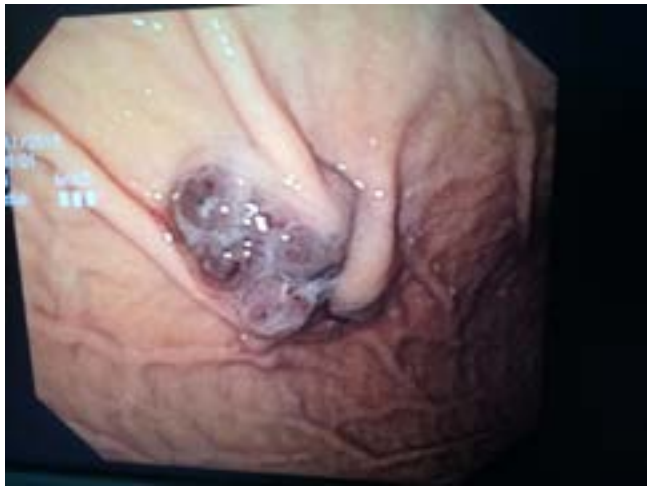
Нема утврдени критериуми за хируршка интервенција. Ресекција на метастазите во желудникот дури и ако се нецелосни, нудат симптоматска корист, исто така може да го продолжи преживувањето. Хемотерапија исто така се користи како начин на лекување кај овие пациенти, но може да доведе до тешки компликации како последица на имунокомпромитирана состојба. Историски гледано, се верува дека меланомот е радио резистентен тумор. Радиотерапија се користи како адјувантна терапија после хируршка ресекција, со добри ветувачки резултати[13,14,15].

ПРИКАЗ НА СЛУЧАЈ

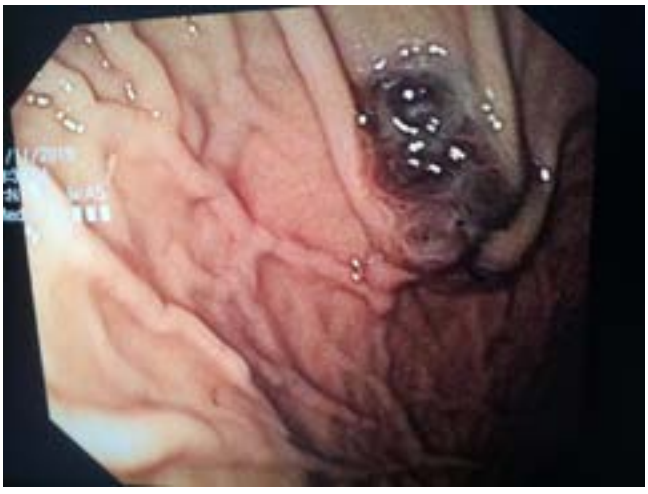
Пациентка на 58 годишна возраст со низа коморбидитети и тоа, прележано цереброваскуларен инсулт, симптоматска епилепсија, атријална фибрилација, вграден вештачки електростимулатор, десна нефректомија, на антикоагулантна и кардиолошка терапија. Во јуни 2017 година консултирала на Клиника за Дерматовенерологија поради крварење на голема бенка на левото рамо месец дена, бенка за која пациентката тврдила дека е со променета структура и пораснала последните 2-3 години. По еден месец истата е оперирана на Клиника за Пластична и реконструктивна хирургија. Во текот на овој период иследувана со имицинг методи, истите со уреден наод. После две години забележала израсток на капилициум поради што повторно консултирала на Клиника за Дерматовенерологија. Пациентка веќе со силни нејасно опишани дифузни абдоминални болки, гадење и повраќање, замор и слабост. Беше иследувана на Клиника за Токсикологија, лабораториски со редукција на крвната слика, сонографски наод на абдомен за перипанкреатични зголемени лимфни жлезди и гастроскопски наод за нејасно опишани васкуларни-тм формации. Истиот месец беше примена на нашата Клиника за понатамошни иследувања и терапија. Комплетната крвна слика на прием откри редукција на крвната слика со Хгб 63g/L, тромбоцитоза 511x10 9/L и нарушен коагулационен статус (протромбинско време 51сек, протромбински индекс 5.6), поради што пациентката беше трансфундирана со крвни деривати, примаше кристалоидни раствори, нискомолекулрен хепарин, инхибитори на протонска пумпа и останатата нејзина хронична терапија. Пациентка со висок титар на антитела за Хеликобактер пилори во серум, но и покачен алфа фетопротеин и специфичниот тумор маркер за меланом S100. Во наредниот период направена е гастроскопија при што се видени две топчести формации, од кои едната е на големата кривина и е поголема околу 3 cm и втората на малата кривина со дм 2 cm. Од поголемата се земени 4 биопсии за хистопатолошка анализа.



Слика 1. Ендоскопски приказ на малата формација на малата кривина на желудникот на пациентката.



Слика 2.



Слика 2 и 3 . Ендоскопски приказ на две топчести формации на големата кривина на желудникот на пациентката. Земени се 4 биопсии за хистопатолошка анализа

Доставениот материјал микроскопски го сочинуваат фрагменти од желудочната лигавица кои се дифузно инфилтрирани од малигно неопластично ткиво сочинето од крупни, плеоморфни клетки, со обилна еозинофилна цитоплазма и крупни јадра во дел со видливи проминентни јадренца и изразита митотска активност. Во цитоплазмата на дел од туморските клетки се гледаше и жолто-кафеникав пробоен пигмент.

Дополнително е направена имунохистохемиска анализа која покажа дифузен позитивитет на туморските клетки за Melan A и HMB45, додека истите беа негативни за LCA I CK AE1/AE3 .

Хистопатолошкиот наод од доставениот материјал оди во прилог на метастатски меланом.

Сонографски детектирани две нејасно ограничени хипоехогени промени во левиот и десниот лобус на црниот дроб, кои одат во прилог на секундарни депозити и наголемени лимфни жлезди перипанкреатично и параортално. Поради тешката општа состојба и сомнение за дифузно метастатско заболување, испишана со препорака да консултира онколог. Во амбулантски услови реализирано е КТ на белите дробови, абдомен и малата карлица со контраст, кои ги потврдиа сомнежите за дисеминирана малигна болест, односно покажа секундарни депозити во базата на белите дробови обострано, понагласени десно, секундарни промени на црниот дроб, пакети на наголемени лимфни жлезди дифузно во абдоменот и голема фокална промена во ложата на отстранетиот бубрег.

Поради повраќање на крвава содржина, без редукција на крвната слика повторно консултирала во амбулантата на нашата клиника, каде и е даден совет за исхрана.

Пациентка започна со третман со Зелбораф на Клиника за Онкологија. Поради редукција на крвната слика беше хоспитализирана на Клиника за Онкологија за трансфузија со крвни деривати.

ДИСКУСИЈА

При сомнение за метастатски меланом на гастроинтестиналниот тракт треба се направат низа испитувања и тоа горно дигестивна и долно дигестивна ендоскопија, со биопсија на лезијата доколку се најде.

Бидејќи меланомот најчесто метастазира во тенкото црево, потребно се освен горенаведените испитувања да се изведе и капсулна ендоскопија [6,7,9].

Хистопатолошкиот наод од биопсија, ја потврдува дијагнозата и е супериорна метода за диференцирање на стадиумите, во однос на ендоскопските иследувања.

КТ имиџинг методите задолжително се за рано откривање на новонастанатите метастази во телото.

Времетраењето од дијагностицирање на примарниот тумор до појава на метастази, во различни студии различно е прикажано. Во најголем број на студии ново настанати метастатски меланом на желудникот се пронајдени во рок од една година од времето на дијагностика на примарниот тумор (вклучувајќи и рак на белите дробови, карцином на дојка и меланом) а најдолгиот период изнесува 48 месеци. Другата студија се приближува со нашата студија односно 3 години по дијагностицирање на примарниот тумор е појавен метастатски меланом. [10,11]

ЗАКЛУЧОК

Кај пациент со историја на меланом со неспецифични гастроинтестинални симптоми и редукција на крвната слика, метастатски меланом треба да се исклучи со горно и долно дигестивна ендоскопија но и со ендоскопска капсула за испитување на тенкото црево. За жал неспецифични гастроинтестинални симптоми ја маскираат болеста, поради тоа се одложуваа навремено дијагностика и третирање

кај овие пациенти. Кај нашата пациентка 2 години пред појава на метастазите и беше дијагностициран меланом на кожата. Раната дијагноза е клучно за навремено преземање на сите мерки за спречување на унапредување на болеста.

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Numri i faqeve (përfshirë tabelat dhe/ose figurat/ ilustrimet) varet nga lloji i artikullit:

punim origjinal hulumtues –deri ne12 faqe dhe jo më shumë se 6 tabela dhe/ose grafikone/fotografi;

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prezantim rasti apo kumtesë e shkurtër – deri 6 faqe dhe maksimum 3 tabela dhe/ose figura/imazhe.

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Së bashku me dorëshkrimin, dorëzoni një faqe me **titullin** e artikullit; **emrin/at e autorit/ve**, duke përfshirë emrin me jo më shumë se dy tituj shkencor; emrin e departamentit dhe institucionit në të cilin është bërë punimi; institucioni ku punon (për secilin autor); si dhe emri dhe adresa e autorit të cilit do ti adresohen kërkesat nga ana e Redaksisë (shihni Informacionet plotësuese për autorët)

Abstrakti duhet te jete me jo më shumë se 250 fjalë. Duhet të konsistojë në katër paragrafë, i klasifikuar në Hyrje, Metodat, Rezultatet dhe Diskutimi (Përfundimet). Ato duhet të përshkruhen shkurt, respektivisht, problem qenësor i studimit, se si është kryer studimi, rezultatet e fituara, dhe perfundimi.

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Fjalët kyqe -Tri deri pesë flaje apo fraza te shkurtëra duhet t'i shtohen pjesës së fundme të faqes së abstraktit.

Citatet e referencave në tekst duhet fillimisht të jenë nga revistat e indeksuara në **PubMed**. Stili i referencave që kërkohet nga Medicus është i formatit Vancouver (shihni Informacionet plotësuese për autorët).

Shkurtimet (**akronimet**) përdoren për njësitë matëse, kurse në raste tjera kur përmendet për herë të parë, ai duhet të jetë i sqaruar me fjalën bazë bashkangjitur.

Për të gjitha barnat duhet të përdoren **emrat gjenerik** ndërkombëtar. Nëse në hulumtim janë të përdorura brendet e patentuara, përfshini emrin e brendit në kllapa në paragrafin e Metodave.

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Autorët marrin dy kopje të botimit përkatës.

The number of pages (including tables and/or figures/ illustrations) is dependent upon the type of the article:

original research paper - up to 12 pages and no more than 6 tables and / or graphs / pictures;

professional or review paper - up to 8 pages and no more than 4 tables and / or figures / images;

case report or brief communication - up to 6 pages and a maximum of 3 tables and / or figures/images.

Leter up to 2 pages

With the manuscript, provide a page giving the title of the paper; the name(s) of the author(s), including the first name(s) and no more than two graduate degrees; the name of the department and institution in which the work was done; the institutional affiliation of each author; and the name and address of the author to whom reprint requests should be addressed. (see Additional Information for Authors)

Provide an **abstract** of not more than 250 words. It should consist of four paragraphs, labeled Backround, Methods, Results and Conclusions. They should briefly describe, respectively, the problem being in the study, how the study was performed, the salient results, and what the authors conclude from the results.

Tables, figures and legends (see Additional Information for Authors)

Three to five **key words** or short phrases should be added to the bottom of the abstract page.

Quotations of references in the text should primarily be from journals indexed in **PubMed** which have proven their significance. The style of references required by **Medicus** is the Vancouver format (see Additional Information for Authors).

Except for units of measurement, abbreviations are discouraged. The first time an abbreviation appears it should be preceded by the words for which it stands.

The international **generic names** should be used for all drugs. When proprietary brands are used in research, include the brand name in parentheses in the Methods section.

All manuscript sent to the editor should be noted by the authors whether they are meant for the "original research papers" section or the rest of the journal's content.

The authors receive two copies of the relevant issue.

Informacione plotësuese për autorët

I. Faqja e parë – *ballina*: Duhet të përmbajë: (a) titullin e punimit, të shkurtër, por informativ; (b) emri, inicialet e emrit të mesëm dhe mbiemrit të secilit autor; (c) institucioni; (d) emri i departamentit që i atribuohet punës shkencore; (e) emri dhe adresa e autorit për t'iu përgjigjur në lidhje me dorëshkrimin; (f) burimi/përkrahja në formë të granteve, paisjeve, barnave dhe në përgjithësi.

II. Faqja e dytë – *abstrakti dhe fjalët kyqe*: Abstrakti duhet të shkruhet me maksimum prej 150 fjalësh për abstraktet e pastrukturuara, dhe me 250 fjalë për abstraktet e strukturuara (pjesët përmbajtësore: objekti/ete studimit ose hulumtimit, procedurat bazë, siç është përzgjedhja e subjekteve apo kafshët laboratorike, metodat vrojtuese dhe analitike, pastaj, rezultatet/gjetjet përfundimtare (të dhënat dhe rëndësia e tyre statistikore, nëse është e mundur), dhe konkluzionet kryesore. Vini theksin mbi aspektet e reja dhe të rëndësishme të studimit apo vrojtimit. Nën abstraktin indentifikoni dhe shkruani fjalët kyqe: 3-5 fjalë apo fraza të shkurtëra që do të ndihmojnë në paisjen me tregues të punimit dhe publikimit të abstraktit. Përdorni terme nga lista e Index Medikus për Nëntituj Mjekësor (Medical Sub-Headings [MeSH]); nëse nuk ka term të përshtatshëm në MeSH për disa terme të reja, mund të përdorni termet e dhëna.

III. Faqja e tretë dhe të tjerat – *teksti i plotë i artikullit*: Teksti i plotë I artikujve hulumtues ose vrojtues normalisht, por jo domosdoshmërisht, duhet të jetë i ndarë në paragraf me këta nëntituj: hyrja, metodat dhe materialet, rezultatet dhe diskutimi.

1. Hyrja: Krijoni një kontekst apo prapavijë(trualli) të studimit (që në fakt është natyra e problemit dhe rëndësia e tij). Për të bërë këtë duhet të bëni një hulumtim të literaturës – duke kërkuar, gjetur dhe lexuar punimet përkatëse, që duhet të jenë si referencë në dorëshkrimin tuaj. Sqaroni hipotezat tuaja dhe planifikoni t'i testoni ato, si dhe përshkruani qëllimet tuaja. Kini qëndrim të qartë se çka prisni të gjeni dhe arsyet që ju udhëhoqën tek hipotezat që keni krijuar. Objekti i hulumtimit më së shpeshti fokusohet kur parashtrohet si pyetje. Mos përfshini të dhëna apo rezultate nga puna që do të raportohet.

2. Metodat & Materialet: Ky paragraf duhet të përfshijë atë informacion që ishte në dispozicion në kohën që plani apo protokoli i studimit po shkruhej. Të gjitha informacionet e marra gjatë studimit i takojnë paragrafit të Rezultateve.

Përshkruani përzgjedhjen tuaj të pjesëmarrësve së vrojtimit ose eksperimentit (pacientët ose kafshët laboratorike, përfshirë kontrollat) qartë, duke përfshirë kriteret e përshtatshme (inkluzive) dhe përjashtuese (ekskluzive).

Parimi udhëheqës duhet të jetë i qartë se si dhe pse studimi është bërë në një mënyrë të caktuar. Jepni detaje të mjaftueshme për metodat, mjetet dhe materialet (jepni emrin dhe adresën e prodhuesit në kllapa), dhe procedurat për të lejuar të tjerët të kuptojnë dhe riprodhojnë rezultatet tuaja.

Nëse një metodë e caktuar që është përdorur është e njohur, atëherë nuk është e nevojshme të jepet përshkrim komplet i saj. Mund t'i referoheni punimit në të cilin së pari herë është përshkruar dhe të

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I. First page - *front page*: It should contain: (a) title of paper, a short, but informative; (b) the first name, initials of middle name and last name of each author; (c) the institution; (d) the name of the department that is attributable to the scientific work; (e) the name and address of the author with whom to correspond about the manuscript (f) source/support in the form of grants, equipment, drugs, or all.

II. Second page - *abstract and keywords*: The abstract should be written with a maximum of 150 words for unstructured abstracts and 250 words for structured abstracts (containing parts: objective(s) of study or research, basic procedures, such as selection of subjects or laboratory animals, observational and analytical methods, then, the main findings/results (data and their statistical significance, if possible), and the main conclusions. Emphasize the new and important aspects of the study or observation.

Below the abstract identify and write the keywords: 35 words or short phrases that will assist in indexing the paper and publication of the abstract.

Use terms from the list of Index Medicus for Medical Sub-Headings (MeSH); if there is no appropriate MeSH term for some newly introduced terms, we can use the given terms.

III. Third and further pages – *full text of the article*: The full text of research or observational articles should normally be, but not necessarily, divided into sections with the following headings: introduction, material and methods, results and discussion.

1. Introduction: Provide a context or background for the study (that is, the nature of the problem and its significance). To do this you must complete a literature review – searching for, finding and reading relevant papers, which must be referenced in your manuscript. Explain your hypotheses and the plan to test them, and describe your aims. Clearly state what you expect to find and the reasoning that led you to the hypotheses that you have made. The research objective is often more sharply focused when stated as a question. Do not include data or conclusions from the work being reported.

2. Methods & Material: This section should include only information that was available at the time the plan or protocol for the study was being written. All information obtained during the study belongs in the Results section.

Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria.The guiding principle should be clarity about how and why a study was done in a particular way.

Give sufficient details of the methods, apparatus and materials (give the manufacturer's name and address in parentheses), and procedures to allow others to understand and reproduce your results.

If a particular method used is well known then there is no need to give a complete description. You can reference the paper in

përmendni ndonjë modifikim/ndryshim që keni bërë. Jepni arsyet për përdorimin e tyre dhe vlerësoni kufizimet e tyre. Në fund, përshkruani se si i keni analizuar të dhënat tuaja, duke përfshirë metodat statistikore dhe pakon programore që keni përdorur.

Autorët e doreshkrimeve të rishqyrtuara duhet të përfshijnë një paragraf që përshkruajnë metodat që kanë përdorur për lokalizimin, përzgjedhjen, ekstrahimin dhe sintetizimin e të dhënave. Përdorni formën joveprore të foljes, në vetën e tretë, kur dokumentoni metodat, gjë që do të fokusonte vëmendjen e lexuesit tek puna që është bërë e jo tek hulumtuesi (P.sh. Janë marrë, janë realizuar, janë prezantuar etj.)

2. a) Statistikat: Përshkruani metodat statistikore me detaje të mjaftueshme për t'ia mundësuar një lexuesi me njohje në atë fushë t'i qaset të dhënave origjinale për të verifikuar rezultatet e raportuara. Kur është e mundur, përcaktoni sasinë e zbulimeve dhe prezantoni ato me indikatorë përkatës të gabimeve në matje apo pasiguri (siç janë inter-valet e besueshmërisë). Evitoni mbështetjen vetëm në testet statistikore të hipotezave, siç janë vlerat p, që dështojnë të transmetojnë informacion të rëndësishëm mbi madhësinë e efektit. Jepni detaje rreth përzgjedhjes së rasteve (randomizimi) dhe përshkruani metodat dhe sukseset e vro¬jtimit gjatë realizimit të studimeve të verbuara. Definoni termet statis¬tikore, shkurtesat dhe më së shumti simbolet. Specifikoni programin kompjuterik që është përdorur.

3. Rezultatet: Ky paragraf duhet t'i bëjë gjetjet tuaja të qarta. Prezantoni rezultatet tuaja në rend logjik në tekst, tabela dhe ilustrime, duke dhënë së pari rezultatet kryesore ose më të rëndësishme. Mos i përsërisni të gjitha të dhënat në tabela apo ilustrime, në tekst. Nënvizoni ose përm-bledhni shkurtimisht vetëm vrojtimet më të rëndësishme.

Kur të dhënat përmblidhen në paragrafin e Rezultateve, jepni rezultate numerike jo vetëm si derivate (për shembull, përqindja) por gjithashtu si numra absolut nga të cilët derivatet janë llogaritur, dhe specifikoni metodat statistikore që janë përdorur për t'i analizuar ato.

Kufizoni tabelat dhe figurat në aq sa janë të nevojshme për të sqaruar argumentin e punimit dhe për të vlerësuar të dhënat ndihmëse. Duke përdorur grafikonet për të reprezentuar të dhënat tuaja si alternativë e tabelave, do të rrisë kuptueshmërinë e lexuesit. Mos i dyfishoni të dhënat në grafikone dhe tabela. Duhet të jeni të qartë se cili lloj i grafikoneve është i përshtatshëm për informacionet tuaja. Për shembull, për të reprezentuar korelimin mes dy ndryshoreve, preferohet grafiku vijëzor, krahasuar me grafikun rrethor apo në formë shtyllash.

Sa i përket të gjitha paragrafeve, qartësia dhe të qënit i thuktë është kyçe. Mos prezantoni të njëjtat të dhëna më shumë se një herë. Kufizojeni veten në të dhënat që ndihmojnë në adresimin e hipotezave tuaja. Kjo është e rëndësishme edhe nëse të dhënat i aprovojnë ose nuk i pranojnë ato. Nëse keni bërë analiza statistikore, duhet të jepni vlerën e proba¬bilitetit (p) dhe të tregoni se është shprehës (sinjig në nivelin që ju po testoni. Varësisht nga analizat e përdorura, gjithashtu mund të jetë e rëndësishme të jepni intervalet e besueshmërisë së rezultateve (Confidence Interval –

which it was first described and mentioned any modifications you have made. Give the reasons for using them, and evaluate their limitations. Finally,, describe how you analysed your data, including the statistical methods and software package used.

Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data.

Use the third person passive voice when documenting methods which would focus the readers' attention on the work rather than the investigator.(e.g. Were taken, was performed, were presented itd.)

2. a) Statistics: Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as p values, which fail to convey important information about effect size. Give details about the randomization and describe the methods and success of observations while using blinded trials. Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

3. Results: This section should make your findings clear. Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all the data in the tables or illustrations in the text. Emphasize or summarize only the most important observations.

When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them.

Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Using graphs to represent your data as an alternative to tables will improve the reader's understanding. Do not duplicate data in graphs and tables. You need to be clear what type of graphs is suitable for your information. For example, to represent the correlation between two variables, a line graph is preferred to a pie chart or a bar chart.

As with all sections, clarity and conciseness is vital. Don't present the same data more than once. Restrict yourself to the data that helps to address your hypotheses. This is important whether the data supports or disproves them. If you have carried out a statistical analysis, you should give the probability (P) value and state it is significant at the level you are testing. Depending on the analysis used, it may also be important to give the confidence intervals of the results, or the statistical parameters such as the odds ratios. Provide a caption for each figure making the gen¬eral meaning clear without reference to the main text, but don't discuss the results. Let the readers decide for themselves what they think of the data. Your chance to say what you think comes next, in the discussion.

3. Tables: Each table should be inserted at the point of the text where they have to be placed logically, typed by the same rules

CI), ose parametrat statistikorë si proporcionet e rastit (odds ratio). Bëni përshkrimin tek secila figurë duke bërë të qartë domethënien e përgjithshme pa referencë në tekstin kryesorë, por mos diskutoni rezultatet në të. Lëreni lexuesin të vendosë vetë se çfarë men-don për të dhënat. Mundësia juaj për të thënë se çfarë mendoni, është në vazhdim, tek diskutimi.

3. Tabelat: Secila tabelë duhet të vendoset në vendin e tekstit ku duhet të vihet logjikisht, e plotësuar me të njëjtat rregulla sikur teksti i plotë. Mos i dërgoni tabelat si fotografi. Secila tabelë duhet të citohet në tekst. Tabelat duhet të jenë me numra ashtu që të jenë në koordinim me refer-encat e cituara në tekst. Shkruani një përshkrim të shkurtë të tabelës nën titullin. Çdo sqarim shtesë, legjendë ose sqarim i shkurtesave jostan¬darde, duhet të vendoset menjëherë poshtë tabelës.

4. Diskutimi: Ky paragraf është pjesa ku ju mund të interpretoni të dhë-nat tuaja dhe të diskutoni duke ballafaquar dhe krahasuar gjetjet tuaja me ato të hulumtuesve të mëparshëm. Rishikoni referencat e literaturës dhe shihni nëse mund të përfundoni se si të dhënat tuaja përkojnë me atë që keni gjetur.

Ju gjithashtu duhet të llogarisni rezultatet, duke u fokusuar në mekaniz¬mat në prapavij të vrojtimit. Diskutoni nëse rezultatet tuaja mbështesin hipotezat tuaja origjinale. Gjetjet negative janë aq të rëndësishme në zhvillimin e ideve të ardhshme sikur gjetjet pozitive.

E rëndësishme është se, nuk ka rezultate të këqija. Shkenca nuk të bëjë me të drejtën dhe të gabuarën, por merret me zgjerimin e njohjeve të reja.

Diskutoni si janë paraqitur gabimet në studimin tuaj dhe çfarë hapa keni ndërmarrë për të minimizuar ato, kështu duke treguar se ju çmoni ku¬fizimet e punës tuaj dhe fuqinë e përfundimeve tuaja. Duhet gjithashtu të merrni në konsideratë ndërlikimet e gjetjeve për hulumtimet në të ardhmen dhe për praktikën klinike. Lidhni përfundimet me qëllimet e studimit, por evitoni qëndrimet dhe përfundimet e pakualifikuara, që nuk mbështeten në mënyrë adekuate nga të dhënat. Shmangni prioritetet deklarative apo të aludoni në punën që nuk është krahasuar.

5. Referencimi: Referencat janë baza mbi të cilën është ndërtuar raporti juaj. Shqyrtimi i literaturës dhe leximi i referencave gjithmonë duhet të jetë pikë fillestare e projektit tuaj. Ky paragraf duhet të jetë i saktë dhe të përfshijë të gjitha burimet e informacionit që keni përdorur.

Në formatin " Vancouver" , referencat numërohen një nga një, sikur që shfaqen në tekst dhe identifikohen me numra në bibliografi..

Një punim mund të ketë më së shumti një autor dhe 4 koautor. Koautori i fundit duhet të jetë mentori ose koautori më i afëërt me punimin. Pas emrave të autorëve shkruhet titulli i artikullit; emri i revistës i shkurtuar sipas mënyrës së Index Medicus; viti i botimit; numri i vëllimit; dhe numri i faqes së parë dhe të fundit.

Referencat e librave duhet të jepen sipas emrit të autorit, titulli i librit (mund të citohet edhe titulli i kapitullit para titullit), vendi i botimit, botuesi dhe viti.

as for the full text. Do not send tables as photographs. Each table should be cited in the text.Tables should be numbered so that they will be in sequence with references cited in the text. Provide a brief explanation of the table below the title. Any additional explanations, legends or explanations of non¬standard abbreviations, should be placed immediately below the table.

4. Discussion: This section is where you interpret your data and discuss how your findings compare with those of previous researchers. Go over the references of your literature review and see if you can determine how your data fits with what you have found.

You also need to account for the results, focusing on the mechanisms be¬hind the observation. Discuss whether or not your results support your original hypotheses. Negative findings are just as important to the de¬velopment of future ideas as the positive ones.

Importantly, there are not bad results. Science is not about right or wrong but about the continuing development of knowledge.

Discuss how errors may have been introduced into your study and what steps you took to minimise them, thus showing that you appreciate the limitations of your work and the strength of your conclusions. You should also consider the implications of the findings for future research and for clinical practice. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. Avoid claiming priority or alluding to work that has not been compared.

5. Referencing: The references are the foundation on which your report is built. Literature searches and reading of references should always be the starting point of your project. This section must be accurate and in¬clude all the sources of information you used.

In the Vancouver format, references are numbered consecutively as they appear in the text and are identified in the bibliography by numerals.

One article can have one author and 4 co-author. Last co-author is the mentor of the article or closest co-author of the paper." The authors' namer are fol-lowed by the title of the article; the title of the journal abbreviated ac-cording to the style of Index Medicus; the year of publication; the volume number; and the first and last page numbers.

References to books should give the names of any editors, place of publication, editor, and year.

In the text, reference numbers are given in superscript. Notice that issue number is omitted if there is continuous pagination through¬out a volume, there is space between volume number and page numbers, page numbers are in elided form (51-4 rather than 51-54) and the name of journal or book is in italics.The following is a sample reference:

Në tekst, numrat e referencave jepen me indeks të sipërm. Vëreni se çështja e numrave neglizhohet nëse ka numërtim të vazhdueshëm përg¬jatë gjithë vëllimit, ka hapësirë mes numrit të vëllimit dhe numrit të faqes, numrat e faqeve janë në këtë formë: 51-4 në vend të 51-54, dhe emri i revistës ose librit është në italic. Në vazhdim është një shembull i referencës:

Artikujt e revistave:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. *N Engl J Med* 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. *BMJ* 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. *Lancet* 1997;349: 1498-504.

Librat dhe tekste tjera:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. *National service framework for coronary heart disease*. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
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Shmangni përdorimin e abstrakteve si referenca; "të dhëna të papub-likuara" dhe "komunikime personale". Referencat e pranueshme, por ende të papublikuara lejohet të merren, vetëm nëse shënoni se janë "në shtyp".

6. Mirënjohjet: Ju mund të keni dëshirë të falënderoni njerëzit që ju kanë ndihmuar. Këto mund të rangohen prej atyre që ju kanë përkrahur me teknika eksperimentale deri tek ata që ju kanë këshilluar deri në bër¬jen e dorëshkrimit final.

7. Formati i fajllit të të dhënave për **ilustrimet** (**figurat**): JPG

Nëse përdoren fotografitë e pacientëve, qoftë subjekti, qoftë fotografitë e tyre nuk duhet të jenë të identifikuara, ato duhet të shoqërohen me lejen e shkruar nga ta për përdorimin e figurës. Format e lejuara janë në dispozicion nga redaksia.

Nëse fajllet e të dhënave janë shumë të mëdha për t'u dërguar me e-mail, rekomandohet dërgimi me CD në adresën tonë.

8. Legjendat për Ilustrimet (Figurat)

Legjenda e tabelës duhet të vendoset mbi tabelë. Referenca e një tabeleje, e cila është marrë nga ndonjë publikim tjetër, duhet të vendoset poshtë tabelës. (Është përgjegjësi e autorit të sigurojë lejen e ribotimit nga botuesit e atij botimi) Legjenda e figurës duhet të vendoset në fund të faqes. Referenca e figurës e marrë nga ndonjë tjetër publikim vendoset në fund të legjendës. (Leja e ribotimit duhet të sigurohet nga botuesi i këtij botimi).

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Avoid using as references abstracts; "unpublished data" and "personal communications". References to accepted but yet unpublished articles are allowed to be made, only if you note "in press".

6. Acknowledgements: You may wish to acknowledge people who have helped you. These can range from those who supported you with exper¬imental techniques to those who read or offered advice on your final manuscript.

7. Data file format for **illustrations** (**figures**): JPG

If photographs of patients are used, either the subjects should not be identifiable or their pictures must be accompanied by written permis-sion to use the figure. Permission forms are available from the Editor.

If data files are too big for transmission as an Email attachment submis¬sion of a CD to our address is recommended.

8. Legends for Illustrations (Figures)

The legend of a table has to be placed above the table. The reference of a table, which has been taken from another publication, must be placed below the table. (It is the author's responsibility to obtain the permission of reproduction from the publishers of the publication.) Figure legends are to be placed at the end of the paper. The reference of a figure taken from another publication stands at the end of the legend. (Permission of reproduction must be obtained from the publishers of this publication).