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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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REPRESENTATION OF MALIGNANT TUMORS OF THE TESTIS AND CORRELATION OF TUMOR MARKERS IN RELATION TO THE CLINICAL PICTURE AND THE FINDINGS OF ULTRASOUND, MAGNETIC RESONANCE AND COMPUTERIZED TOMOGRAPHY, OPERATED IN OUR INSTITUTION IN THE LAST 5 YEARS

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ABSTRACT

Introduction: Malignant tumors of the testicle are rare tumors that usually occur between the ages of 15 and 40. They represent about 1% in relation to other neoplasm and about 5% in relation to malignant tumors of the urogenital tract. In 2020, 74,458 new cases were registered worldwide. The incidence in recent years is about 3 to 12 cases per 100,000 men per year (1). Although serum tumor markers: alpha fetoprotein (AFP), beta human chorionic gonadotropin (bHCG), and lactate dehydrogenase (LDH), represent important parameters for diagnosis and postoperative monitoring of testicular germinal tumors, in clinical practice so far, they have shown that in a large percentage they are not strictly specific and they should be supplemented with other diagnostic procedures: Doppler ultrasonography, computerized tomography, magnetic resonance and percutaneous or open biopsy of the testicle (2,3).

Material and methods: At the Urology Department in the City General Hospital "8th of September" in Skopje, R. North Macedonia, in the last 5 years, 25 patients with malignant testicular tumors have been diagnosed and operated on. The study includes an analysis of the preoperative findings of serum tumor markers and their correlation in relation to the clinical picture and other diagnostic procedures for the early detection of neoplastic changes in the testicle. The obtained data are statistically processed and shown through mean value, percentage representation and graphic representation of the correlation between the parameters.

Aims: Determination of the relevance of serum tumor markers: alpha fetoprotein (AFP), beta human chorionic gonadotropin (bHCG), and lactate dehydrogenase (LDH) in the early detection of germinal malignant testicular tumors. Determination of the correlation of serum tumor markers of the testis with the findings obtained from the other diagnostic procedures: Doppler ultrasound examination, CT of the abdomen, pelvis and scrotum and MR of the scrotum. Determining the correlation between the preoperative findings of the serum tumor markers of the testis with the postoperative pathohistological findings and stage of the disease.

Results: From a total of 25 patients operated for malignant testicular tumor, the pathohistological findings in 12 (48%) showed that it was a pure seminoma, in 6 (24%) a mixed embryonal and Yolk Sac tumor, in 2 (8%) a mixed seminoma with embryonic carcinoma, in 2 (8%) mixed seminoma with choriocarcinom, in 2 (8%) teratoma and in 1(4%) pure embryonal carcinoma. From a total of 12 seminomas preoperatively elevated bHCG was found only in 2 patients (16.7%) and 3 (25%) patients with elevated values of lactate dehydrogenase (LDH) above 234 U/L, while in 7 patients (58.3%) tumor the markers were in normal values. From a total of 11 patients (44%) with mixed embryonal carcinoma, elevated values of alpha fetoprotein (AFP) were found preoperatively in only 3 patients (27.27%), while in 6 (54.54%) elevated values of lactate dehydrogenase were found the enzyme (LDH) (from 273 to 1562 U/L). In 2 patients (8%) with postoperative PTH finding of teratoma, elevated values of bHCG and LDH were found preoperatively. Preoperative "imaging" diagnostic findings showed high accuracy and selectivity in determining the presence of a neoplastic process in clinically suspicious testicular changes, namely: with Doppler ultrasound of vascularization

of the tumorous change in 23 patients (92%), in 17 (68%) with CT scan of the scrotum and retroperitoneum and in 23 (92%) a clearly positive finding of neoplasm on magnetic resonance, which is why no open or puncture biopsy was performed preoperatively in any of the patients. Postoperative pathohistological findings showed: stage 1A (pT1NoMo) in 4 patients (16%), stage 1B (pT2NoMo) in 17 patients (42.5%), in 2 patients (8%) benign tumor teratoma and in 2 (8%) metastatic tumor stage 4A (pT4N1,M1). Out of a total of 25 patients, metastatic disease was diagnosed preoperatively in 2 patients (8%). Postoperative death was determined in 2 (8%) patients. Five-year survival was found in 23 patients or 92% of patients. All patients received preventive chemotherapy postoperatively at the Oncology Clinic, and all 23 patients obtained normal values of serum markers. The average age of the patients is 37.48 years (the youngest is 26 and the oldest is 74).

Conclusion: The positive preoperative finding of bHCG in only 16.7% of patients with a postoperative pathohistological finding of pure seminoma, as well as AFP values found in only 27.27% of mixed embryonal carcinomas confirm the current practice that they are not strictly specific and reliable as parameters for diagnosing a neoplastic testis process and have a limited role in establishing the definitive diagnosis. Although the LDH enzyme is considered a non-specific marker present in up to 30% of testicular tumor patients (4,5), in our study it was shown to be a significant parameter for determining a high stage of malignancy and metastatic disease with values from 422 to 1562 U/L .

The high percentage of preoperative diagnostic accuracy of "imaging" diagnostic investigations ("Doppler" ultrasonography with an accuracy of 92%, CT of the scrotum and retroperitoneum with an accuracy of 68% and MR of the testis with an accuracy of 92%), in our practice so far, are showed that diagnostic methods are sufficient to establish an indication for surgical treatment without performing a percutaneous or open biopsy of the tumorous changes of the testis.

The high percentage of 5-year survival of 92%, as a result of the so-called multimodal treatment (orchifuniculectomy combined with preventive oncological therapy) and in our study was confirmed as the best method in the successful treatment of patients with malignant testicular tumors, diagnosed staged from pT1aNoMo to pT2bNoMo.

-The insufficient specificity and limitation of serum biomarkers indicates the need for the introduction of new so-called epigenetic markers such as microRNA-371a-3p, whose specificity is 94%, sensitivity 90.1% and percentage of predicting recurrent disease in 82% of patients.

Key words: testicular tumors, Alfaphetoprotein -AFP, Beta Choriogonadotropin - bHCG, Lactate Dehydrogenase - LDH, Color doppler ultrasonography, Magnetic Resonance, Computed Tomography, serum biomarkes.

INTRODUCTION

Malignant tumors of the testicle are rare tumors that usually occur between the ages of 15 and 40. They represent about 1% in relation to other neoplasm and about 5% in relation to malignant tumors of the urogenital tract. In 2020, 74,458 new cases were registered worldwide. The incidence in recent years is about 3 to 12 cases per 100,000 men per year (1). Although serum tumor markers: alpha fetoprotein (AFP), beta human chorionic gonadotropin (bHCG), and lactate dehydrogenase (LDH), represent important parameters for diagnosis and postoperative monitoring of testicular germinal tumors, in clinical practice so far, they have shown that in a large percentage they are not strictly specific and they should be supplemented with other diagnostic procedures: Doppler ultrasonography, computerized tomography, magnetic resonance and percutaneous or open biopsy of the testicle (2,3).

MATERIAL AND METHODS

At the Urology Department in the City General Hospital "8th of September" in Skopje, R. North Macedonia, in the last 5 years, 25 patients with malignant testicular tumors have been diagnosed and operated on. The study includes an analysis of the preoperative findings of serum tumor markers and their correlation in relation to the clinical picture and other diagnostic procedures for the early detection of neoplastic changes in the testicle. The obtained data are statistically processed and shown through mean value, percentage representation and graphic representation of the correlation between the parameters.

AIMS

- Determination of the relevance of serum tumor markers: alpha fetoprotein (AFP), beta human chorionic gonadotropin (bHCG), and lactate dehydrogenase (LDH) in the early detection of germinal malignant testicular tumors.

- Determination of the correlation of serum tumor markers of the testis with the findings obtained from the other diagnostic procedures: Doppler ultrasound examination, CT of the abdomen, pelvis and scrotum and MR of the scrotum.

- Determining the correlation between the preoperative findings of the serum tumor markers of the testis with the postoperative pathohistological findings and stage of the disease.

RESULTS

From a total of 25 patients operated for malignant testicular tumor, the pathohistological findings in 12 (48%) showed that it was a pure seminoma, in 6 (24%) a mixed embryonal and Yolk Sac tumor, in 2 (8%) a mixed seminoma with embryonic carcinoma, in 2 (8%) mixed seminoma with choriocarcinom, in 2 (8%) teratoma and in 1(4%) pure embryonal carcinoma. From a total of 12 seminomas preoperatively elevated bHCG was found only in 2 patients (16.7%) and 3 (25%) patients with elevated values of lactate dehydrogenase (LDH) above 234 U/L, while in 7 patients (58.3%) tumor the markers were in normal values. From a total of 11 patients (44%) with mixed embryonal carcinoma, elevated values of alpha fetoprotein (AFP) were found preoperatively in only 3 patients (27.27%), while in 6 (54.54%) elevated values of lactate dehydrogenase were found the enzyme (LDH) (from 273 to 1562 U/L). In 2 patients (8%) with postoperative PTH finding of teratoma, elevated values of bHCG and LDH were found preoperatively. Preoperative "imaging" diagnostic findings showed high accuracy and selectivity in determining the presence of a neoplastic process in clinically suspicious testicular changes, namely: with Doppler ultrasound of vascularization of the tumorous change in 23 patients (92%), in 17 (68%) with CT scan of the scrotum and retroperitoneum and in 23 (92%) a clearly positive finding of neoplasm on magnetic resonance, which is why no open or puncture biopsy was performed preoperatively in any of the patients. Postoperative pathohistological findings showed: stage 1A (pT1NoMo) in 4 patients (16%), stage 1B (pT2NoMo) in 17 patients (42.5%), in 2 patients (8%) benign tumor teratoma and in 2 (8%) metastatic tumor stage 4A (pT4N1,M1). Out of a total of 25 patients, metastatic disease was diagnosed preoperatively in 2 patients (8%). Postoperative death was determined in 2 (8%) patients. Five-year survival was found in 23 patients or 92% of patients. All patients received preventive chemotherapy postoperatively at the Oncology Clinic, and all 23 patients obtained normal values of serum markers. The average age of the patients is 37.48 years (the youngest is 26 and the oldest is 74).

DISCUSSION

The increasing incidence of malignant testicular tumors in the young population, especially characteristic of highly developed countries, represents a significant medical challenge and the need to use increasingly modern diagnostic procedures and biochemical analyses. The introduction of the so-called serum tumor markers for early diagnosis and postoperative monitoring of testicular tumors since 1970 represents a new quality in treatment. While the following are the basic tumor markers used in daily practice for diagnosing, prognosticating and monitoring the recurrence of the malignancy of germinal tumors: bHCG - Beta choroidal gonadotropin (glycoprotein of 38000 Daltons molecular mass, produced by syncytiotrophoblastic giant cells, mostly in the choroid cancer), Alphafetoprotein-AFP (glucoprotein with 70,000 Daltons, mol. mass, which is produced by the cells of the so-called Yolk Sac tumors and less often the cells of the embryonal carcinoma and the LDH-Lactate dehydrogenase enzyme, which is non-specific and is released from the cells after cell death.

Previous studies have shown that the two basic serum markers AFP and bHCG are not always elevated in germinal testicular tumors and that the frequencies of elevation are correlated with histology and tumor size (3,4,5). On the other hand, the LDH enzyme, although it has no validity in the preoperative differentiation of the malignant tumor, has a special diagnostic value for determining the advanced stages, that is, the metastatic disease or postoperative relapse of the neoplastic process.

Out of a total of 25 patients operated on at the Urology Department at the GOB "8th of September" in the last five years, the following types of testicular tumors were confirmed post-operatively pathohistologically: 12 seminomas (48%), 1 embryonal carcinoma (4%), 6 mixed embryonal carcinomas with elements of Yolk Sac tumor (24%), 2 mixed seminomas with embryonal carcinoma

(8%), 2 mixed embryonal carcinomas with elements of choriocarcinom (8%) and 2 teratomas (8%) (table 1).

Postoperative pathohistological finding	Number of patients	Percentage representation
Seminomas	12	48%
Mixed embryonal carcinoma with Yolk Sac tumor cells	6	24%
Mixed seminoma with embryonal carcinoma	2	8%
Mixed seminoma with choriocarcinoma	2	8%
Embrional carcinoma	1	4%
Teratomas	2	8%

Table No. 1. Types of testicular malignant tumors in the studied group according to pathohistological analysis

The average age of the operated patients in the studied group is 37.48 years, of which the youngest patient is 26 years old and the oldest is 74 years old.

The following clinical examinations were performed preoperatively on all patients: complete laboratory and biochemical blood analysis, basic hemostasis tests, serum tumor markers AFP, bHCG and LDH, color Doppler of the testis and funiculus spermaticus, CT of the pelvis, abdomen and retroperitoneum and MR on the scrotum. At the same time: out of a total of 12 seminomas preoperatively elevated bHCG was found in only 2 patients or 16.7% (57 mlU/ml and 69.7 mlU/ml), and in the rest normal values between 0.01 and 1.7 mlU were found / ml. In 3 (25%) patients with seminoma, elevated values of lactate dehydrogenase (LDH) above 234 U/L (356, 273 and 1562 U/L) were found, while in 7 patients with seminoma (58.3%) all tumor markers were in normal values (bHCG < 10 mlU/ml, AFP from 0 to 6.72 u/ml and LDH from 81 to 234 U/L).

From a total of 11 patients (44%) with mixed embryonal carcinoma, elevated values of alpha fetoprotein (AFP) were found preoperatively in only 3 patients, i.e. 27.27% (21.8 u/ml, 152 u/ml and 830 u/ml) while in 6 (54.54%) elevated values of lactate dehydrogenase enzyme (LDH) were found (from 273 to 1562 U/L). In two patients with mixed tumor, all serum markers were with normal values. In 2 patients (8%) with postoperative PTH finding of teratoma, elevated values of bHCG (>57 mlU/ml) and LDH (273 U/L) were found preoperatively (table no. 2).

Type of tumor	Elevated values of AFP (u/ml), No. of patients (percentage representation)	Elevated bHCG values (mlU/ml No. of patients (percentage representation)	Elevated values of LDH (U/L) no. of patients (percentage representation)	Normal values of all three tumor markers No. of patients (percentage representation)
Seminomas(12)	0 (0%)	2 (16,7%)	3(25%)	7 (58,3%)
Embrional carcinoma (1)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
Mixed tumor with Yolk Sac or ChorioCa (11)	3 (27,27%)		6(54,54%)	2 (8%)
Teratomas (2)	0 (0%)	1 (4%)	1 (4%)	0 (0%)

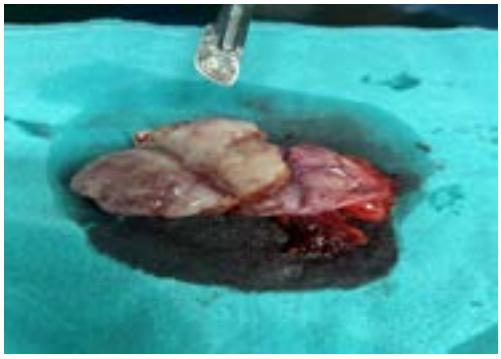
Table no. 2 - Preoperative findings of serum tumor markers in the study group

Compared to the last published data, where the percentage of positive findings of AFP in embryonal and mixed germinal malignant tumors varies in various studies from 10 to 60%, that is, on average 28% (4,5,6), the elevated values in our study group of 27, 27% fully coincide with previous studies in other countries. The relationship between published data on elevated bHCG values in seminomas in 8 to 35% of patients, compared to 16.7% in our study group, confirms the previous experience that serum markers are not always relevant for establishing a diagnosis or differential diagnosis of malignant tumors. of the testicle. The high percentage (58.3%) of patients with malignant testicular tumors in which preoperatively all three tumor markers are normal values indicates the need for mandatory use of other diagnostic procedures, including fine-needle or open biopsy of suspicious testicular changes.

In contrast to the low percentage of relevance of the two basic tumor markers bHCG and AFP, the positive finding of LDH in 10 patients, i.e. 40% of the total of 25 operated patients, and the high values in the advanced stage of seminoma and mixed tumor (from 273 to 1562 U/L), in our study group it turned out to be a very relevant prognostic parameter.

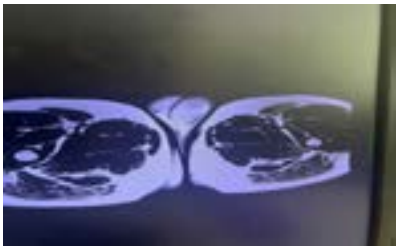
The analysis of the correlation between the size of the tumor change (which in our study group ranged from 1 to 6 cm in diameter) and the clinical picture of the patient was found to be irrelevant in this study. An example of this are two patients in whom, although the size of the tumor was from 1 to 2 cm, they had a severe clinical picture, with numerous metastases in the lungs and a rapid death immediately after the orchifuniculectomy (Figure 1, 2).

Picture No. 1. Testicular tumor with a diameter of 1.5 cm in a 42-year-old patient with metastatic changes in the lungs, operated on in the GOB "8mi Septemvri"-Skopje



Picture no. 2. Seminoma with a diameter > 6cm in a 29-year-old patient, with bHCG 69.7 mlU/ml, operated in the GOB "8th of September"-Skopje

The so-called diagnostic recording "imaging" diagnostic procedures play a key role especially in the preoperative phase, that is, in the assessment of the primary tumor before performing orchiectomy, as well as in the assessment of the possible existence of regional or distant metastases. Today, it is a common practice to use the so-called multimodal imaging in which ultrasound with or without color Doppler and computed tomography (CT) are used in combination for initial diagnosis and Magnetic resonance (ordinary or multiparametric) for differentiating the type of testicular tumoral change (Figure no. 3).



Picture no. 3. MRI in a 30-year-old patient with a tumor on the left testicle (GOB "8mi Septemvri" - Skopje

The analysis of each of the cases in our study group through the used diagnostic recordings using the multimodal principle of diagnosis showed that this approach has a very high diagnostic value and accuracy, compared to the results of serum tumor markers. Preoperative "imaging" diagnostic findings showed high accuracy and selectivity in determining the presence of a neoplastic process in clinically suspicious testicular changes, namely: with Doppler ultrasound of vascularity of the tumorous change in 23 patients (92%), in 17 (68%) with CT scan of the scrotum and retroperitoneum and in 23 (92%) a clearly positive finding of neoplasm on magnetic resonance, which is why no open or puncture biopsy was performed preoperatively in any of the patients.

CONCLUSION

- The positive preoperative finding of bHCG in only 16.7% of patients with postoperative pathohistological findings of pure seminoma, as well as the AFP values found in only 27.27% of mixed embryonal carcinomas confirm the current practice that they are not strictly specific and reliable as parameters for diagnosing a neoplastic testis process and have a limited role in establishing the definitive diagnosis. Although the LDH enzyme is considered a non-specific marker present in up to 30% of testicular tumor patients (4,5), in our study it was shown to be a significant parameter for determining a high stage of malignancy and metastatic disease with values from 422 to 1562 U/L .

- The high percentage of preoperative diagnostic accuracy of "Imiging" diagnostic investigations ("Doppler" ultrasonography with an accuracy of 92%, CT of the scrotum and retroperitoneum with an accuracy of 68% and MR of the testis with an accuracy of 92%), in our practice so far are showed that they are sufficient diagnostic methods for setting an indication for operative treatment without performing a percutaneous or open biopsy of the tumorous changes of the testis.

- The high percentage of 5-year survival of 92%, as a result of the so-called multimodal treatment (orchifuniculectomy in combination with preventive oncology therapy) and in our study it was confirmed as the best method in the successful treatment of patients with malignant testicular tumors, diagnosed in stages from pT1aNoMo to pT2bNoMo.

- The insufficient specificity and limitation of serum biomarkers indicates the need for the introduction of new so-called epigenetic markers such as microRNA-371a-3p, whose specificity is 94%, sensitivity 90.1% and percentage of predicting recurrent disease in 82% of patients.

Key words: testicular tumors, Alfaphetoprotein -AFP, Beta Choriogonadotropin - bHCG, Lactate Dehydrogenase - LDH, Color doppler ultrasonography, Magnetic Resonance, Computed Tomography, serum biomarkes.

REFERENCES

1. Barber N, Ali A. ed. Urologic Cancers. Exon Publications. Brisbane (AU) ; 2022 Sep 12. ISBN-13: 978-0-6453320-5-6.
2. Murray M. J., Huddart R. A., Coleman N., "The present and future of serum diagnostic tests for testicular germ cell tumours," Nature Reviews Urology, vol. 13, no. 12, pp. 715–725, 2016.
3. Lange P. H., McIntire K. R., Waldmann T. A., Hakala T. R., Fraley E. E., "Serum alpha fetoprotein and human chorionic gonadotropin in the diagnosis and management of nonseminomatous germ-cell testicular cancer," The New England Journal of Medicine, vol. 295, no. 22, pp. 1237–1240, 1976.
4. Bassoulet J., Pabot du Chatelard P., Ricordel I., Auberget J. L., Guillemot M. C., Merrer J. et al., "Biological markers and germinal tumors of the testis. Value and limitations of the assay of chorionic gonadotrophin hormone and alpha-fetoprotein," Journal of Urology, vol. 94, no. 8, pp. 393–396, 1988.
5. Kausitz J., Ondrus D., Belan V., Matoska J., "Monitoring of patients with non-seminomatous germ cell tumors of the testis by determination of alpha-fetoprotein and beta-human chorionic gonadotropin levels and by computed tomography," Neoplasma, vol. 39, no. 6, pp. 357–361, 1992.
6. Javadpour N., "Current status of tumor markers in testicular cancer. A practical review," European Urology, vol. 21, no. 1, pp. 34–36, 1992.
7. Kulkarni J. N., Kamat M. R., "Value of tumor markers in nonseminomatous germ cell tumor of the testis," European Urology, vol. 24, no. 2, pp. 166–171, 1993.
8. Germà-Lluch J. R., Garcia del Muro X., Maroto P. et al., "Clinical pattern and therapeutic results achieved in 1490 patients with germ-cell tumours of the testis: The experience of the Spanish Germ-Cell Cancer Group (GG)," European Urology, vol. 42, no. 6, pp. 553–563, 2002.
9. Neumann A., Keller T., Jocham D., Doehn C., "Human placental alkaline phosphatase (hPLAP) is the most frequently elevated serum marker in testicular cancer," Aktuelle Urologie, vol. 42, no. 5, pp. 311–315, 2011
10. Dieckmann K.P., Düe W., Bauer H. W., "Seminoma testis with elevated serum Beta-HCG-a category of germ-cell cancer between seminoma and nonseminoma," International Urology and Nephrology, vol. 21, no. 2, pp. 175–184, 1989.
11. Fosså A., Fosså S. D., "Serum lactate dehydrogenase and human choriogonadotrophin in seminoma," British Journal of Urology, vol. 63, no. 4, pp. 408–415, 1989.
12. Rüther U., Rothe B., Grunert K. et al., "Role of human chorionic gonadotropin in patients with pure seminoma," European Urology, vol. 26, no. 2, pp. 129–133, 1994.
13. 13 Weissbach L., Bussar-Maatz R., Mann K., "The value of tumor markers in testicular seminomas. Results of a prospective multicenter study," European Urology, vol. 32, no. 1, pp. 16–22, 1997.
14. National Cancer Institute Surveillance, Epidemiology and End Results Program. SEER Stat Fact Sheets: Testicular Cancer. [(accessed on 3 May 2022)];
15. Mittal P.K., Abdalla A.S., Chatterjee A., Baumgarten D.A., Harri P.A., Patel J., Moreno C.C., Gabriel H., Miller F.H. Spectrum of Extratesticular and Testicular Pathologic Conditions at Scrotal MR Imaging. Radiographics. 2018;38:806–830. doi: 10.1148/rg.2018170150.
16. Ghazarian A.A., Trabert B., Devesa S.S., McGlynn K.A. Recent trends in the incidence of testicular germ cell tumors in the United States. Andrology. 2015;3:13–18. doi: 10.1111/andr.288.
17. Petterson A., Richiardi L., Nordenskjold A., Kaijser M., Akre O. Age at surgery for undescended testis and risk of testicular cancer. N. Engl. J. Med. 2007;356:1835–1841. doi: 10.1056/NEJMoa067588.
18. La Vignera L., Calogero A.E., Condorelli R., Marziani A., Cannizzaro M.A., Lanzafame F., Vicari E. Cryptorchidism and its long-term complications. Eur. Rev. Pharmacol. Sci. 2009;13:351–356.
19. Richenberg J., Belfield J., Ramchandani P., Rocher L., Freeman S., Tsili A.C., Cuthbert F., Studniarek M., Bertolotto M., Turgut A.T., et al. Testicular microlithiasis imaging and follow-up: Guidelines of the ESUR scrotal imaging subcommittee. Eur. Radiol. 2015;25:323–330. doi: 10.1007/s00330-014-3437-x.
20. Kreydin E.I., Barrisford G.W., Feldman A.S., Preston M.A. Testicular Cancer: What the radiologist needs to know.

Am. J. Roentgenol. 2013;200:1215–1225. doi: 10.2214/AJR.12.10319.

21. Marko J., Wolfman D.J., Aubin A.L., Sesterhenn I.A. Testicular seminoma and its mimics: From the Radiologic Pathology. Archives. Radiographics. 2017;37:1085–1098. doi: 10.1148/rg.2017160164.

Original scientific paper

THE CONSEQUENCES OF COVID 19 IN PATIENTS WITH LARYNGEAL CANCER

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ABSTRACT

Background: The global pandemic, triage and telemedicine have contributed to late diagnosis of patients with advanced carcinoma of the larynx. Warming and humidification of air in this type of patient are completely cut off and lost, which devotes to the occurrence of chronic lung disease.

Aim: Representing patients with laryngeal carcinoma who became infected with Covid 19, recognizing the severity of Covid 19 manifestation and its outcome.

Material and methods: University ENT Clinic in Skopje was Covid Center for treatment and care of patients with Covid 19. A total of 405 patients with moderate and severe clinical picture were hospitalized in the period from 2019 to 2021. There were 8 patients with laryngeal cancer.

Results: In all 8 patients auscultatory, oxygen saturation, CT scan presents massive interstitial pneumonia, typical of Covid 19. Four patients who survived had high oxygen saturation, low CRP and laryngectomy performed more than 10 years ago. The other four patient who failed the disease had low saturation, high CRP, and total laryngectomy which was performed not more than 4 years ago.

Conclusion: According to our experience, the reasons for the presented number of lethal outcome cannot be fully determined that is in line of the professional literature, which was confirmed in this case. It is estimated that a lack of tracheostomal warmers and humidifiers leads to increased mortality in cancer patients, especially in Covid 19 pandemic. Application of protection and rehabilitation protocols in these patients is necessary to improve the quality of life and reducing the risk factor for Covid disease 19.

Key words: Covid-19, advanced cancer, pneumonia, survival rate, tracheostoma

NTRODUCTION

The routine, way and style of living have completely changed with the emergence of the pandemic Covid 19. The global pandemic, triage and telemedicine have contributed to the late diagnosis of patients with an advanced stage of the carcinomatous disease (1, 2). The terminal stage of the disease has significantly impaired the quantity and quality of life in those patients. Patients who are immunosuppressed, including oncology patients, have a higher risk of diseases with Covid 19 and are often accompanied by concomitant comorbidities (3,4). In advanced stages of laryngeal cancer, it is necessary to provide a permanent tracheostomal opening. Thus, the upper respiratory tract is completely separated from the lower respiratory tract. The nose and its primary physiological function of mucociliary clearance, warming and moistening of the air in this type of patients are completely cut of (5,6). Covid 19 is strongly associated with rapid progression of acute respiratory distress leading to include intensive care and therapy. (7, 8, 9)

MATERIAL AND METHODS

University Clinic for Ear, Nose and Throat was a Covid center for the treatment and care of patients with Covid 19. Four hundred and five patients with medium and severe clinical symptoms were hospitalized in the ENT CLINIC Covid center. Of them, twenty-six were patients with oncological diseases. There were eight patients with laryngeal cancer.

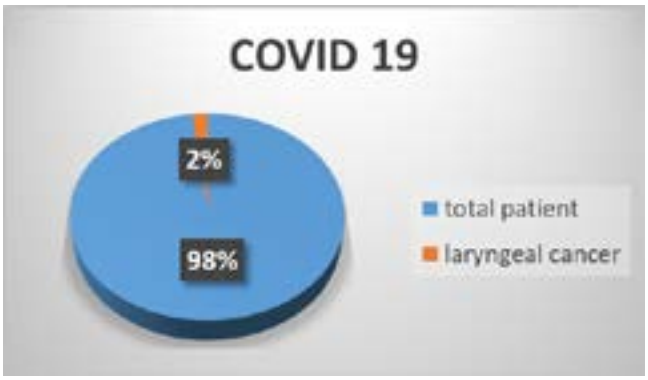
In this retrospective study, we present patients with laryngeal cancer who required hospitalization. Inclusion criteria: nasal swab and tracheostomal opening for Covid 19 is positive, verified cancer of the larynx. Exclusion criteria: neoplasms of other origins, patients who have a positive smear during hospitalization. In each patient in the inclusion criteria we contain a statement indicating patient permission for using their data information and clearance by the institute research or ethics committee.

Daily measurements of vital parameters (blood pressure, pulse, temperature, saturation, respiration) were performed for each patient. Auscultation was performed every day. Complete laboratory analyzes of: degradation products, hematological, electrolyte, protein and enzyme status were performed every 2 days. Analysis of hemostasis and dimers was also carried out. Regarding imaging studies, chest CT or lung X-ray were performed in each patient. All patients underwent endoscopic evaluation through flexible and rigid tracheobronchoscopy as well as daily tracheobronchial lavages. From the medical detail records, we retrospectively tracked demographic, epidemiologic, clinical, and surgical information. The complete medical documentation in PHI UK for Ear, Nose and Throat is attached in ENT clinic. Throw-out that period; it had been completely document of each stage of the disease from the patients.

RESULTS

University ENT Clinic in Skopje was Covid center for treatment and care of patients with Covid 19. A total of 405 patients with moderate and severe clinical picture were hospitalized in the period from 2019 to 2021. There were 8 patients with laryngeal cancer.

Diagram 1: contribution of patient in Covid 19 intensive care unit.



In this retrospective study, we showed eight patients with laryngeal cancer infected with COVID 19 who needed to be hospitalized. Middle aged of the patient was 70 years old. None of the patient have provox prothesis. Four patients underwent total laryngectomy, block dissection and radiotherapy an average of 7 years ago, and the other four patients underwent tracheotomy with verified laryngeal cancer an average of 6 months ago. Seven patient were male gender and only one patient was female gender. At the moment when patients were hospitalized at the ENT clinic, two patient have had saturation 95 % and the other six patient below 90%. In terms of symptomatology: one patient diarrhea, 5 patients fever and dry cough, 1 patient throat and chest pain, 1 patient bleeding from the tracheostomal opening.

Table 1. Signs and symptoms

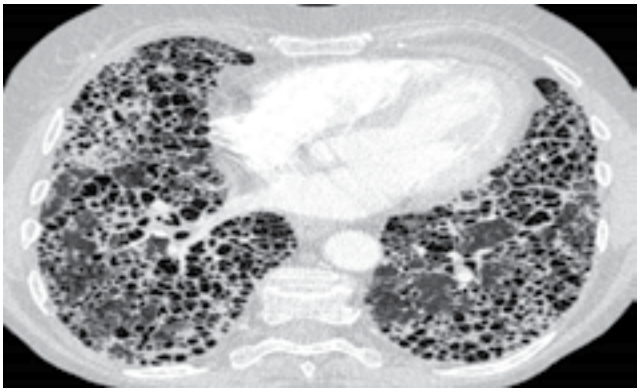
Sings and symptoms	1	2	3	4	5	6	7	8
diarrhea	x							x
fever	x	x	x	x	x			x
Dry cough	x	x		x	x	x	x	
Bleeding through tracheostoma						x		
Pain in throat				x	x		x	x
Pain in chest					x	x		

Regarding the endoscopic evaluation, a flexible endoscopic evaluation along the tracheostomal opening was realized and performed in all patients. Aspiration of secretion and removal of crusted masses was performed in all patients.

Our patients had accompanying comorbidities: 3 patients had diabetes mellitus type 2, 1 obesity, 1 operated on

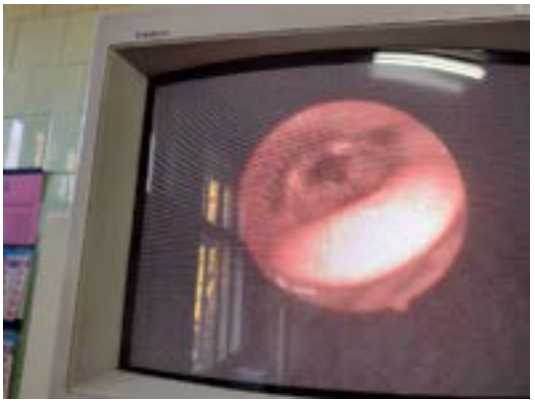
the abdominal aorta, 1 after previous infarction, 1 after empyema of the pleura, 1 after malignant melanoma of the forearm. Regular control laboratory analyzes were carried out, where they are followed in detail: we have an increase in d dimers in all patients. Patients with a fatal outcome of the disease have a deterioration of the electrolyte, protein, and enzyme status as well as degradation products. In all 8 patients, pneumonia typical of Covid 19 was observed, in 2 it was with a milder clinical picture. In all 8 patients with laryngeal cancer who had a tracheostomal opening, auscultatory findings, saturation, CT or chest X-ray findings were in favor of massive interstitial pneumonia, typical of Covid 19 .

icture 1: CT scan COVID 19 pneumonia from out patient I.G



Immediately on admission, oxygen support through a tracheostomal opening and aerosol administration of mucolytics was carried out in all patients. Broad-spectrum parenteral antibiotic therapy, anticoagulant, gastroprotective, multivitamin therapy, corticotherapy A tracheobronchial aspirate was taken for microbiological analysis, to rule out a possible superinfection, but it turned out to be negative in all patients (13).

Picture 2: laryngeal carcinoma, from our patient ENT ambulance



n all patients, during their hospitalization, tracheobronchial controls were performed to evaluate whether the given therapy gives progress in relation to the local finding, whether there is airway obstruction as well as the removal of crusted changes. All patients underwent aspiration of secretions and removal of crustose masses through tracheobronchial trunk.

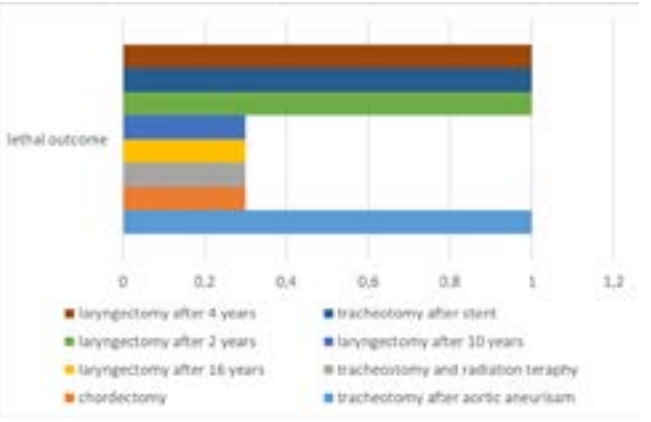
Rigid bronchoscopy was required in 5 patients. The biopsy material from 1 patient in terms of histopathological verification showed erosive chronic inflammation.

On average patient have had hospital day stay for 9 to 14 days.

Two patients, one patient underwent chordectomy, and the other patient underwent radiation therapy as a therapeutic modality, with a milder clinical picture and a good outcome of the disease. Two patients after surgical treatment of total laryngectomy with bilateral block dissection more than 10 years ago, managed to survive the disease. Two patients, after operative treatment total laryngectomy with bilateral block dissection, which was performed no more than 4 years ago and two tracheotomized patients, with accompanying comorbidities aortic aneurysm and stent at admission with low saturation 83% and high SRP 130, failed to survive the disease.

Patients with a lethal outcome of the disease have high rate of electrolyte, protein, enzyme status and degradation products as well as low saturation, prolonged hospital stay and massive crustose change along tracheobronchial trunk.

Table 2: The lethal outcome and the type of the patient after treatment



DISCUSSION

In patients with a tracheostomal opening, the risk of infection multiplies. Aerosols with their dissemination fall directly on the trachea and lower respiratory tract. There are recommendations for post-operative care in the world, but there was still no official protocol for their care. The Covid 19 pandemic is an enigma whose consequences we have yet to describe.(10, 11, 12) Although patients with laryngeal cancer represent a relatively small group of subjects, our experience is necessary to continue to understand the consequences of Covid 19 on this group of patients regardless of their treatment and outcome of the disease (13, 14,15).

In our retrospective study, we presented 8 patients with inflammation of the tracheobronchial trunk, development of interstitial pneumonia and its manifestation. These patients also have concomitant comorbidities that further influence the further outcome of the disease.

Covid 19 develops crusted changes along the tracheobronchial stem that obstruct the breathing lumen. Management of tracheobronchial tree obstruction through bronchoalveolar lavage and rigid tracheobronchoscopy to establish an airway is mandatory (16). Panderno et al in their report of 2 laryngectomy patients presented respiratory distress with bilateral pneumonias and tracheal inflammations (17). In the study of Fernández, it shows us that daily flexible tracheobronchoscopy reduces the risk of acute airway obstruction by preventing the development of bilateral pneumonias and further deterioration of the outcome in this group of patients (18). Weger showed signs of tracheobronchitis in covid 19 patients detected by lung scintigraphy (19).

The patient in who had bleeding from the tracheostomal opening, is the same patient in whom the biopsy material shows us erosive strong horn inflammation, biopsy material which is typical for covid 19. His fatal outcome also confirms the seriousness of approach in this group of patients.

CONCLUSION

The Ear, Nose and Throat Clinic had the opportunity, in a multidisciplinary approach of anesthesiologists and pulmonologists, to provide adequate care for this type of patients (20,21). According to the professional literature, and it is confirmed in our experience, it is not possible to fully determine the reasons for a high percentage of fatal outcome in this group of patients (22). It is estimated that the lack of tracheostomal warmers and air humidifiers leads to increased mortality in oncology patients, especially in the conditions of the Covid 19 pandemic (23,24). Compliance with the recommendations for protection in terms of social distance, regular hygiene of the tracheostomal opening and the vocal prostheses, as well as the application of a mask and protection of the tracheostomal opening are necessary (25). Application of protection and rehabilitation protocols for these patients in pandemic conditions is necessary to improve the quality of life and reduce the risk factor of getting sick with Covid 19 (26).

REFERENCES

1. Tevetoğlu, Fırat, Sinem Kara, Chinara Aliyeva, Rafet Yıldırım, and H. Murat Yener. "Delayed presentation of head and neck cancer patients during COVID-19 pandemic." European Archives of Oto-Rhino-Laryngology 278, no. 12 (2021): 5081-5085.
2. Singh, Arpana, Abhishek Bhardwaj, Nivedhan Ravichandran, and Manu Malhotra. "Surviving COVID-19 and multiple complications post total laryngectomy." BMJ Case Reports CP 14, no. 7 (2021): e244277.
3. Rygalski, Chandler J., Songzhu Zhao, Antoine Eskander, Kevin Y. Zhan, Edmund A. Mroz, Guy Brock, Dustin A. Silverman et al. "Time to surgery and survival in head and neck cancer." Annals of surgical oncology 28, no. 2 (2021): 877-885.
4. Venkatasai, Jeyaanth, Christopher John, Satish Srinivas Kondavetti, Mallika Appasamy, Lakshminarasimhan Parasuraman, Ravichandran Ambalathandi, and Hemavathi Masilamani. "Impact of COVID-19 Pandemic on Patterns of Care and Outcome of Head and Neck Cancer: Real-World Experience From a Tertiary Care Cancer Center in India." JCO Global Oncology 8 (2022): e2100339.
5. Galloway, Thomas J., Luiz Paulo Kowalski, Leandro L. Matos, Gilberto Castro Junior, and John A. Ridge. "Head and neck surgery recommendations during the COVID-19 pandemic." The Lancet Oncology 21, no. 9 (2020): e416.
6. Santos CG, Bergmann A, Coça KL, Garcia AA, Valente TC. Olfactory function and quality of life after olfaction rehabilitation in total laryngectomees. Codas. 2016 Nov-Dec;28(6):669-677. Portuguese, English. doi: 10.1590/2317-1782/20162015255. Epub 2016 Nov 16.

PMID: 27849216

7. Nittala, Mary, Eswar Mundra, Maria Smith, William Woods, Robert Hamilton, Gina Jefferson, Lana Jackson, and Srinivasan Vijayakumar. "Improved Clinical Outcomes with Shorter Intervals between Surgery and Postoperative Radiotherapy in T4 Laryngeal Cancers." International Journal of Radiation Oncology, Biology, Physics 108, no. 2 (2020): E40.
8. Nishiya Y, Mori E, Akutsu T, Takeshita N, Kessoku H, Shimura E, Otori N. A comparison between sniffing and blowing for olfactory testing before and after laryngectomy. Eur Arch Otorhinolaryngol. 2022 Mar 29. doi: 10.1007/s00405-022-07343-5. Epub ahead of print. PMID: 35348858
9. Vergara J, Starmer HM, Wallace S, Bolton L, Seedat J, de Souza CM, Freitas SV, Skoretz SA. Swallowing and Communication Management of Tracheostomy and Laryngectomy in the Context of COVID-19: A Review. JAMA Otolaryngol Head Neck Surg. 2020 Oct 15. doi: 10.1001/jamaoto.2020.3720. Epub ahead of print. PMID: 33057590.
10. Patil, Vijay, Vanita Noronha, Pankaj Chaturvedi, Kaustav Talapatra, Amit Joshi, Nandini Menon, Durgatosh Pandey, and Kumar Prabhash. "COVID-19 and head and neck cancer treatment." Cancer Research, Statistics, and Treatment 3, no. 5 (2020): 15.
11. Chuang, Hung-Jui, Ming-Yen Hsiao, Tyng-Guey Wang, and Huey-Wen Liang. "A multi-disciplinary rehabilitation approach for people surviving severe COVID-19—a case series and literature review." Journal of the Formosan Medical Association (2022).
12. Patel, Tirth R., Joshua E. Teitcher, Bobby A. Tajudeen, and Peter C. Revenaugh. "Disparate nasopharyngeal and tracheal COVID-19 diagnostic test results in a patient with a total laryngectomy." Otolaryngology–Head and Neck Surgery 163, no. 4 (2020): 710-711
13. Hennessy, Max, Darrin V. Bann, Vijay A. Patel, Robert Saadi, Greg A. Krempl, Daniel G. Deschler, Neerav Goyal, and Karen Y. Choi. "Commentary on the management of total laryngectomy patients during the COVID- 19 pandemic." Head & neck 42, no. 6 (2020): 1137-1143.
14. Varghese JJ, Aithal VU, Rajashekhar B. Self-care and clinical management of persons with laryngectomy during COVID-19 pandemic: a narrative review. Support Care Cancer. 2021 Dec;29(12):7183-7194. doi: 10.1007/s00520-021-06333-3. Epub 2021 Jun 28. PMID: 34181072; PMCID: PMC8236747
15. Searl J, Kearney A, Genoa K, Doyle PC. Clinical Experiences of People With a Laryngectomy During the SARS COVID-19 Pandemic. Am J Speech Lang Pathol. 2021 Nov 4;30(6):2430-2445. doi: 10.1044/2021_AJSLP-21-00117. Epub 2021 Oct 19. PMID: 34665653.
16. Kearney A, Searl J, Erickson-DiRenzo E, Doyle PC. The Impact of COVID-19 on Speech-Language Pathologists Engaged in Clinical Practices With Elevated Coronavirus Transmission Risk. Am J Speech Lang Pathol. 2021 Jul 14;30(4):1673-1685. doi: 10.1044/2021_AJSLP-20-00325. Epub 2021 Jun 23. PMID: 34161739.
17. Paderno, Alberto, Milena Fior, Giulia Berretti, Francesca Del Bon, Alberto Schreiber, Alberto Grammatica, Davide Mattavelli, and Alberto Deganello. "COVID-19 and total laryngectomy—a report of two cases." Annals of Otology, Rhinology & Laryngology 130, no. 1 (2021): 104-107.
18. Fernandez, Ignacio, Federico Spagnolo, Sara Valerini, Francesco Mattioli, Alessandro Marchioni, and Gabriele Molteni. "SARS-CoV-2 tracheitis in laryngectomized patients: a consecutive case-series study." Authorea Preprints (2021).
19. Antoine Verger, Achraf Bahloul, Saifeddine Melki, et al. Tracheobronchitis signs observed on ventilation lung scintigraphy during the course of COVID-19 infection. European Journal of Nuclear Medicine and Molecular Imaging. https://doi.org/10.1007/s00259-020-04834-7
20. Soldin, D., Grier, W.R., Leong, K., Holden, V.K., Pickering, E. and Sachdeva, A., 2021. Removal of an Aspirated Foreign Body from a Post-Laryngectomy Patient via Flexible Bronchoscopy. In TP38. TP038 INTERESTING AND CHALLENGING CASES IN INTERVENTIONAL PULMONOLOGY (pp. A2202-A2202). American Thoracic Society.
21. Norton, Alice, Piero Olliaro, Louise Sigfrid, Gail Carson, Giuseppe Paparella, Claire Hastie, Charu Kaushic, Geneviève Boily-Larouche, Jake C. Suett, and Margaret O'Hara. "Long COVID: tackling a multifaceted condition requires a multidisciplinary approach." The Lancet Infectious Diseases 21, no. 5 (2021): 601-602.
22. Bertolin, Andy, Marco Lionello, Valentina de Robertis, Francesco Barbara, Francesco Cariti, and Michele Barbara. "Fragility and contagiousness of the total laryngectomy patient in the COVID-19 pandemic." ACTA Otorhinolaryngologica Italica 42 (2022): S68-S72.
23. Sarsfield, Erin, Melissa Montano, Karen Choi, and Neerav Goyal. "Laryngectomy care in the COVID-19 era." JAMA Otolaryngology–Head & Neck Surgery 146, no. 8

(2020): 776-776.

24. Kligerman, Maxwell P., Neelaysh Vukkadala, Raymond KY Tsang, John B. Sunwoo, F. Christopher Holsinger, Jason YK Chan, Edward J. Damrose, Ann Kearney, and Heather M. Starmer. "Managing head and neck cancer patients with tracheostomy or laryngectomy during the COVID-19 pandemic." Head & Neck 42, no. 6 (2020): 1209-1213.
25. Goldman, Richard A., Brian Swendseid, Jason YK Chan, Michelle Lewandowski, Jacqueline Adams, Monica Purcell, and David M. Cognetti. "Tracheostomy management during the COVID-19 pandemic." Otolaryngology–Head and Neck Surgery 163, no. 1 (2020): 67-69.
26. Pernambuco, Leandro, Ana Maria Bezerra de Araujo, and José Márcio Carvalho da Silva. "Specific management of total laryngectomy patients during the COVID-19 pandemic in the Brazilian reality." (2020).

Original scientific paper

FORENSIC COMPARATIVE ANALYSIS OF ETIOLOGICAL FACTORS OF MEDICAL MALPRACTICE

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ABSTRACT

Introduction: The concept of medical malpractice, which is accountable before the law, was introduced for the first time in the year 1200 in Roman law, and the earliest litigation of a reported case of medical malpractice was registered in 1374 in England. According to a Johns Hopkins study in 2023, more than 250,000 deaths each year are due to medical errors. This number makes medical malpractice the third leading cause of death in the United States, behind heart disease and cancer, and it has increased by 50,000 cases in the last five years alone. According to the latest statistics, in all developed countries, the number of medical errors is dominated by three dominant factors: a wrong diagnosis, a surgical error and the prescribing of inadequate therapy (1). Today Lathology, which deals with the causes of medical errors, divides the factors into two groups: external and internal. External factors are not related to the human factor and include: working conditions, technical equipment, poor administrative and legal management, poor planning, communication errors, inadequate education, etc. Internal or human factors can be objective and subjective and directly depend on the cognitive and sensory-mechanical abilities of the medical practitioner.

Materials and methods: The study includes forensic medical expertise and analysis of 44 cases related to complaints by patients or their relatives about the existence of medical error in the treatment by the general practitioner. The analysis is retrospective for the period 2018 and 2019. The forensic expert reports were made at the Institute for Forensic Medicine, Criminology and Medical Deontology, at the University “St. Cyril and Methodius” in Skopje.

The subjects are analyzed according to the etiology, demographic representation and the possible cause-and-effect relationship of the factors for the occurrence of the medical error. The data are presented statistically through percentage representation, mean value, tabular and graphic display.

Objectives: Determination of the most common etiology for the occurrence of medical errors in the examined group in the last two years, Determination of the percentage representation of internal (human) and external factors in the occurrence of medical errors in our study group. Comparative analysis of the types and etiological representation in the occurrence of medical errors in our study group in relation to the data published in the last reference studies. Determining preventive measures to reduce the number of medical errors in our health system based on the analysis of the cause-and-effect relationship of the factors causing the death or disability of the patients.

Results: Out of a total of 44 cases related to medical malpractice, in 36 cases a forensic medical examination was done by order of the Prosecutor’s Office, and in 8 cases by a private request by the family of the injured or deceased. The average age of the studied group is 38.9 years, of which 27 (61.3%) are male and 17 (38.7%) are female. Six subjects or 13.6% of the examined group refer to children from 0 to 5 years old. According to the etiology, the largest number of forensic reports in two years were made in connection with medical errors in gynecology and obstetrics, a total of 13 or 29.54%, in internal medicine 9 or 20.45%, orthopedics 4 or 9.09%, ophthalmology 4 (9.09%), abdominal surgery 3 (6.81%) and pediatrics 2 (4.54%). Therefore, the death rate from medical error in our study group is 17% per year. From a total of 44 cases, the existence of some kind of medical error was determined in 33 cases or 72.72%. Absence of medical error was determined in 12 cases or 27.27%. A total of 47 errors related

to the treatment of injured patients were determined. 35 (79.54%) medical errors were determined as a result of human factors and 9 medical errors as a result of omissions in the organization of the health organization's work.

Conclusion: The analysis of the type of medical branches for which forensic medical expertise is most often required for the possible existence of a medical error, in our examined group for a period of two years, is mostly related to: gynecology and obstetrics, internal medicine branches gastroenterology and nephrology, orthopedics and ophthalmology. In 72.72% of the cases, the forensic-medical analysis showed a high percentage of the existence of some kind of medical error. At the same time, the representation of the so-called An "internal" or human factor was determined in 80.85%, and an "external" factor that did not occur due to human error was determined in 19.15% of the total number of identified errors that led to the deterioration of the health condition or death in patients. The comparative analysis in relation to the available literature, where the cause of death due to medical error occurs annually in an average of 9.5% of cases (2,3,4), compared to 34% in our study group and the most common medical error due to omission or an untimely diagnosis in 32% (2,3,4), in contrast to the analyzes in our study where the most common medical error occurs when performing an operation in 29.78% of the studied group, indicates a serious need to improve the medical educational system and the conditions, that is, the organization of work in health facilities in our health system.

Key words: medical error, external and internal factors of medical error, doctor-patient relationship, postoperative complications, postoperative care, medical education, organization of health work, retrospective study.

ВОВЕД

Поимот лекарска грешка за која се одговара пред закон е воведена за прв пат 1200-та година во римското право, а најраниот судски спор на пријавен случај за лекарска грешка е регистриран 1374 година во Англија. Според студијата на Џонс Хопкинс во 2023 година, повеќе од 250.000 смртни случаи секоја година се должат на медицински грешки. Оваа бројка ја прави медицинската небрежност трета водечка причина за смрт во САД, зад срцевите болести и ракот и истата е за 50000 случаи зголемена само за последниве пет години. Според последните статистики во сите развиени земји доминира бројот на лекарски грешки поврзани со три доминантни фактори : поставена погрешна дијагноза, направена хируршка грешка и ординирање на неадекватна терапија (1).

Денес Латологијата која се занимава со причините за настанување на лекарска грешка ги дели факторите на две групи: надворешни и внатрешни. Надворешните фактори не се поврзани со човечкиот фактор и во нив спаѓаат: работните услови, техничката опременост, лошо административно и правно раководење, лошо планирање, грешки во комуникација, неадекватна едукација и др. Внатрешните или човечки фактори можат да бидат објективни и субјективни и директно зависат од когнитивните и сензорно механичките способности на лекарот ординариус.

МАТЕРИЈАЛИ И МЕТОДИ

Студијата опфаќа судско-медицинско вештачење и анализа на 44 предмети поврзани со жалби од страна на пациенти или нивни роднини за постоење на лекарска грешка во лекувањето од страна на лекарот ординариус. Анализата е ретроспективна за периодот 2018 и 2019 година. Судските вештачења се направени на Институтот за судска медицина, криминалистика и медицинска деонтологија, при Универзитетот "Св Кирил и Методиј" во Скопје.

Предметите се анализирани според етиологијата, демографската застапеност и можната причинско-последична поврзаност на факторите за настанување на лекарската грешка. Податоците се статистички презентирани преку процентуална застапеност, средна вредност, табеларен и графички приказ.

ЦЕЛИ

-Утврдување на најчестата етиологија за настанување на лекарска грешка во испитуваната група.

-Утврдување на процентуалната застапеност на внатрешните (човечки) и надворешните фактори во настанување на лекарската грешка во нашата студиска група.

-Компаративна анализа на видовите и етиолошката застапеност при настанување на лекарските грешки

во нашата испитувана група во однос на податоците објавени во последните референтни студии.

-Одредување на превентивни мерки за намалување на бројот на лекарски грешки во нашиот здравствен систем врз основа на анализата на причинско-последичната поврзаност на факторите за настанување на смрт или инвалидитет на пациентите.

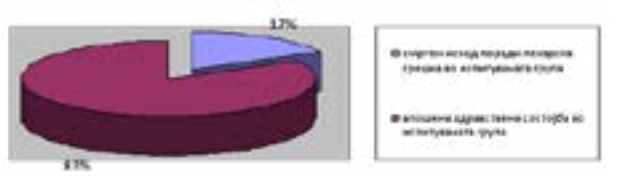
Резултати: Од вкупно 44 случаи поврзани со лекарска грешка, во 36 случаи судско-медицински преглед е извршен по наредба на Обвинителство, а во 8 случаи по приватно барање од страна на семејството на повредениот или починатиот. Просечната возраст на испитуваната група е 38,9 години, од кои 27 (61,3%) се мажи и 17 (38,7%) се жени. Шест субјекти или 13,6% од испитуваната група се однесуваат на деца од 0 до 5 години. Според етиологијата, најголем број форензички извештаи за две години се направени во врска со лекарски грешки во гинекологија и акушерство, вкупно 13 или 29,54%, во интерна медицина 9 или 20,45%, ортопедија 4 или 9,09%, офталмологија 4 (9,09%), абдоминална хирургија 3 (6,81%) и педијатрија 2 (4,54%). Останатите медицински гранки: патологија, урологија, орална хирургија, пластична хирургија, ОРЛ, градна хирургија, ургентна медицина, радиологија и фармакологија се застапени со само по еден случај.

Карактеристична е поголемата застапеност на тужбите за лекарска небрежност поднесени во државните здравствени установи во однос на приватните здравствени установи, во однос 61,36% спрема 38,63% (Табела 1).

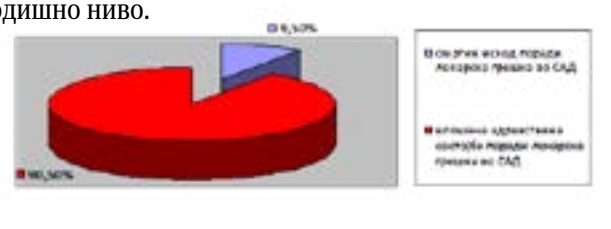
Медицинска специјалност тужена за лекарска грешка	Број на судско-медицински вештачења за лекарска грешка	Тужби за лекарска грешка во државни здравствени установи	Тужби за лекарска грешка во приватни здравствени установи
Гинекологија и акушерство	13 (29,54%)	7	6
Интерна медицина (гастроентерологија и нефрологија)	9 (20,45%)	8	1
Ортопедија	4 (9,09%)	4	0
Офталмологија	4 (9,09%)	1	3
Хирургија	3 (6,81%)	1	2
Педијатрија	2 (4,54%)	2	0
Урологија	1 (2,27%)	1	0
Патологија	1 (2,27%)	1	0
ОРЛ	1 (2,27%)	0	1
Пластична хирургија	1 (2,27%)	0	1
Градна хирургија	1 (2,27%)	0	1
Орална хирургија	1 (2,27%)	0	1
Ургентна медицина	1 (2,27%)	1	0
Радиологија	1 (2,27%)	0	1
Фармацевски факултет	1 (2,27%)	1	0
Вкупно	44 (100%)	27 (61,36%)	17 (38,63)

Табела бр. 1. Застапеност на медицински грешки во проучуваната група според видот на медицинската специјалност и видот на здравствената установа.

За период од две години во 15 или 34,09% од случаите поврзани со лекарска грешка, вештачење е извршено поради настаната смрт, а во 29 или 65,9% поради сериозно влошување на здравствената состојба или инвалидитет. Според тоа на годишно ниво во испитуваната група смртноста поради лекарска грешка изнесува 17% (Дијаграм 1).

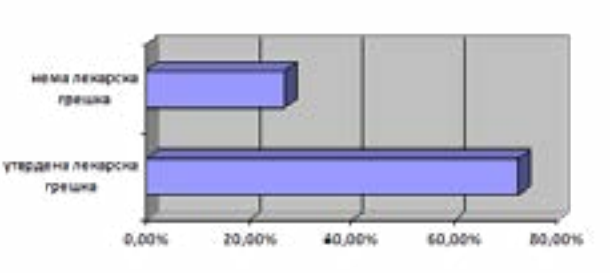


Дијаграм 1. Просечен смртен исход поради лекарска грешка (17 %) и влошена здравствена состојба поради лекарска грешка (83 %) во испитуваната група на годишно ниво.



Дијаграм 2. Просечен смртен исход поради лекарска грешка (9,0%) и влошена здравствена состојба поради лекарска грешка (90,5%) на годишно ниво во Соединетите американски држави.

Од вкупно 44 случаи, по извршеното вештачење, постоење на некаква лекарска грешка е утврдено во 32 случаи или 72,72%, односно отсуство на лекарска грешка во 12 случаи или 27,28 % од испитуваната група (Дијаграм 3).



Дијаграм 3. Утврдено постоење на лекарски грешки во испитуваната група.

Во испитуваната група беа утврдени вкупно 47 грешки поврзани со третманот на повредени пациенти. Притоа, утврдени се 35 (79,54%) медицински грешки како резултат на човечки фактор и 9 лекарски грешки како резултат на пропусти во организацијата на работата на здравствената организација. Од нив, 14 или 29,78% се резултат на грешка при операција, 12 или 25,53% поради ненавремена или погрешна дијагностика, 7 (14,89%) поради неадекватен конзервативен третман, 5 (10,63%) поради пропуст во постоперативното лекување, а во 9 случаи или 19,14%, лекарската грешка настанала поради пропусти во организацијата на работата во соодветната здравствена установа (табела 2).

Видови на лекарска грешка во испитуваната група	Број на лекарски грешки	Процентуална застапеност
Пропуст во дијагностиката	12	25,53%
Грешки при конзервативен третман	7	14,89%
Грешки при оперативен третман	14	29,78%
Грешки поради пропуст во постоперативниот третман	5	10,63%
Грешки поради пропусти во организацијата на работа	9	19,14%
Вкупно	47	

Табела бр 2. Видови на лекарски грешки утврдени во испитуваната група

ДИСКУСИЈА

Под медицинска грешка се подразбира секој вид на намерна или ненамерна активност од страна на здравствениот работник, која може да доведе до влошување на здравствената состојба или настанување на смрт кај пациентот. Факторите кои доведуваат до настанување на лекарска грешка се делат на т.н. "внатрешни" и "надворешни".

Внатрешните или човечки фактори, се субјективни и зависат од когнитивната или механичката способност на ординирачкиот лекар. При тоа лекарските грешки можат да се поделат во две основни групи: грешки настанати поради небрежност и грешки настанати поради медицинска некомпетентност-нестручност.

Во секој здравствен систем постои закон за медицинска небрежност кој предвидува надокнада на пациентот за нарушување на здравјето или смрт од неадекватен третман. Само во САД годишно се поднесуваат од 15000 до 19000 тужби за лекарска грешка поради небрежност (5). Конкретно, до 1,1% од приемите во болница резултирале со смртни случаи поради медицински грешки. Во 2013 година, повеќе од 400.000 смртни случаи биле предизвикани од медицински грешки (6). Во Обединетото Кралство, 101 грешка при земање лекови се случуваат на 1.000 случаи при препишување на лекови, а исто така се проценува дека грешките со лекови предизвикуваат 12.000 смртни случаи годишно според Националната здравствена служба (7).

Како најчести лекарски грешки поради небрежност во достапната литература се вбројуваат: ненавремена или неточно поставена дијагноза, непотребно или неправилно изведен хируршки зафат, предвремено отпуштање на пациентот, ненаправени или неточно прочитани соодветни дијагностички тестови, небрежно постоперативно следење, препишување на погрешна доза или погрешен лек, заборавање на инструмент или завоен материјал во пациентот, извршена операција на погрешен орган или ткиво, постојана болка после операција, добивање на тешка болничка инфекција поради небрежен третман на оперативна рана, појава на декубитуси поради неадекватна постоперативна нега и др.

Во втората категорија на внатрешни или човечки лекарски грешки спаѓаат сите фактори кои се поврзани со некомпетентност на лекарот ординариус: недоволна стручна способност или едукација, неадекватна специјалност при лекување на одредена болест, недоволно лекарско искуство, слаба мануелна хируршка способност, слаба комуникација меѓу пациентот и лекарот, преморeност, стрес, непочитување на упатствата и протоколите за безбедност и лекување и др.

Во надворешни фактори кои можат да доведат до лекарска грешка спаѓаат: неефикасно управување, одвлекување на вниманието во тек на работното време, лоша тимска работа, лоши меѓучовечки односи на здравствениот персонал, несоодветна медицинска и технолошка опременост на здравстените установи, работна култура, религиозна лимитираност, неадекватна комуникација и администрација и др.

Споредено со достапните податоци од последните студии, каде најчесто застапени се вбројуваат

лекарските грешки поврзани со ненавремена или погрешна дијагноза (околу 32%), повреди при породувања и грешки при ординирање на лекови (2,3,4), во оваа студија најбројни се лекарските грешки за време на изведување на оперативниот зафат со 29,78%, на второ место пропусти во дијагностицирање со 25,53% а на трето место се лекарски грешки настанати поради разни пропусти во организацијата на работа со 19,14% од вкупниот број на судски спорови. За разлика од современите здравствени системи каде околу 2,7% до 3% од вкупниот број на лекарски грешки отпаѓаат на грешки поврзани со анестезија (2), во оваа студија не е забележан ниеден случај на тужба за анестезиолошка грешка.

Во САД, како земја со најголем број на судско-медицински вештачења поврзани со тужби за лекарска грешка или небрежност, 9,5% од утврдените грешки резултираат секоја година со летален исход. Споредено со резултатите во нашата студија каде процентот на летален исход поради лекарска грешка на годишно ниво изнесува 17% од случаите, ја вбројува нашата држава меѓу здравствените системи со многу висок степен на смртност настаната поради лекарска грешка.

Последните статистички податоци објавени во САД, укажуваат на фактот дека спроведувањето на т.н. принцип на "одбранбена медицина" резултирал со добивање на ослободителни пресуди во околу 80% од случаите поврзани со небрежност или лекарска грешка. При тоа под "одбранбена медицина" американското медицинско здружение (AMA) ја дефинира како „изведба на дијагностички тестови и третмани кои, не би биле направени при небрежност од страна на лекарот". Од друга страна, Борган и сор. ја дефинираат одбранбената медицина како „рутинска медицинска нега за да се избегне или намали ризикот од реални или согледани идни правни последици" (8). Користењето на т.н. "одбранбена медицина", во значајна мера би ги подобрила резултатите на судските спорови во корист на здравствените работници, кои според оваа студија со само 27,27% ослободителни пресуди од вкупниот број на судско-медицински вештачења за постоење или непостоење на лекарска грешка, претставуваат голем медицински и финансиски терет за нашиот здравствен систем.

ЗАКЛУЧОК

Анализата на видот на медицинските гранки за кои најчесто се бара судско медицинско вештачење за евентуално постоење на лекарска грешка, во нашата испитувана група за период од две години, најмногу се однесува на: гинекологија и акушерство, интерна медицина (гастроентерохепатологија и нефрологија), ортопедија и офталмологија. Во 72,72% од случаите судско-медицинската анализа покажала постоење на некаква медицинска грешка. Застапеноста на таканаречениот „внатрешен" или човечки фактор е утврдена во 80,85%, а „надворешен" фактор кој не настанал поради човечка грешка е утврден во 19,15% од вкупниот број на идентификувани грешки кои довеле до влошување на здравствената состојба или смрт кај пациентите.

Компаративната анализа во однос на достапната литература, каде причината за смрт поради медицинска грешка се јавува годишно во просек во 9,5% од случаите (2,3,4), наспроти 17% во нашата студиска група, го вбројува нашиот здравствен систем во земји со висока смртност.

За разлика од објавените достапни податоци, каде во 32% од судските вештачења, како најчеста медицинска грешка се јавува пропуст или ненавремена дијагноза (2,3,4), во нашата студија најчеста медицинска грешка се јавува при извршување на операција (во 29,78% од испитуваната група), што укажува на потреба од превземање на мерки за подобрување на медицинскиот образовен систем и условите, односно организацијата на работата во здравствените установи во нашиот здравствен систем.

Клучни зборови: медицинска грешка, надворешни и внатрешни фактори на медицинска грешка, однос лекар-пациент, постоперативни компликации, постоперативна нега, медицинско образование, организација на здравствена работа, ретроспективна студија.

ЛИТЕРАТУРА

1. Wilson Michael M. Medical Malpractice Statistics. Nov. 21. Washington DC Medical Maplractice Lawyer 2003.
2. National Institutes of Health. Medical Malpractice.
3. National Institutes of Health. Clinical Errors and Medical Negligence.
4. Johns Hopkins Medicine. Johns Hopkins Medicine Researchers Identify Health Conditions Likely to be Misdiagnosed

5. Medicina (Kaunas). 2020 Jun; 56(6): 259. Published online 2020 May 27. doi: 10.3390/medicina56060259
6. Van Den Bos J, Rustagi K, Gray T, Halford M, Ziemkiewicz E, Shreve J. The $17.1 billion problem: The annual cost of measurable medical errors. Health Aff (Millwood) 2011;30(4):596–603.
7. Department of Health and Social Care. The report of the short life working group on reducing medication-related harm. 2018. [cited October 2022].
8. S.M. Borgan, L. Romeus, S. Rahman, A. Asmar. Internal medicine residents and the practice of defensive medicine: a pilot study across three internal medicine residency programs. Cureus, 12 (2020), pp. e6876
9. Garon-Sayegh P. Analysis of medical malpractice claims to improve quality of care: Cautionary remarks. J Eval Clin Pract. 2019 Oct;25(5):744-750.
10. 10 Jena, AB, Seabury, S, Lakdawalla, D, and Chandra, A. Malpractice risk according to physician specialty. N Engl J Med. (2011) 365:629–36. doi: 10.1056/NEJMsa1012370
11. Madea, B, and Preuss, J. Medical malpractice as reflected by the forensic evaluation of 4450 autopsies. Forensic Sci Int. (2009) 190:58–66. doi: 10.1016/j.forsciint.2009.05.013
12. Hwang, CY, Wu, CH, Cheng, FC, Yen, YL, and Wu, KH. A 12-year analysis of closed medical malpractice claims of the Taiwan civil court: a retrospective study. Medicine (Baltimore). (2018) 97:e0237. doi: 10.1097/md.0000000000010237
13. Chen, KY, Yang, CM, Tsai, SH, Chiou, HY, Lin, MR, and Chiu, WT. Medical malpractice in Taiwan: injury types, compensation, and specialty risk. Acad Emerg Med. (2012) 19:598–600. doi: 10.1111/j.1553-2712.2012.01360.x
14. Mello, MM, Studdert, DM, Schumi, J, Brennan, TA, and Sage, WM. Changes in physician supply and scope of practice during a malpractice crisis: evidence from Pennsylvania. Health Aff (Millwood). (2007) 26:w425–35. doi: 10.1377/hlthaff.26.3.w425
15. Berlin, L. Medical errors, malpractice, and defensive medicine: an ill-fated triad. Diagnosis (Berl). (2017) 4:133–9. doi: 10.1515/dx-2017-0007
16. Studdert, DM, Mello, MM, and Brennan, TA. Medical malpractice. N Engl J Med. (2004) 350:283–92. doi: 10.1056/NEJMhpr035470
17. Selbst, Steven M.; Friedman, Marla J.; Singh, Sabina B. Epidemiology and Etiology of Malpractice Lawsuits Involving Children in US Emergency Departments and Urgent Care Centers. Pediatric Emergency Care 21(3):p 165-169, March 2005. | DOI: 10.1097/01.pec.0000161471.57959.28
18. Malpractice definition, Garner, Bryan A. (2009). Black's Law Dictionary (9 ed.). West. ISBN 978-0314199492. Retrieved 7 December 2017.
19. 19."Malpractice". Merriam-Webster.com. Merriam-Webster, Inc. Retrieved 7 December 2017.
20. Jacobs, Douglas (1992). Suicide and Clinical Practice. American Psychiatric Association Publishing. p. 148. ISBN 0880484551. Retrieved 7 December 2017.
21. See, e.g., Bal, B. Sonny (February 2009). "An Introduction to Medical Malpractice in the United States". Clinical Orthopaedics and Related Research. 467 (2): 339–347. doi:10.1007/s11999-008-0636-2. PMC 2628513. PMID 19034593.
22. Marcus, Paul (1981). "Book Review of Medical Malpractice Law: A Comparative Law Study of Civil Responsibility Arising from Medical Care". Hastings International and Comparative Law Review: 235–243. Retrieved 7 December 2017.
23. Kamaker, Dorothy (September 26, 2015). "Patient advocacy services ensure optimum health outcomes". smh.com.au. The Sydney Morning Herald. Retrieved August 23, 2016.
24. Avraham R, "An Empirical Study of the Impact of Tort Reforms on Medical Malpractice Settlement Payments," Journal of Legal Studies, Vol. 36, No. S2, June 2007, pp. S183–S229.
25. Born P, Viscusi WK, Baker T, "The Effects of Tort Reform on Medical Malpractice Insurers' Ultimate Losses," Harvard Law School, John M. Olin Center, Discussion Paper Series, No. 554, July 1, 2006. As of May 28, 2009:
26. Danzon P, "The Frequency and Severity of Medical Malpractice Claims," Journal of Law and Economics, Vol. 27, No. 1, January 1984, pp. 115–148.
27. Danzon PM, "The Frequency and Severity of Medical Malpractice Claims: New Evidence," Law and Contemporary Problems, Vol. 49, No. 2, 1986, pp. 57-84.
28. Donohue JJ, Ho DE, "The Impact of Damage Caps on Malpractice Claims: Randomization Inference with Difference-in-Differences," Journal of Empirical Legal Studies, Vol. 4, No. 1, March 2007, pp. 69-102.

Original scientific paper

THE ROLE OF IONIZED WATER AND ITS IMPACT ON THE ACTIVITY OF GLUTATHIONE PEROXIDASE ON RATS BLOOD PLASMA, LIVER AND KIDNEYS DURING HYPERTHERMIC STRESS

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ABSTRACT

Introduction: The antioxidant potential of ionized water or electrolyzed reduced water (ERW) mimics the function of antioxidant enzymes such as glutathione peroxidase (GPx) by scavenging ROS. Using non-enzymatic antioxidants, glutathione, and vitamin C, our research aimed to investigate the effects of ERW on GPx activity in the plasma, the liver, and the kidneys during hyperthermic stress (HS).

Material and methods: White laboratory rats of the female Wistar breed, weighing 180 to 220 grams, were selected as an experimental model. They were split into three groups of 15 rats. Rats in the first group (CPM), which served as the control, drank commercial mineral water. Rats in the second group (TAM), who drank ERW with a pH of 9.4, and rats in the third group (TAD), who drank ERW with a pH of 9.4 but added glutathione and vitamin C. For 21 days, the experiment was carried out. The animals of the various groups were exposed to a hyperthermic environment for five hours after receiving the appropriate treatment on the twenty-first day and continued to do so until they reached secondary hyperthermia (a body temperature of 43 °C).

Results: Acute hyperthermic exposure on the 21st day in the CPM and TAD groups for blood plasma has a statistically significant difference ($p < 0.001$); also, in both TAM and TAD groups for blood plasma there is a statistically significant difference ($p < 0.001$), which is in contrast to the difference in GPx activity in liver and kidney between the remaining compared groups, which was found to be statistically insignificant.

Conclusion: Acute hyperthermic exposure leads to a decrease in GPx activity and also to a decreased enzymatic antioxidant capacity in the liver and kidneys.

Keywords: glutathione peroxidase, ionized water, hyperthermic stress, liver, kidneys

INTRODUCTION

The generation of ROS is induced by heat stress, and their excessive buildup lowers cell viability and proliferation and triggers apoptosis. Additionally, high ROS production brought on by heat stress decreases the effectiveness of antioxidant defense mechanisms, increasing oxidative damage. Physical stressors like heat stress have the potential to cause protein structural alterations that result in cell death (1). Rats exposed to acute heat stress had higher levels of lipid peroxidation, protein oxidation, and inflammation (2). The body encloses a complex antioxidant defense grid that relies on endogenous enzymatic and nonenzymatic antioxidants. These molecules collectively act against free radicals to resist their damaging effects on vital biomolecules and ultimately body tissues (3). Antioxidants are compounds

that can shield cells from the harmful effects of medications, xenobiotics, carcinogens, and hazardous radical molecules. According to reports, a number of natural substances have antioxidant properties. Ionized water or electrolyzed reduced water (ERW) is a kind of antioxidant (4). Ionized water, also known as Electrolyzed-Reduced Water (ERW), also known as "alkaline ionized water," is a form of the alkaline water created using water electrolysis. Hydrogen gas is frequently made by electrolyzing water. The unique antioxidant, anti-inflammatory, and anti-cellular-stress properties of hydrogen gas have recently been the subject of intense research (5). The oxidation-reduction potential of ERW is quite low. The bioactivity of ERW is its antioxidant activity. By scavenging ROS, ERW mimics the activities of antioxidant enzymes including superoxide dismutase (SOD) and catalase (CAT) (6). When exposed to carbon tetrachloride, ERW protects the liver by lowering plasma AST and ALT levels to normal control values, suppressing oxidative stress, and restoring GPx, CAT, and SOD activity (7). One of the key enzymes in the host's defense against oxidative stress in the cytosol is glutathione peroxidase (GPx). Using glutathione as a reducing agent, GPx is a selenium-containing enzyme that detoxifies hydrogen peroxide and other hydroperoxides. An essential extracellular antioxidant known as plasma glutathione peroxidase is produced mostly in the kidney but has been found in a variety of bodily fluids (8). The reduction of hydroperoxides is carried out by the cytosolic enzyme glutathione peroxidase. GPx is an enzyme that eliminates hydroperoxides produced in cells. It is assumed to be a selenoenzyme that defends cells against numerous harms because its subunits include a Se atom. In 1957, Mills discovered this enzyme for the first time in mammalian erythrocytes. In endothelial cells, especially those in the lung, it is the most efficient enzyme. The cytoplasm of eukaryotic cells contains about 60–75% of the enzyme activity, whereas mitochondria only contain 25–40% of it. Erythrocytes and the liver exhibit the clearest enzyme activity. The most significant enzyme for preventing intracellular peroxidation of lipids is GPx (9). The liver, the second-largest organ in the body, is responsible for more than 500 critical processes, including protein synthesis, excretion, metabolism, and detoxification of strong poisons. Several physiological processes need the storage of fat-soluble vitamins, glycogen, and fat in the liver parenchyma. The liver produces plasma proteins, clotting components, urea, and glucose, which are then discharged into the bloodstream. The liver produces bile, which aids in the body's excretion of toxins and other metabolic waste products. The glutathione (oxidized and reduced state) level varies in response to hyperthermic stress (HS), which has an impact on the antioxidant system (10). Both the proximal and distal tubules of the kidneys as well as the smooth muscle cells of the renal arteries have high levels of Gpx. Among the identified Gpx isoforms, Gpx1 and Gpx4 are easily discovered in kidney tubular epithelial cells, Gpx3 is only weakly detectable in kidney proximal tubules, and Gpx2 and 5 have not been identified in the kidney. With 96% of kidney Gpx activity being accounted for by Gpx1, Gpx1 is the predominant Gpx isoform expressed in healthy kidneys. The ability of the kidney to deal with oxidative stress is therefore thought to be significantly influenced by the alteration of renal Gpx1 expression and function (11). A selenoprotein antioxidant enzyme, GPx3 was formerly known as extracellular glutathione peroxidase (Gpx), and it is produced in the basolateral compartment of the kidney. With actions in the plasma, vessel wall, and moving platelets, it is delivered to the systemic circulation. The only GPx subtype known to have predominant action in the extracellular compartment is GPx3 (12). In order to create an antioxidant defense system, glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) must work together. These three enzymes are important reactive oxygen species (ROS) scavengers. By controlling glutathione, GPx uses a reducing agent to remove hydrogen peroxide and lipid peroxides, limiting peroxidative damage to the cell membrane and other organelles (13).

OBJECTIVES

Our research's objective came from our presumptions that drinking ionized, or electrochemically reduced water (ERW) will improve the body's alkaline reserve. We highlight this ionized water (ERW) feature in situations where the organism is exposed to high external temperatures as a stress factor. We assumed that ERW as an antioxidant would increase the body's tolerance to glutathione peroxidase (GPx) activity in blood plasma, liver, and kidneys.

MATERIAL AND METHODS

Experimental model

White laboratory rats of the female Wistar breed, weighing 180 to 220 grams, were utilized as an experimental model.

They were split into three groups of 15 animals each (n = 45), and the proper therapy was administered to each group. The animals were kept in a 20 2 °C chamber during the experiment, and they were exposed to light every 12 hours. Standard laboratory food and unlimited water were provided to all of the experiment's animals.

Three different groups of treated rats were created.

1) Rats in the control group (CPM) drank commercial mineral water.

2) Rats in the second group (TAM) drank electrochemically reduced water with a pH of 9.4. (measured immediately after water activation)

3) The third set of rats (TAD) ingested electrochemically lowered water (pH = 9.4) along with supplemental glutathione and vitamin C.

Experimental protocol

The three groups of rats underwent a 21-day study in which they received daily treatments of modified natural water in the morning. Over the course of the allotted time, the control group only received natural water. Ionized water (ERW) and ionized water with additional glutathione and vitamin C were given to the other two groups, respectively. At the Faculty of Science and Mathematics in Skopje's Institute of Chemistry, quantities of this type of functional water were prepared every three days. Intragastrically, 2 ml-sized doses of water were administered. On the seventh, fourteenth, and twenty-first days of treatment, samples were collected for the investigation of specific parameters. On days 7 and 14, the rats' tails were pricked to collect the blood needed for analysis into correctly labeled Eppendorf tubes. After 5 minutes of centrifugation at 1500 rpm, blood serum was collected for examination. It was then frozen at -80°C for the required assays. On the 21st day, the animals in the corresponding groups were subjected to a hyperthermic environment for five hours after receiving the appropriate treatment and continued to be exposed to it until they reached secondary hyperthermia (a body temperature of 43 °C). Individual exposures were conducted for 80 minutes at a temperature of 40 ± 1 °C in air-conditioned chambers. During the hyperthermic exposure, rectal temperature was also measured. Every 20 minutes, the animals' body temperatures were taken, and 10 minutes after the last reading, 3 ml of thiopental was applied subcutaneously to sacrifice the animals. The aorta in the abdomen was used to draw blood. The obtained blood serum was then divided into smaller amounts and refrigerated at -80°C pending additional testing.

Determination of glutathione peroxidase (GPx) activity

A family of enzymes known as glutathione peroxidases is present in mammalian cells and aids in preventing membrane lipid peroxidation by oxidizing free peroxides. The enzyme reacts with lipid hydroperoxides, cholesterol hydroperoxide, and, at low concentrations, hydrogen peroxide as well. It works with glutathione reductase in a system and utilizes glutathione as a cofactor.

Principle of the method

With some adjustments, the Lawrence and Burk (1976) approach was used to calculate GPx activity. It requires observing the oxidation of NADPH at 340 nm for three minutes at 25 °C while both GR and GSH are present. The reaction mixture included a sample, 50 mM potassium phosphate buffer, pH 7.0, 1 mM sodium azide, 2 mM GSH, 0.2 mM NADPH, 1 U/ml GR, and 1.5 mM cumene hydroperoxide. At 25°C, the absorption was observed for 5 minutes.

Test procedure

By introducing cumene hydroperoxide, the reaction was triggered. The quantity of enzyme needed to catalyze the oxidation of one mol of NADPH for one minute under the aforementioned circumstances is referred to as one unit of enzyme activity. In terms of U/mg-proteins, the data are shown.

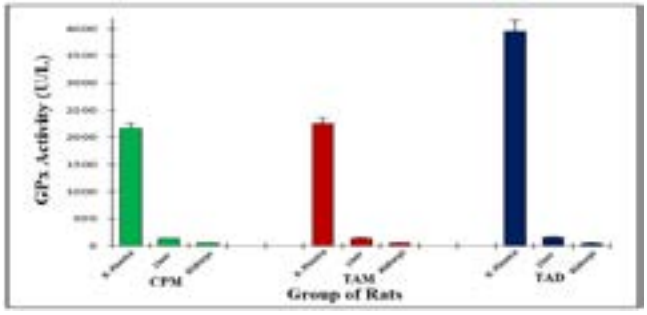
$$\text{GPx activity (U/mg)} = \frac{\text{The direction of the curve}}{0.5433 * 6220 * (\text{mg/m protein}) * 10^6}$$

Analytical statistics

Utilizing the statistical software "InStat," the experiment's results were statistically processed. The findings are displayed as mean values with standard error (SEM). Application of a One-way analysis of variance (ANOVA) was used to assess the impact of individual alkaline water treatment, as well as its addition of vitamin C and GSH, in combination with the experimental model's exposure to high temperatures. It was evaluated whether a statistically significant difference existed both within a single group and when comparing three distinct groups. Repeated measures ANOVA, rather than Ordinary ANOVA, was employed to assess the significance of differences in comparisons between the same group of rats in respect to time. Significant changes were defined as values with $p < 0.001$.

RESULTS

The results of our research on the impact of treatment with ionized water, without and with the addition of appropriate antioxidants to it, as well as acute hyperthermic exposure introduced on the 21st day of treatment on GPx activity in blood plasma, liver and kidneys are shown in Graph 1.



Graph 1. Glutathione peroxidase activity in blood plasma, liver, and kidneys

Legend: CPM – control group treated with natural water; TAM – group treated with ionized water; TAD – group treated with ionized water with added glutathione and vitamin C

Table 1. Results of the statistical analysis of data on the activity of GPx in serum

Statistical analysis - GPx activity in blood plasma, liver, and kidneys				
Compared groups			Results	
CPM b. plasma	vs	TAM b. plasma	p > 0,05	Ns
CPM b. plasma	vs	TAD b. plasma	p < 0,001	***
TAM b. plasma	vs	TAD b. plasma	p < 0,001	***
CPM liver	vs	TAM liver	p > 0,05	Ns
CPM liver	vs	TAD liver	p > 0,05	Ns
TAM liver	vs	TAD liver	p > 0,05	Ns
CPM kidneys	vs	TAM kidneys	p > 0,05	Ns
CPM kidneys	vs	TAD kidneys	p > 0,05	Ns
TAM kidneys	vs	TAD kidneys	p > 0,05	Ns

The treatment applied respectively to each group during the period of hyperthermic exposure caused a significant difference in GPx activity in blood plasma among the three groups (table 1). Acute hyperthermic exposure on the 21st day in the CPM and TAD groups for blood plasma has a statistically significant difference ($p < 0.001$); also, in both TAM and TAD groups for blood plasma there is a statistically significant difference ($p < 0.001$), which is in contrast to the difference in GPx activity in liver and kidney between the remaining compared groups, which was found to be statistically insignificant.

DISCUSSION

Electrolysis is the process by which water (H2O) breaks down into oxygen (O2) and hydrogen gas (H2) under the influence of an electric current. The development of ERW generation has developed and advanced. Most recently, renewable energy can now be used to produce it. To enhance its anti-inflammatory and healing properties, ERW can also be produced using a variety of additions, including alkaline minerals and nanoparticles (14). Ionized water or ERW is distinguished by having a high pH, a low concentration of dissolved oxygen gas, a high concentration of dissolved hydrogen gas, and a negative oxidation-reduction potential (ORP). The concentration of dissolved hydrogen gas was not used to measure the effectiveness of ERW; instead, pH and ORP were used. In fact, the majority of these earlier research did not provide information on the concentration of the dissolved hydrogen gas until 2007, which was when the therapeutic benefits of H2 were first amply established (5). In order to provide a secure source of free electrons to prevent the oxidation of healthy tissue by free oxygen radicals, alkaline ionized water (AIW), also known as alkaline electrolysis-treated water, has the potential to boost its reduction potential. According to some studies, it contains a lot of hydrogen (H2) molecules, which have some therapeutic benefits by functioning as antioxidants (15). Only five of the eight unique GPxs found in humans, GPxs 1-4 and 6, are selenoproteins. A selenocysteine residue (Sec) can be found in their active site, which also includes glutamine (Gln), tryptophan, and asparagine to form a conserved tetrad. Rodents, GPx6, GPx5, GPx7, and GPx8 all have cysteine in the active site location of Sec. Not only are sec-containing GPxs seen in vertebrates, but also occasionally in lower species (16) One of the enzymes that are crucial in the host's defense against oxidative stress in the cytosol is glutathione peroxidase (GPx). A selenium-containing enzyme called glutathione peroxidase uses glutathione as a reducing agent to detoxify different hydroperoxides, including hydrogen peroxide. An essential extracellular antioxidant known as plasma glutathione peroxidase is produced mostly in the kidney but has also been found in a variety of bodily fluids (8). The detoxification of lipid peroxides and H2O2 by reduced glutathione is catalyzed by glutathione peroxidase. As a result, it prevents peroxide oxidation of hemoglobin and membrane lipids (9). GPx3, commonly known as plasma GPx, is an extracellular antioxidant selenoprotein. GPx3 binds to the basement membrane of renal cortical epithelial cells and is primarily produced in the basolateral compartment of the kidney (17). The most prevalent Gpx isoenzyme, Gpx1, is expressed in the liver. As an electron donor, glutathione (GSH) is used by Gpx1 to decrease H2O2 to water in the cytoplasm. The

most significant H2O2 scavenger is likely to be Gpx1 (18). A selenoprotein antioxidant enzyme produced in the basolateral compartment of the kidney, GPx3 was formerly known as extracellular glutathione peroxidase (Gpx). It is carried to the systemic circulation and has effects on platelets, the vessel wall, and plasma. The only known GPx subtype that primarily functions in the extracellular compartment is GPx3.

Acute temperature stress speeds up metabolic processes by increasing O2 intake and flux through the mitochondrial respiratory chain, both of which result in the production of ROS. Heat stress increases oxygen flow across the mitochondrial electron transport chain, which results in the production of oxygen radicals at the level of the entire cell. We are confident that in our study, the above-mentioned mechanisms for the relationship between temperature stress and oxidative stress were also in play in the rats, and we can state without a possible doubt that the rats, on the 21st day of the treatment when they were exposed to acute temperature stress, were also strongly exposed to oxidative stress.

In situations where the body is exposed to stressful circumstances, the antioxidant capability is very important. Free radicals are produced in the body as a result of stressful factors, whether they be emotional, physical, or both. Work must be done to improve the body's antioxidant defense because of this. In our study, ionized water, glutathione, and vitamin C were added to the experimental model to help us reach this objective. Maintaining homeostasis at a low level means the entire organism is working normally, with the exception of circumstances that favor the emergence and progression of pathological disorders.

According to the results we obtained from our research, in the control group CPM, treated with natural water, during the 14th day, we observed an increased activity of GPx, which decreases during hyperthermic exposure in the same group. GPx activity during hyperthermic exposure also decreases in the second TAM group treated with ionized water. In the third TAD group, treated with ionized water with added glutathione and vitamin C, higher GPx activity was registered. Acute hyperthermic exposure caused a significant increase in GPx activity in blood serum in the third group.

The treatment applied respectively to each group during the hyperthermic exposure period caused a significant difference in GPx activity only in the blood plasma of the three groups. Acute hyperthermic exposure on the 21st day in the CPM and TAD groups for blood plasma has a statistically significant difference; also, in the TAM and TAD groups, there is a statistically significant difference in relation to blood plasma, which is opposite to the difference in the remaining compared groups in relation to the liver and kidneys, in which we have significantly reduced GPx activity. On the other hand, GPx also metabolizes peroxidized organic molecules as well as H2O2 with relatively high affinity and catalyzes these molecules even at normal physiological concentrations. Hence, the activity of GPx is considered to represent the basic protection of the cell, which brings the concentration to normal physiological values.

CONCLUSION

Only the blood plasma of the three groups demonstrated a significant increase in GPx activity after acute hyperthermia, but the liver and kidneys showed decreased GPx activity as well as lower enzymatic antioxidant capacity.

REFERENCES

1. Ibtisham, F., Zhao, Y., Nawab, A., Liguang, H., Wu, J., Xiao, M., Zhao, Z. and An, L. (2018). The Effect of High Temperature on Viability, Proliferation, Apoptosis and Antioxidant Status of Chicken Embryonic Fibroblast Cells. Brazilian Journal of Poultry Science Vol. .20 (3) 463-470
2. Ilievska, J., Cicimov, V., Emilija Antova, E., Icko Gjorgoski, I., Nikola Hadzy-Petrushev, N. and Mladenov, M. (2016). Heat-induced oxidative stress and inflammation in rats in relation to age. Research in Physical Education, Sport and Health, Vol. 5, No. 2, pp.123-130
3. Ighodaro, O.M. and Akinloye, O.A (2017) First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. Alexandria Journal of Medicine 54 (2018) 287–293
4. Franceschelli, S., Pia Gatta, D. M., Pesce, M., Ferrone, A., Patruno, A., de Lutiis, M. A., Grilli, A., Felaco, M., Croce, F. and Speranza, L. (2016). New Approach in Translational Medicine: Effects of Electrolyzed Reduced Water (ERW) on NF-κB/iNOS Pathway in U937 Cell Line under Altered Redox State. Int. J. Mol. Sci. 2016, 17, 1461
5. LeBaron, T. W., Sharpe, R. and Ohno, K. (2022). Electrolyzed–Reduced Water: Review I. Molecular Hydrogen Is the Exclusive Agent Responsible for the Therapeutic Ef-

fects. Int. J. Mol. Sci, 23, 14750

6. Ridwan R. D., Wuliastuti,W. S.,Setijanto, R. D. (2017). Effect of electrolyzed reduced water on Wistar rats with chronic periodontitis on malondialdehyde levels. Dent. J. Majalah Kedokteran Gigi; 50(1): 10–13
7. Cheng, T-C., Hsu, Y-W., Lu, F-J., Chen, Y-Y., Tsai, N-M., Chen, W-K. and Tsai, C-F. (2018). Nephroprotective effect of electrolyzed reduced water against cisplatin-induced kidney toxicity and oxidative damage in mice. Journal of the Chinese Medical Association: Volume 81 - Issue 2 - p 119-126
8. Palathingal, P., Mahendra, J., Annamalai, P. T., Varma, S. S., Mahendra, L., Thomas, L., Baby, D., Jose, A., Srinivasan, S., and Ambily, R. (2022) A Cross-Sectional Study of Serum Glutathione Peroxidase: An Antioxidative Marker in Chronic Periodontitis and Chronic Kidney Disease. Cureus 14(2): e22016. DOI 10.7759/cureus.22016
9. Sarıkaya, E. and Doğan, S. (2022) Glutathione Peroxidase in Health and Diseases DOI: http://dx.doi.org/10.5772/intechopen.91009
10. Gupta, A., Chauhan, N.R., Singh, A., Chowdhury, D., Meena, R.C., Chakrabarti, A., Ganju, L., Kumar, B., and Singh, S.B. (2019) Heat Induced Oxidative Stress and Aberrations in Liver Function Leading to Hepatic Injury in Rats. Defence Life Science Journal, Vol. 04, No. 01.
11. de Haan, J. B., Stefanovic, N., Nikolic-Paterson, D., Scurr, L. S., Croft, K. D., Mori, T. A., Hertzog, P., Kola, I., Atkins, R. C. and Tesch, G. H. (2005). Kidney expression of glutathione peroxidase-1 is not protective against streptozotocin-induced diabetic nephropathy. Am J Physiol Renal Physiol 289: F544 –F551
12. Pang, P., Abbott, M., Abdi, M., Fucci, Q-A., Chauhan, N., Mistri, M., Proctor, B., Chin, M., Wang, B., Yin, W., Lu, T-S., Halim, A., Lim, K., Handy, D. E., Loscalzo, J. and Siedlecki, A. M. (2018). Pre-clinical model of severe glutathione peroxidase-3 deficiency and chronic kidney disease results in coronary artery thrombosis and depressed left ventricular function. Nephrol Dial Transplant (2018) 33: 923–934 doi: 10.1093/ndt/gfx304
13. Shao, X., Yan, C., Sun, D., Fu, C., Tian, C., Duan, L., and Zhu, G. (2020) Association Between Glutathione Peroxidase-1 (GPx-1) Polymorphisms and Schizophrenia in the Chinese Han Population. Neuropsychiatric Disease and Treatment:16 2297–2305
14. Reyes, F. S., Mamaril, A. C., Matias, T. J., Tronco, M. K., Samson, G. R., Javier, N. D., Fadriquela, A., Antonio, J. M. and Sajo, M. E. (2021). The Search for the Elixir of Life: On the Therapeutic Potential of Alkaline Reduced Water in Metabolic Syndromes. Processes, 9, 1876. https://doi.org/10.3390/ pr9111876
15. Ramadhan, A., Wicaksono, S. A., Nugroho, T. E. and Utami, S. B. (2021). The Effects of Alkaline Ionized Water Administration to the Total Cholesterol Levels in Patients with Type 2 Diabetes Mellitus Accompanied by Dyslipidemia. P J M H S Vol. 15, NO. 5. DOI: https://doi.org/10.53350/pjmhs211551449
16. Brigelius-Flohe, R. and Flohe, L. (2020) Regulatory Phenomena in the Glutathione Peroxidase Superfamily. Antioxidants & redox signaling Volume 33, Number 7. DOI: 10.1089/ars.2019.7905
17. Hong, Y. A. and Park, C. W. (2021). Catalytic Antioxidants in the Kidney. Antioxidants, 10, 130. https://doi.org/10.3390/antiox10010130
18. Moossavi, S., Besharat, Sharafkhah, S. M., Ghanbari, R., Sharifi, A., Rezanejad, P., Pourshams, A., Poustchi, H. and Mohamadkhani, A. (2016) Inverse Association of Plasma Level of Glutathione Peroxidase with Liver Fibrosis in Chronic Hepatitis B: Potential Role of Iron. Middle East Journal of Digestive Diseases/ Vol.8/ No.2.

Profesional paper

ALZHEIMER'S DISEASE AS A CONSEQUENCE OF DISEASES OF THE CARDIOVASCULAR SYSTEM

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ABSTRACT

Degenerative diseases are progressive neurological disorders characterized by damage to specific nerve cells. Alzheimer's disease was first described by physician Alois Alzheimer as an insidious and slowly progressive neurodegenerative disorder of the human central nervous system (CNS). Cardiovascular diseases (CVD) are a group of disorders of the heart and blood vessels. Hypertension as one of the most frequent cardiovascular diseases, which lasts for a longer period, which is related to endothelial dysfunction, arterial stiffness and atherosclerosis, is associated with cerebral hypoperfusion. Hyperlipidemia is a risk factor for atherosclerosis as well as neurodegenerative diseases such as AD, as evidenced by epidemiological, clinical, and animal studies. This is a retrospective paper. Retrospective studies investigate a phenomenon or issue that took place in the past The data show that 66.7% of Alzheimer's patients N=40 also manifest cardiovascular disease, while 20 or 33.3% of Alzheimer's patients do not report cardiovascular disease. Based on several studies, we see that hypertension is associated with brain atrophy, white matter lesions and neurofibrillary. Therefore, a link between hypertension and AD is conceivable. Further research is still needed to verify this hypothesis. Based on clinical and neuropathological studies, further study on these two diseases is more than necessary, so that a more accurate and comprehensive conclusion can be drawn, based on evidence that will enable us to clarify the risk factors of cardiovascular diseases and Alzheimer's disease

Key words: amyloid beta (Aβ); hypertension; degenerative diseases; hyperlipidemia.

INTRODUCTION

Degenerative diseases are progressive neurological disorders characterized by damage to specific nerve cells. (David et al. 2008)

The group of degenerative diseases includes Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Friedreich's ataxia, Huntington's disease, etc.

Alzheimer's disease was first described by physician Alois Alzheimer as an insidious and slowly progressive neurodegenerative disorder of the human central nervous system (CNS). (Alzheimer 1906; Alzheimer et al. 1995). This disease (AD) is a neurological disorder of the human central nervous system. It presents a progressive disorder and causes brain cells to degenerate and die. It causes a continuous decline in thinking ability (loss of recognition of persons and loss of memory), social skills and disables the ability to function independently. (Lane et al. 2018)

One of the most accepted theories of Alzheimer's pathology is the accumulation of amyloid-beta (Aβ) in cortical and hippocampal extracellular plaques. (Justin Longenberger, Zahoor A Shah. 2011). It is expected that by 2050, the prevalence of dementia will double in Europe and triple worldwide, and this estimate is 3 times higher when based on a biological (not clinical) definition of Alzheimer's disease. (Philip et al. 2021)

Cardiovascular diseases (CVD) are a group of disorders of

the heart and blood vessels. They include: Coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism.

Heart attacks and strokes are usually acute events and are mainly caused by a blockage that prevents blood flow to the heart or brain. The most common reason for this is the accumulation of fatty deposits on the inner walls of the blood vessels that supply the heart or brain. (WHO, 11 June 2021).

Evidence shows that cardiovascular disease (CVD) is on the rise and cardiovascular disease risk factors are closely related to the risk of developing Alzheimer's disease. Both AD and CVD are progressive diseases with developmental periods of decades. Cardiovascular disease may appear clinically several years earlier than Alzheimer's disease, making CVD and its risk factors a potential predictor of future AD. (Anum et al. 2023)

Hypertension as one of the most frequent cardiovascular diseases, which lasts for a longer period, which is related to endothelial dysfunction, arterial stiffness and atherosclerosis, is associated with cerebral hypoperfusion. (Qiu et al. 2005; Katayama T., Hasebe N 2013)

Furthermore, as shown by the changes found in hypertensive patients suffering from strokes, hypertension causes cerebral microinfarcts, lacunar infarcts, macrobleeds and microbleeds. These phenomena are closely related to cognitive dysfunction in general and also to Alzheimer's disease. Hypertension also causes white matter changes and is associated with abnormal Aβ accumulation, which are typical features of AD. (Iadecola C. 2014; Katayama T., Hasebe N 2013) Animal models have shown that hypertension causes disruption of the blood-brain barrier and affects Aβ (β-amyloid peptides)-related gene expression in the hippocampus. (Giacomo et al. 2020)

Another underlying mechanism is the association between white and gray matter lesions and coronary atherosclerosis, and even valvulopathies (perhaps through an embolic mechanism) may be associated with AD. (Giacomo et al. 2020)

Hyperlipidemia is a risk factor for atherosclerosis as well as neurodegenerative diseases such as AD, as evidenced by epidemiological, clinical, and animal studies. (Kivipelto et al. 2002) (Solomon et al. 2007). Studies show that total cholesterol is a risk factor for the onset of AD in middle age. The risk of developing neurodegenerative diseases is lower if antihyperlipidemic therapy is used. (Shepardson et al. 2011) (Longenberger J and Shah ZA. 2011)

MATERIAL AND METHODS

This is a retrospective paper. Retrospective studies investigate a phenomenon or issue that took place in the past. Descriptive studies are in cases where the researcher is not in direct contact with the participant, the study includes data collected from existing data, e.g. Medical histories of patients, this material included in this study. The data were obtained from the Department of Neurology in Skopje, from January 2013 to December 2023. That is, a period of 10 years. The results were processed with the help of the Pearson Chi-Square test. It is used to determine whether the data is significantly different from what you expected, to test whether two categorical variables are related to each other.

RESULTS

From a total of 943 patients, whose files we analyzed, we reached the result that only 60 patients who were hospitalized for this period were affected by Alzheimer's disease, while 271 were with cardiovascular disease.

Table 1

		Number of patients	%
Alzheimer	No	884	93.64%
	Yes	60	6.36%
Cardiovascular	No	672	71.26%
	Yes	271	28.74%
	Total	943	100.00%

The data show that 66.7% of Alzheimer's patients N=40 also manifest cardiovascular disease, while 20 or 33.3% of Alzheimer's patients do not report cardiovascular disease. From the total number of patients without Alzheimer's N=883, only 26.2% report cardiovascular disease, namely 231 patients. Considering the relationship between these two diseases, was found a very weak relationship between Alzheimer's and cardiovascular diseases, but statistically significant Phi=.218, p=.03.

Alzhajmer * Kardiovaskulare Crosstabulation

			Cardiovascular		
			No	Yes	Total
Alzhajmer	Jo	Count	652	231	883
		% within Alzhajmer	73.8%	26.2%	100.0%
		% within Kardiovaskulare	97.0%	85.2%	93.6%
		% of Total	69.1%	24.5%	93.6%
	Jo	Count	20	40	60
		% within Alzhajmer	33.3%	66.7%	100.0%
		% within Kardiovaskulare	3.0%	14.8%	6.4%
		% of Total	2.1%	4.2%	6.4%
Total		Count	672	271	943
		% within Alzhajmer	71.3%	28.7%	100.0%
		% within Kardiovaskulare	100.0%	100.0%	100.0%
		% of Total	71.3%	28.7%	100.0%

Pearson Chi-Square 45.011, df=1, p=.000

Phi=.218, p=.03

DISCUSSION AND CONCLUSION

Based on several studies, we see that hypertension is associated with brain atrophy, white matter lesions and neurofibrillary tangles (van Dijk EJ et al. 2004; Petrovic H et al. 2000). Therefore, a link between hypertension and AD is conceivable. However, this relationship is complex and changes with age. (Qiu et al. 2005). These discrepancies have not yet been clarified, but it is suggested that blood pressure decreases in the years before the clinical onset of dementia due to reduced physical activity and decreased body weight. Further research is still needed to verify this hypothesis (Duron E, Hanon O.2008).

Arterial stiffness results in increased pulsatile pressure, causing damage to the microvascular system of the brain, which in turn causes cognitive decline (O'Rourke MF, Safar ME. 2005). Indeed, several studies found an association between higher pulse pressure or higher pulse wave velocity and an increased prevalence and risk of cognitive decline or Alzheimer's disease (Hanon et.al 2005; Qiu C et al .2003) however, others could not demonstrate such an association (Poels MM et al. 2007; Dhoat S et al. 2008). Given the role of cholesterol in the clearance of amyloid β, hypercholesterolemia has been suggested as a risk factor for AD. Support for this hypothesis comes from a recent imaging study showing that higher cholesterol levels are associated with higher β amyloid levels (Reed B et al. 2014). However, the results of epidemiological studies on the association between hypercholesterolemia and AD have been inconsistent.

So far, based on our results and the papers we have analyzed, we have noticed that there is a very weak correlation between Alzheimer's and cardiovascular diseases. In order to avoid cardiovascular diseases and Alzheimer's disease, the creation of a healthier lifestyle, including good nutrition and physical activities starting from middle age and older, is undoubtedly more than necessary.

In order to reach accurate conclusions, the role of risk factors in the analyzed subjects should be continuously investigated, as well as the improvement of diagnostic criteria and neuropsychological norms.

Based on clinical and neuropathological studies, further study on these two diseases is more than necessary, so that a more accurate and comprehensive conclusion can be drawn, based on evidence that will enable us to clarify the risk factors of cardiovascular diseases and Alzheimer's disease.

In conclusion, we can freely say that the effect of cardiovascular disease and cardiovascular risk factors on Alzheimer's disease remains a broad active area for future scientific research.

REFERENCES

1. Albert MS, Dekosky St, Dickson D et al (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendation from the National Institute on Aging- Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer Dement 7:270-279
2. Alzheimer A (1906) Uber einen eigenartigen schweren Erkrankungsprozess der Hirnrinde. Neurolog Centralbl 23:1129-1136
3. Alzheimer A, Stelzmann RA, Schnitzlein HN, Murtagh R (1995) An English translation of Alzheimer's 1907 paper, "Uber eine eigenartige Erkrankund der Hirnrinde". Clin Anat 8:429-431
4. Anum Saeed, Oscar Lopez, Ann Cohen, Steven E Reis. Cardiovascular Disease and Alzheimer's Disease: The Heart Brain Axis. J Am Heart Assoc. 2023 Nov 7;12(21)
5. David E. Golan, Armen H Tashjian, Junior, Ehrin J. Arm-

strong, April W. Armstrong: Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy; 2008 ISBN 978-608-229-752-1

6. Dhoat S, Ali K, Bulpitt CJ, Rajkumar C. Vascular compliance is reduced in vascular dementia and not in Alzheimer's disease. Age Ageing. 2008;37:653–659. doi: 10.1093/ageing/afn158.
7. Duron E, Hanon O. Vascular risk factors, cognitive decline, and dementia. Vasc Health Risk Manag. 2008;4:363–381.
8. Giacomo Tini, Riccardo Scagliola, Fjammetta Monacelli, Giovanni La Malfa, Italo Porto, Claudio Brunelli and Gian Marco Rosa. Alzheimer's Disease and Cardiovascular Disease: A Particular Association. Cardiol Res Pract. 2020
9. Hanon O, Haulon S, Lenoir H, Seux ML, Rigaud AS, Safar M, Girerd X, Forette F. Relationship between arterial stiffness and cognitive function in elderly subjects with complaints of memory loss. Stroke. 2005;36:2193–2197. doi: 10.1161/01.STR.0000181771.82518.1c.
10. Hebert L. E., Beckett L. A., Scherr P. A., Evans D. A. Annual incidence of alzheimer disease in the United States projected to the years 2000 through 2050. Alzheimer Disease and Associated Disorders. 2001;15(4):169–173. doi: 10.1097/00002093-200110000-00002.
11. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol 2003; 60: 1119–22.
12. Iadecola C. Hypertension and dementia. Hypertension. 2014;64(1):3–5.
13. Justin Longenberger, Zahoor A Shah. Simvastatin and othet |HMG-CoA reductase inhibitors on brain cholesterol levels in Alzheimer's disease. Curr Alzheimer Res. 2011 Jun;8(4):434-42
14. Katayama T., Hasebe N. Angiotensin-receptor blockers, hypertension and alzheimer disease. Circulation Journal. 2013;77(2):315–316.
15. Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, Iivonen S, Mannermaa A, Tuomilehto J, Nissinen A and Soininen H: Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med. 137:149–155. 2002.
16. Lane CA, Hardy J, Schott JM. Alzheimer's disease. Eur J Neurol. 2018.
17. Longenberger J and Shah ZA: Simvastatin and other HMG-CoA reductase inhibitors on brain cholesterol levels in Alzheimer's disease. Curr Alzheimer Res. 8:434–442. 2011.
18. Medline Plus U.S. Department of Health and Human Services National Institutes of Health (2017) from: https://medlineplus.gov/alzheimersdisease.html
19. Morris JC, Blennow K, Froelich L et al (2014) Harmonised diagnostic criteria for Alheimer disease: recommendations. J Intern Med 275:204-210
20. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension. 2005;46:200–204. doi: 10.1161/01.HYP.0000168052.00426.65.
21. Petrovitch H, White LR, Izmirilian G, Ross GW, Havlik RJ, Markesbery W, Nelson J, Davis DG, Hardman J, Foley DJ, Launer LJ. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia aging Study. Neurobiol Aging. 2000;21:57–62.
22. Philip Scheltens, Bart De Strooper, Miia Kivipelto, Henne Holstege, Gael Chetelat, Charlotte E Teunissen, Jeffrey Cummings, Wiesje M van der Flier. Alheimer's disease. Lancet. 2021;397(10284):1577-1590
23. Poels MM, van Oijen M, Mattace-Raso FU, Hofman A, Koudstaal PJ, Witteman JC, Breteler MM. Arterial stiffness, cognitive decline, and risk of dementia: the Rotterdam study. Stroke. 2007;38:888–892. doi: 10.1161/01.STR.0000257998.33768.87.
24. Qiu C, Winblad B, Viitanen M, Fratiglioni L. Pulse pressure and risk of Alzheimer disease in persons aged 75 years and older: a community-based, longitudinal study. Stroke. 2003;34:594–599. doi: 10.1161/01.STR.0000060127.96986.F4.
25. Qiu C., Winblad B., Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. The Lancet Neurology. 2005;4(8):487–499.
26. Reed B, Villeneuve S, Mack W, Decarli C, Chui HC, Jagust W. Associations between serum cholesterol levels and cerebral amyloidosis. JAMA Neurol. 2014;71:195–200. doi: 10.1001/jamaneurol.2013.5390.
27. Shepardson NE, Shankar GM and Selkoe DJ: Cholesterol level and statin use in Alzheimer disease: I. Review of epidemiological and preclinical studies. Arch Neurol. 68:1239–1244. 2011.
28. Solomon A, Kåreholt I, Ngandu T, Winblad B, Nissinen A, Tuomilehto J, Soininen H and Kivipelto M: Serum

cholesterol changes after midlife and late life cognition: Twenty-one-year follow-up study. Neurology. 68:751–756. 2007.

29. Sumic A., Michael Y. L., Carlson N. E., Howieson D. B., Kaye J. A. Physical activity and the risk of dementia in oldest old. Journal of Aging and Health. 2007;19(2):242–259. doi: 10.1177/0898264307299299.
30. van Dijk EJ, Breteler MM, Schmidt R, Berger K, Nilsson LG, Oudkerk M, Pajak A, Sans S, de Ridder M, Dufouil C, Fuhrer R, Giampaoli S, Launer LJ, Hofman A. The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study. Hypertension. 2004;44:625–630. doi: 10.1161/01.HYP.0000145857.98904.20.

Profesional paper

CORRELATION BETWEEN SFLT/PLGF RATIO HIGHER THAN 200 AND ALTERED LABORATORY PARAMETARS OF PREECLAMPSIA IN HOSPITAL SETTINGS PATIENTS

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ABSTRACT

Preeclampsia affects 2–7% of all pregnancies. Worldwide it is responsible for 500,000 fetal/neonatal deaths and 70,000 maternal deaths every year.

Anti-angiogenic factor, soluble fms-like tyrosine kinase 1 (sFlt-1) and the pro-angiogenic factor, placental growth factor (PlGF) are usefull markers for screening, diagnosis and prognosis of preeclampsia.

Aim: To show our experience about the correlation between angiogenic levels and laboratory blood and urine parametars in hospital settings patients with preeclampsia.

Material and methods : Retrospective clinical study was performed in 2 years period. One hundred pregnant women with preeclampsia hospitalized in University clinic for obstetrics and gynecology in peripartal intensive care unite were evaluated .SFLT/PLGF ratio (Elecsys sFlt-1 and PlGF immunoassays), differential blood count, AST, ALT, LDH, uric acid, urine analysis (qualitative, quantitative proteinuria) were evaluated in all patients. Questionaire about sociodemographic data, age, parity, BMI, poor obstetric history, cigarette smoking, use of Aspirin or Clexane during actual pregnancy was taken during admission. Related to the sFlt-1/PIGF ratio (< 200 or ≥ 200) women were divided into two groups with 50% participants each.

Results: Our patients with SFLT/PLGF ratio >200 were significantly younger, had significantly higher proteinuria (++,+++ and quantitative), had significantly higher levels of LDH and AST and were admitted at hospital treatment at significantly lower gestational week compared to ratio < 200.

Key words: sflt/plgf, preeclampsia, laboratory parametars

BACKGROUND

Preeclampsia(PE) is a syndrome characterized by the onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive woman (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg and 0.3g proteinuria in a 24-hour urine sample). Worldwide, preeclampsia occurs in about 3–14% of all pregnancies [1].

The pathophysiology of PE is characterized by many factors such as defect in deep trophoblastic invasion, poor maternal spiral artery remodeling, intraplacental (intervillous) malperfusion during the second half of pregnancy [2].

PE carries great risk of adverse maternal and perinatal outcomes: end-organ complications, pulmonary edema, placental abruption, preterm delivery, perinatal death, fetal growth restriction, neonatal respiratory distress syndrome (RDS), intensive neonatal care admissions [3]. Also PE is associated with increased risks for cardiovascular disease later in life [4].

The recent new definition by the International Society for the Study of Hypertension in Pregnancy (ISSHP) is

including uteroplacental dysfunction (altered angiogenic profile) in the diagnostic criteria for PE. The more inclusive ISSHP definition and adding uteroplacental dysfunction to the definition of PE provides better identification of women and babies at risk of unfavourable outcome [3].

Anti-angiogenic factor, soluble fms-like tyrosine kinase 1 (sFlt-1) and the pro-angiogenic factor, placental growth factor (PlGF) are measured in serum on automated platforms, usually reported as a ratio. The cutoff of values that came out of the PROGNOSIS study are 38 which rules out preeclampsia for 1 week with a NPV of 99.3%. If the ratio is between 38 and 85 retesting in a week or two is indicated. SFlt-1/PlGF ratio > 85 is a criteria for diagnosing preeclampsia [5].

There is increasing evidence to support the use of placental growth factor and soluble fms-like tyrosine kinase-1 as well as ultrasound and clinical parametars in predicting the severity of preeclampsia [6] and the occurrence of adverse outcomes [7].

SFLT/PLGF ratio >200 requires intensive monitoring as inpatients since reports show that all have worsening preeclampsia[5].

Pre-eclampsia is the most common cause of liver and kidney dysfunction due to hypoxia and endothelial dysfunction. Maternal uric acid levels are associated with risk of pre-eclampsia[8]. Hyperuricemia indicates kidney dysfunction and is considered a predictor of the severity of preeclampsia. The levels of serum uric acid and liver function tests [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] can be used as biomarkers of preeclampsia-related organ damage[9].

Qualitative and quantitative measurement of proteinuria is one of the most common tests performed during pregnancy. Standard approach is urine dipstick test, 24-hour urine collection and urine protein-to-creatinine ratio [10]. For a long time proteinuria was necessary for the diagnosis of preeclampsia, but recent recommendations say that proteinuria is sufficient but not necessary for the diagnosis [11].

AIM

To show our experience about the correlation between angiogenic levels higher than 200 and altered standard laboratory parametars of preeclampsia in hospital settings patients.

MATERIAL AND METHODS

Retrospective clinical study was performed in 2 years period. It was apropved by local ethical commitie with signed informed consent form of all participants.

One hundred pregnant women with preeclampsia hospitalized in the University clinic for obstetrics and gynecology at the peripartal intensive care unite were evaluated .

Inclusion criteria were: age 18-45, hospitalized pregnant women with signs and symptoms of preeclampsia. Cases of pregnancies with major fetal anomalies, amnioinfectious sy, chronic inflamatory conditions were excluded.

Questionaire about sociodemographic data, age, parity, BMI, poor obstetric history (stillbirth, preeclampsia, spontaneous abortion), cigarette smoking, use of Aspirin or Enoxaparine (Clexane) during actual pregnancy was taken during admission.

Serum samples (sFIt-1/PIGF ratio, Elecsys sFlt-1 and PlGF immunoassays), urine analysis (qualitative, quantitative in 24h urine specimens), laboratory standard parametars: differential blood count, total proteins, albumins, coagulation profile including d dimer levels, lactat dehydrogenase (LDH), uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (CRE), uric acid (UA) were taken from all participants.

STATISTICAL ANALYSIS

The data obtained with the research were processed in SPSS software package, version 22.0 for Windows.

Ordinal and continuous variables were analyzed with the measures of central tendency (mean, median and IQR) as well as the measures of dispersion (standard deviation).

Pearson Chi square test, Fisher exact test were used for the analysis of the categorical variables. The calculation of risks was determined using odds ratios (OR).

The Shapiro-Wilk W test was used to determine the normality of the frequency distribution of the obtained values for the studied variables.

Analysis of ordinal and continous variables was made with Mann Whitney U test for two independent not-normally distributed parameters, and with Independent t-test for two independent parameters which have normal distribution of frequencies.

A two-sided analysis with a significance level of p<0,05 was used to determine statistical significance.

RESULTS

Out of 100 pregnant women due to exclusion criteria the study elaborated a sample of 86 women with preeclampsia.

Related to the sFlt-1/PIGF ratio (< 200 or ≥ 200) women were divided into two groups with 43 (50%) participants each.

-Body mass index

Average BMI was 31,86±5,86 kg/m2, with min/max of 21/50,6 kg/m2 and 50% of the women with BMI ≥31,5 kg/m2.

No significant differences between the groups was found related to the BMI (p=0,427), table 1.

Table 1: BMI and SFLT/PLGF ratio <200 and >200 in preeclampsia

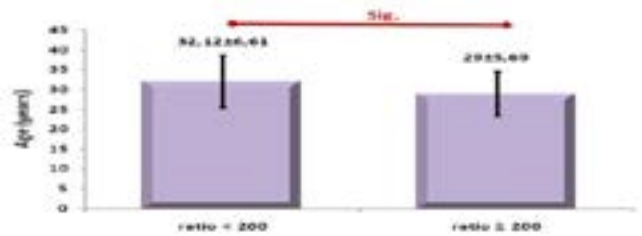
Parameters	sFlt-1/PIGF ratio		p
	< 200	≥ 200	
	(N=43)	(N=43)	
BMI (kg/m2)			
Mean±SD	32,65±5,56	31,48±6,67	t-test (68)=-0,799; p=0,427
Median (IQR)	32,1 (28,2-36,2)	30,2 (26,7-34,1)	

-Age

We found that the women with the ratio ≥ 200 were significantly younger compared to the one with ratio <200 (p=0,033), table 2, graph 1.

Table 2, graph 1: age and SFLT/PLGF ratio <200 and >200 in preeclampsia.

Parameters	sFlt-1/PIGF ratio		p
	< 200	≥ 200	
	(N=43)	(N=43)	
Age (years)			
Mean±SD	32,12±6,61	29±5,69	t-test (84)=-2,168; p=0,033*
Median (IQR)	33 (27-37)	30 (25-33)	



-Nationality, obstetric history

Related to the nationality, most of the women 47 (54,65%) were Macedonian, 28 (32,56%) were Albanian and 10 (11,62%) were from other nationalities.

The average age of the women from the whole sample was 30,68±5,95 years. Macedonians had the average age of 32,68±5,92 years and were significantly older then the Albanians 29±5,08 years (p=0,005) and the other nationalities 26,40±7,97 years (p=0,013).

Only 8 (9,30%) women were with elementary school education, 20 (23,25%) were with secondary school and 24 (27,91 %) had high education.

Previous spontaneous abortion didn't have 74 (86,05%) of the women and 12 (13,95%) reported this experience from one to 6 times in their life.

Spontaneous abortion once in life had 8 (9,30%) of the women, twice in life had 2 (3,32%) of them and three and six times was reported each by 1 (1,16%) woman.

Preeclampsia in previous pregnancy had 9 (10,46%) of the women, with 8 (9,30%) who had it once, and 1 (1,16%) who had it twice.

Single experience of stillbirth reported 6 (6,98%) women, and only 1 (1,16%) had it twice.

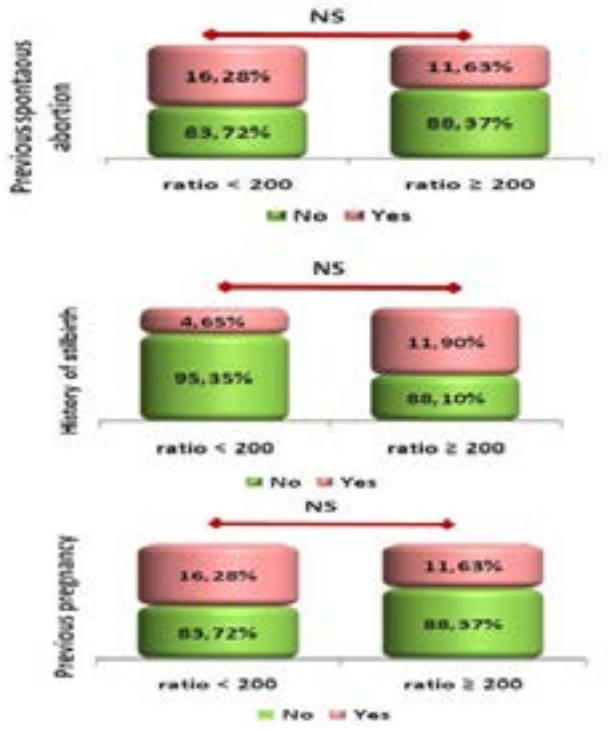
No previous pregnancies had half - 43 (50%) of the women, followed by one previous pregnancy in 21 (24,42%), two in 13 (15,12%), three in 6 (6,98%), and four and seven previous pregnancies in 1 (1,16%) woman each.

There was no significant association of the sFlt-1/PIGF ratio group to which the women belong and the previous spontaneous abortion (p=0,7556), previous preeclampsia (p=0,7246), history of stilbirth (p=0,2652), previous pregnancy (p=0,7556)(table 3, graph 2,3,4).

Table 3, Graph 2, 3, 4: previous spontaneous abortion, previous preeclampsia, history of stillbirth and previous pregnancy in SFLT/PLGF ratio in preeclampsia

Previous spontaous abortion sFlt-1/PIGF ratio < 200		sFlt-1/PIGF ratio>200	
Yes	7 (16,28%)	5 (11,63%)	p=0,7556
No	36 (83,72%)	38 (88,37%)	
Previous preeclampsia			
Yes	4 (9,30%)	5 (11,63%)	p=0,7246
No	39 (90,70%)	38 (88,37%)	
History of stilbirth			
Yes	2 (4,65%)	5 (11,90%)	p=0,2652
No	41 (95,35%)	37 (88,10%)	

Previous pregnancy			
Yes	7 (16,28%)	5 (11,63%)	p=0,7556
No	36 (83,72%)	38 (88,37%)	



-Cigarette smoking, aspirin, clexane use

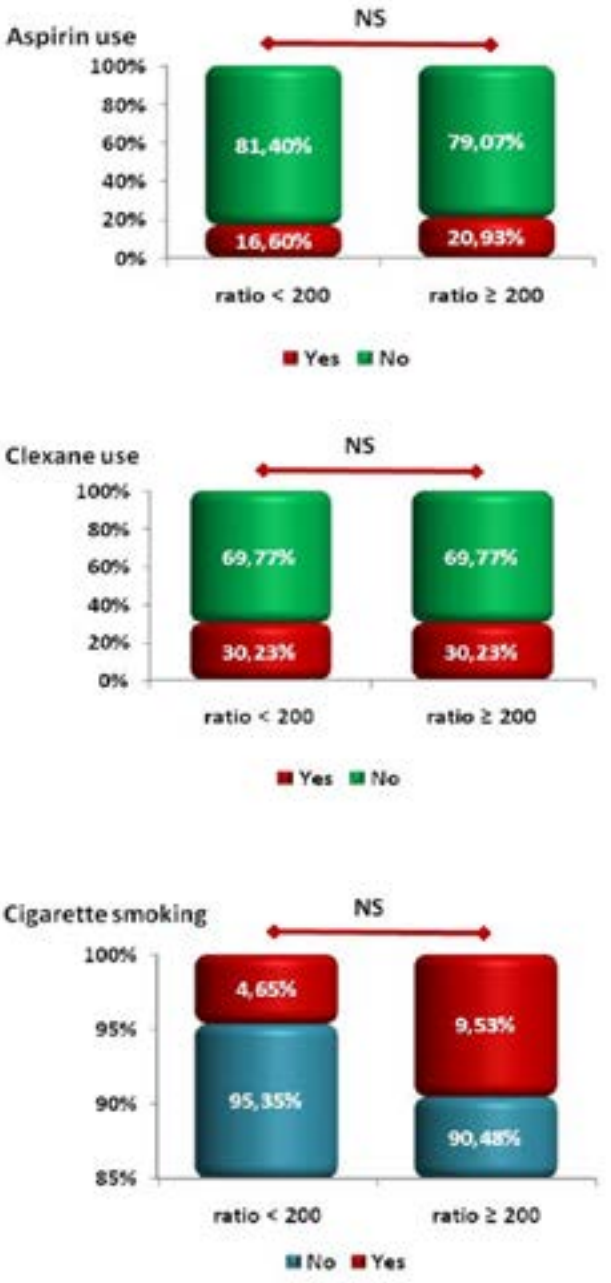
Only 6 (6,98%) of the women with preeclampsia in the whole sample were smokers.

Aspirin and enoxaparin (clexane) use reported 8 (16,60%) vs. 9 (20,93%) and 13 (30,23%) vs 13 (30,23%) of the women respectively.

There was no significant association of the sFlt-1/PIGF ratio and Aspirin use (p=0,7866), Clexane use (p=0,8144) and cigarette smoking (p=0,4331), table 4, graph 5, 6, 7.

Table 4, Graph 5, 6, 7: Aspirin use, Clexane use and cigarette smoking in SFLT/PLGF ratio <200 and >200 in preeclampsia

Aspirin use	sFlt-1/PIGF ratio<200	sFlt-1/PIGF ratio>200	
Yes	8 (16,60%)	9 (20,93%)	p=0,7866
No	35 (81,40%)	34 (79,07%)	
Clexane use			
Yes	13 (30,23%)	13 (30,23%)	p=0,8144
No	30 (69,77%)	30 (69,77%)	
Cigarette smoking			
Yes	2 (4,65%)	4 (9,53%)	p=0,4331
No	41 (95,35%)	38 (90,48%)	
*Significant for p<0,05			



Laboratory parameters in preeclampsia

Presence of proteinuria was monitored in both groups (ratio < 200 vs. ratio ≥ 200) and it was found: a) + - 20 (52,63%) vs. 15 (36,59%); ++ – 7 (18,42%) vs. 11 (26,83%); +++ – 1 (2,63%) vs. 11 (26,83%) and ++++ – o (0%) vs. 1 (2,44%) respectively.

Findings of ++ and +++ was 3,84 times more common in women from the group with ratio ≥ 200 compared to the group with ratio < 200 for OR=3,83 [95% CI (1,34-10,93)].

The average level of 24 hours proteinuria in the group with ratio ≥ 200 was 3,39±2,75 and it was significantly higher compared to 1,12±1,54 in the group with ratio < 200 (p=0,0003).

Also, the women from the group with ratio ≥ 200 had significantly higher level of LDH (p=0,0319) and AST (p=0,0309) compared to the group with ratio < 200 (Table 2).

No differences between groups has been found related to plt (p=0,4471), albumins (p=0,3554), total proteins (p=0,9286), uric acid (p=0,2507), d dimers (p=0,4705) and Hct (p=0,2268) (Table 5).

Table 5: laboratory parametars in preeclampsia with SFLT/PLGF ratio<200 and >200

Parameters	Women with preeclampsia		P
	Mean±SD	Median (IQR)	
24h proteinuria (N=53)			
sFlt-1/PIGF ratio < 200	1,12±1,54	0,6 (0,2-1,5)	Z=3,643; p=0,0003*
sFlt-1/PIGF ratio ≥ 200	3,39±2,75	2,7 (0,9-5,0)	
Plt			
sFlt-1/PIGF ratio < 200	208,40±71,49	206,6 (154-243)	t-test (83)=-0,764; p=0,4471
sFlt-1/PIGF ratio ≥ 200	219,09±56,84	219 (169-256)	
Albumins			
sFlt-1/PIGF ratio < 200	33,67±3,65	34 (31-36)	t-test (83)=-0,929; p=0,3554
sFlt-1/PIGF ratio ≥ 200	32,88±4,09	33 (29-36)	
Total proteins			
sFlt-1/PIGF ratio < 200	61,61±5,06	61 (58-66)	t-test (82)=-0,089; p=0,9286
sFlt-1/PIGF ratio ≥ 200	61,72±6,20	62 (59-65)	
LDH			
sFlt-1/PIGF ratio < 200	222,02±48,42	217,5 (188-253)	Z=2,145; p=0,0319*
sFlt-1/PIGF ratio ≥ 200	286,86±138,74	231 (197-335)	
AST			
sFlt-1/PIGF ratio < 200	27,28±36,61	20 (16-22)	Z=2,158; p=0,0309*
sFlt-1/PIGF ratio ≥ 200	30,67±31,70	22 (17-31)	
ALT			
sFlt-1/PIGF ratio < 200	30,12±75,49	14 (10-18)	Z=2,035; p=0,0419*
sFlt-1/PIGF ratio ≥ 200	23,86±23,09	17 (12-21)	
Uric acid			
sFlt-1/PIGF ratio < 200	325,11±100,87	317 (271-384)	t-test (83)=1,157; p=0,2507
sFlt-1/PIGF ratio ≥ 200	347,63±77,30	349 (281-394)	
d dimers			
sFlt-1/PIGF ratio < 200	2149,24±1919,27	1511 (1012-2349)	Z=0,722; p=0,4705
sFlt-1/PIGF ratio ≥ 200	2563,58±2354,39	1768,5 (989,3-3350)	
Hct			
sFlt-1/PIGF ratio < 200	0,34±0,33	0,3 (0,3-0,4)	t-test (80)=1,2179; p=0,2268
sFlt-1/PIGF ratio ≥ 200	0,35±0,03	0,3 (0,3-0,5)	
*Significant for p<0,05			

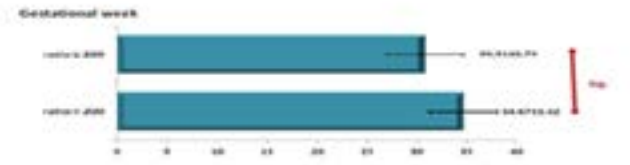
Gestational week at admission

In the group with ratio < 200, the average gestational week at admission was 34,67±3,42 with min/max of 21,4/39,1.

In the group with ratio ≥ 200, the average gestational week at admission was 30,81±3,79 with min/max of 18/37.

The women with ratio ≥200 were admitted at the clinic at significantly lower gestational week compared to the one from the group with ratio < 200 (p=0,00001), graph 8.

Graph 8: gestational age at admission and preeclampsia



DISCUSSION

Pre-eclampsia can be described as new-onset hypertension (blood pressure ≥140/90 mmHg) together with proteinuria (24-hr urinary protein ≥ 0.3 g) or any indication of end-organ damage after 20 weeks of gestation. Liver and kidney dysfunction, thrombocytopenia, pulmonary edema, and neurologic dysfunction are common manifestations of end-organ damage due to pre-eclampsia[1, 2].

Although around 30% of all pregnancies are evaluated for preeclampsia, diagnosis is still difficult, especially in patients who have overlying symptoms from other diseases.

The more inclusive International Society for the Study of Hypertension in Pregnancy definition of preeclampsia seems to be more sensitive. The addition of uteroplacental dysfunction to the broad definition optimizes the identification of women and babies at risk, particularly when angiogenic factors are included [3].

Angiogenic markers are non-invasive markers of placental health and are used for diagnosis, prognosis and prediction of preeclampsia. Use of SFLT/PLGF between 24 and 34 gw is facilitating the very complex, individually-based clinical decision-making process. It significantly improves clinical precision.

SFlt-1/PlGF cut-offs have been described to assess preeclampsia severity. A ratio > 200 should prompt further concern since it carries increased risk for fetal and maternal adverse events[5].

Having that in mind we evaluated hospitalized cases of preeclampsia according to SFLT/PLGF ratio less and more than 200. We performed standard clinical and laboratory tests for all cases as well as SFLT/PLGF ratio and compared the anamnestic, sociodemografic, anamnestic and laboratory parametars in the groups of SFLT/PLGF ratio > and <200.

For years laboratory markers have been a standard approach to clinical management and assessment of clinical condition. Hassen et al revealed that serum uric acid, ALT, and AST levels were higher in pre-eclamptic pregnant women compared to those of normotensive pregnant women. As such, serum uric acid and liver function tests may be considered biomarkers of pre-eclampsia-related end-organ damage[9].

Colmenares-Mejia et al found that there was a positive linear association between increasing uric acid levels and presence of pre-eclampsia[8].

Our results demonstrated that in patients with preeclampsia and angiogenic markers ratio ≥ 200 had significantly higher level of LDH (p=0,0319) and AST (p=0,0309) compared to the group with ratio < 200. No significant differences between groups were found in relation to other standard laboratory parametars like plt (p=0,4471), albumins (p=0,3554), total proteins (p=0,9286), uric acid (p=0,2507), d dimers (p=0,4705) and Hct (p=0,2268).

Fishel Bartal Still et al say that in clinical practice, most patients with gestational hypertension will be diagnosed as having preeclampsia based on the presence of proteinuria[10]. Furthermore, they do not recommend repeated measurement of proteinuria for women with preeclampsia, as monitoring proteinuria may lead to unindicated preterm deliveries and related neonatal complications.

We measured the proteinuria in both groups (SFLT/PLGF < 200 vs. SFLT/PLGF ≥ 200) and findings of ++ and +++ was 3,84 times more common in women from the group with ratio ≥ 200 for OR=3,83 [95% CI (1,34-10,93)]. The average level of quantitative proteinuria in 24h specimen was significantly higher, 3,39±2,75 compared to 1,12±1,54 in the group with ratio > 200 vs ratio<200 (p=0,0003).

Limited data are available regarding angiogenic and other biomarkers in women with chronic kidney disease as a potential aid in distinguishing the worsening of baseline chronic kidney disease and chronic hypertension from superimposed preeclampsia[11].

Regarding prevention of preeclampsia it confirmed that intake of low-dose aspirin starting from 11 to 14 weeks of gestation until 36 weeks of gestation reduces the risk of preterm preeclampsia[13]. Our results revealed Aspirin use in 16,60% vs 20,93% (sFlt-1/PIGF ratio<200 vs sFlt-1/PIGF ratio>200) of the women in the group. However no significant association of the sFlt-1/PIGF ratio and Aspirin use was found, p=0,7866.

Many trials evaluating the effect of low-molecular-weight heparin for the prevention of preeclampsia or small-for-gestational-age have shown conflicting results. Groom et al conducted an open-label randomized controlled trial in 5 tertiary care centers and 3 countries regarding the effectiveness of enoxaparin in addition to high-risk care for the prevention of preeclampsia and small-for-gestational-age in women with a history of these conditions. The trial concluded that use of enoxaparin in addition to standard high-risk care does not reduce the risk of recurrence of preeclampsia and SGA fetuses in a subsequent pregnancy.

In our study same number of patients used Clexane 13 (30,23%) of each group. Significance between Enoxaparin use and angiogenic ratio was not found (p=0,8144).

CONCLUSION

Our patients with SFLT/PLGF ratio >200 were significantly younger, had significantly higher proteinuria (++,+++ and quantitative) and had significantly higher levels of LDH and AST. Pregnant women with preeclampsia and SFLT/PLGF ratio >200 were admitted at our clinic at significantly lower gestational week compared to the one from the group with ratio < 200.

We conclude that combination of clinical and standard laboratory parametars as well as angiogenic profile may be of clinical use in better clinical management.

Further research is needed on their clinical utility in various circumstances.

Keywords: SFLT/PLGF, laboratory parametars, preeclampsia

REFERENCES

1. Lehnen H, Mosblech N, Reineke T, Puchooa A, Menke-Möllers I, Zechner U, Gembruch U. Prenatal Clinical Assessment of sFlt-1 (Soluble fms-like Tyrosine Kinase-1)/ PlGF (Placental Growth Factor) Ratio as a Diagnostic Tool for Preeclampsia, Pregnancy-induced Hypertension, and Proteinuria. Geburtshilfe Frauenheilkd. 2013 May;73(5):440-445. doi: 10.1055/s-0032-1328601. PMID: 24771924; PMCID: PMC3864477.
2. Holger Stepan, Martin Hund and Theresa Andraczek. Combining Biomarkers to Predict Pregnancy Complications and Redefine Preeclampsia, The Angiogenic-Placental Syndrome. doi.org/10.1161/ Hypertension. 2020;75:918–926.
3. Lai J, Syngelaki A, Nicolaides KH, von Dadelszen P, Magee LA. Impact of new definitions of preeclampsia at term on identification of adverse maternal and perinatal outcomes. Am J Obstet Gynecol. 2021 May;224(5):518.e1-518.e11. doi: 10.1016/j.ajog.2020.11.004. Epub 2020 Nov 6. PMID: 33166504.
4. Garovic V.D., White W.M., Vaughan L. et al. Incidence and long-term outcomes of hypertensive disorders of pregnancy. J Am Coll Cardiol. 2020; 75: 2323-2334
5. Stefan Verlohren, Shaun P. Brennecke, Alberto Galindo, S. Ananth Karumanchi, Ljiljana B. Mirkovic, Dietmar Schlembach, Holger Stepan, Manu Vatish, Harald Zeisler, Sarosh Rana. Clinical interpretation and implementation of the sFlt-1/PlGF ratio in the prediction, diagnosis and management of preeclampsia. Review article. Pregnancy Hypertension Volume 27, March 2022, Pages 42-50
6. Kumar N, Das V, Agarwal A, Agrawal S. Correlation of sFlt/PlGF ratio with severity of preeclampsia in an Indian population. AJOG Glob Rep. 2023 Feb 7;3(2):100177. doi: 10.1016/j.xagr.2023.100177. PMID: 36911235; PMCID: PMC9992748.
7. Garcia-Manau P, Mendoza M, Bonacina E, Garrido-Gimenez C, Fernandez-Oliva A, Zanini J, Catalan M, Tur H, Serrano B, Carreras E. Soluble fms-like tyrosine kinase to placental growth factor ratio in different stages of early-onset fetal growth restriction and small for gestational age. Acta Obstet Gynecol Scand. 2021 Jan;100(1):119-128. doi: 10.1111/aogs.13978. Epub 2020 Sep 14. PMID: 32860218.
8. Colmenares-Mejia CC, Quintero-Lesmes DC, Bautista-Niño PK, Guío E, Paez MC, Beltrán M, Williams D, Gray KJ, Casas JP, Serrano NC. Uric acid and risk of preeclampsia: results from a large case-control study and meta-analysis of prospective studies. Sci Rep. 2023 Feb 21;13(1):3018. doi: 10.1038/s41598-023-29651-4. PMID: 36810371; PMCID: PMC9944921.
9. Hassen FS, Malik T, Dejenie TA. Evaluation of serum uric acid and liver function tests among pregnant women with and without preeclampsia at the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia. PLoS One. 2022 Aug 4;17(8):e0272165. doi: 10.1371/journal.pone.0272165. PMID: 35926005; PMCID: PMC9352010.
10. Fishel Bartal M, Lindheimer MD, Sibai BM. Proteinuria during pregnancy: definition, pathophysiology, methodology, and clinical significance. Am J Obstet Gynecol. 2022 Feb;226(2S):S819-S834. doi: 10.1016/j.

ajog.2020.08.108. Epub 2020 Sep 1. PMID: 32882208.

11. George R. Saade. Proteinuria in pregnancy: much ado about nothing, //doi.org/10.1016/AJOG. Volume 224, ISSUE 4, P421, April 2021.
12. Staff AC. The two-stage placental model of preeclampsia: An update. J Reprod Immunol. 2019 Sep;134-135:1-10. doi: 10.1016/j.jri.2019.07.004. Epub 2019 Jul 8. PMID: 31301487.
13. Daniel L. Rolnik, M.D., David Wright, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. N Engl J Med 2017; 377:613-622. DOI: 10.1056/NEJMoa1704559
14. Groom KM, McCowan LM, et al. Enoxaparin for Prevention of Preeclampsia and Intrauterine Growth Restriction Trial Investigator Group. Enoxaparin for the prevention of preeclampsia and intrauterine growth restriction in women with a history: a randomized trial. Am J Obstet Gynecol. 2017 Mar;216(3):296.e1-296.e14. doi: 10.1016/j.ajog.2017.01.014. Epub 2017 Jan 30. PMID: 28153659.

Profesional paper

KNOWLEDGE, EXPERIENCES AND ATTITUDES OF PATIENTS REGARDING THE PHARMACOVIGILANCE SYSTEM IN THE REPUBLIC OF NORTH MACEDONIA

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ABSTRACT

Introduction The enormous amount of information about drugs, adverse reactions during the use of drugs, and the scientific approach to their study led to the creation of a new science - pharmacovigilance, which deals with problems related to drugs. Although, almost all countries have pharmacovigilance systems in place, these systems vary. In recent years, the problem with safety of patients/users of drugs and medical devices is becoming more and more relevant both in the world and in the Republic of North Macedonia.

Aim of the paper: To determine the knowledge, experiences and attitudes of patients regarding the established pharmacovigilance system in the Republic of North Macedonia.

Material and methods: A cross-sectional study was conducted using a survey questionnaire in 200 patients, aged 18 to 65 years with at least a high school education. The purpose of the survey questionnaire was to determine the knowledge, experiences and attitudes of patients regarding the established pharmacovigilance system in our country. Data were statistically processed with tests adequate for the sample characteristics, using Statistica 10.0.

Results:The percentage difference between the affirmative and negative responses of the patients, regarding the knowledge of the pharmacovigilance system, is statistically significant for $p<0.05$ (Difference test, p=.0000). Only 1.0% of the respondents knew that the Agency for Medicines and Medical Devices is the regulatory body responsible for monitoring adverse drug reactions. 32.0% of respondents correctly answered question no. 5, that is, they knew that apart from health professionals, patients can also report an adverse drug reaction. Only 13.0% of the respondents answered that the purpose of reporting is to increase patient safety. The percentage difference in terms of experience with an adverse drug reaction between those respondents who gave an affirmative answer versus those who gave a negative answer is statistically significant for $p<0.05$ (Difference test, p=.0000). The difference in patients' attitudes about the pharmacovigilance system is statistically insignificant for $p>0.05$.

Conclusion: The patients in our study have minimal knowledge of the pharmacovigilance system, and their negative attitude towards reporting adverse reactions caused by drugs is a concern.

Key words: pharmacovigilance, patients, adverse drug reactions

INTRODUCTION

The enormous amount of information about drugs, adverse reactions during the use of drugs, and the scientific approach to their study led to the creation of a new science - pharmacovigilance, which deals with problems related to drugs. According to the WHO, pharmacovigilance is a scientific discipline that includes activities related to the detection, assessment and prevention of adverse effects of drugs, as well as other problems related to their application[1]. Today, pharmacovigilance, quite justifiably, has a significant place both for the research and development of drugs, but also for their post-marketing phase, that is, their monitoring after placing the drug on the market[2].

Although, almost all countries have pharmacovigilance systems in place, these systems vary. Namely, the population of different countries and geographical regions differ from each other in terms of genetic and epigenetic factors, the prevalence of diseases, the manner of prescribing drugs, the application of traditional and herbal medicines, the production processes of drugs, diet and customs. Therefore, the unexpected reactions are different. Exactly for these reasons, it is important that each country has a national system for monitoring the drugs that have been placed on the market. The actors of the pharmacovigilance system in each country are as follows: healthcare professionals, marketing authorization holders, national centers for pharmacovigilance/regulatory institutions, and patients[3].

In recent years, the problem with safety of patients/users of drugs and medical devices is becoming more and more relevant both in the world and in the Republic of North Macedonia. That problem is being discussed more and more in scientific and professional circles between health workers and associates. This problem is incorporated in the relatively new scientific system - medical (health) law. In addition, information related to drug and nursing safety is also presented through print and electronic media, so that the community learns more about the problem. Pharmacovigilance systems are relatively new and dynamic systems that in recent years, after the incidents that have occurred (the thalidomide disaster[4, 5], the mass intoxication with digitoxin[6] and the terodiline hydrochloride case[7]), have gained importance in terms of public health protection. Until now, the experiences, knowledge and attitudes of patients about the pharmacovigilance system have not been investigated in our country. Therefore, the aim of our paper was to determine the knowledge, experiences and attitudes of patients regarding the established pharmacovigilance system in the Republic of North Macedonia.

MATERIAL AND METHOD

In order to answer the set goal, we conducted a cross-sectional study using a survey questionnaire among 200 patients who visited the PHI University Dental Clinical Center, "St. Panteleimon'' in Skopje to receive dental services. Patients aged 18 to 65, and who have completed at least secondary education were included in the research.

The survey questionnaire consisted of 13 questions aimed at determining the knowledge, experiences and attitudes of patients about the established pharmacovigilance system in our country. All collected data were processed using appropriate statistical methods. Statistical analysis was performed in the program Statistica 10.0 (Data Analysis Software System). Results of the study are presented with total numbers and percentages. Chi-square test was used to find the association between two attributes at $P < 0.05$ significance.

RESULTS

Of the 200 patients who were included in our research, 44.5% were male and 55.5% were female. The average age of the respondents in the whole group was 46.1±13.1 years. 45.5% of respondents had secondary education, and 54.5% had higher education. For the most part, the surveyed patients i.e. 88.5% live in an urban settlement, and only 11.5% live in a rural settlement. According to ethnicity, the majority are Macedonians - 61.5%, Albanians - 20.0%, Roma - 8.5% and others (Turks, Serbs, Aromanians, and others) - 10.0%.

Considering the purpose of our paper and the type of questions, and for the sake of greater overview of the obtained results, we have systematized them in 3 parts. Namely, the first part, which refers to patients' knowledge of the pharmacovigilance system, contains two tables. The second part deals with patients' experiences of the pharmacovigilance system, while the third part deals with patients' attitudes towards this system.

Patients' knowledge of the pharmacovigilance system

Table 1: Results obtained from knowledge domain among patients

Question	Positive answer		Negative answer		Didn't answer	
	no.	%	no.	%	no.	%
Q1. Have you ever heard of the term pharmacovigilance?	16	8,0	152	76.0	32	16,0
Q2. Did you know that medications can cause adverse effects?	138	69,0	28	14,0	34	17,0
Q3. Has a pharmacovigilance system been established in the Republic of North Macedonia?	4	2,0	196	98,0	0	0

The percentage difference between confirmed and negative responses of patients shown in table no. 1, which refer to the knowledge regarding the pharmacovigilance system, is statistically significant for $p<0.05$ (Difference test, $p=.0000$).

Table 2: Correct and incorrect knowledge of patients about medicine and pharmacovigilance

Question	Correct answer		Incorrect answer	
	no.	%	no.	%
Q4. If you believe that the pharmacovigilance system is in place, which regulatory body is responsible for monitoring adverse drug reactions?	2	1,0	198	99,0
Q5. In your opinion, who can report an adverse drug reaction?	64	32,0	136	68,0
Q6. What is the purpose of reporting adverse drug reactions?	18	9,0	182	91,0

In table no. 2, to question no. 4, only 1.0% of respondents knew that the Agency for Medicines and Medical Devices is the regulatory agency responsible for monitoring adverse drug reactions. 32.0% of respondents correctly answered question no. 5, that is, they knew that apart from health professionals, patients can also report an adverse drug reaction. Only 13.0% of respondents answered that the purpose of reporting is to increase patient safety (question no. 6).

The percentage difference between those who gave a correct answer versus those who gave an incorrect answer is statistically significant for $p<0.05$ (Difference test, $p=.0000$).

Patients' experiences of the pharmacovigilance system

Table 3: A presentation of patient responses to adverse drug reaction experience

Question	Positive answer		Negative answer		Didn't answer	
	no.	%	no.	%	no.	%
Q7. Have you ever had an adverse reaction to a medication?	54	27,0	70	35,0	76	38,0
Q8. Have you ever seen an adverse drug reaction happen to someone else?	52	26,0	80	40,0	68	34,0
Q9. Have you ever reported an adverse drug reaction?	20	10,0	180	90,0	0	0

The percentage difference between those who gave an affirmative answer versus those who gave a negative answer is statistically significant for $p<0.05$ (Difference test, $p=.0000$) (Table 3).

Patients' attitudes regarding the pharmacovigilance system

Table 4: Results obtained from attitude domain among patients

Question	Positive answer		Negative answer		Didn't answer	
	no.	%	no.	%	no.	%
Q10. Do you think reporting adverse drug reactions is necessary?	90	45,0	76	38,0	34	17,0
Q11. Do you think that establishing a system for reporting adverse drug reactions is useful for the public?	82	41,0	80	40,0	38	19,0
Q12. Do you think patients should know that they can report adverse drug reactions?	4	2,0	188	94,0	8	4,0

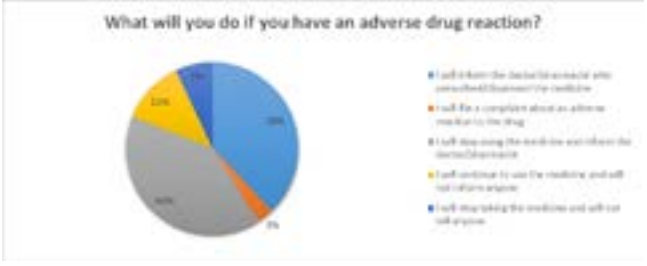
Regarding Q10, the percentage difference between those who have a positive attitude versus those who have a negative attitude is statistically insignificant for p>0.05. No significant association was registered between gender, age (above and below 40 years), level of education, place of residence and ethnicity on the one hand and the answer given by the surveyed patients to question no. 10 (Table 4) on the other hand.

Regarding Q11, the percentage difference between those who have a positive attitude versus those who have a negative attitude is statistically insignificant for p>0.05. No significant association was registered between gender, age (above and below 40 years), level of education, place of residence and ethnicity on the one hand and the answer given by the surveyed patients to question no. 11 (Table 4) on the other hand.

Regarding Q12, the percentage difference between those who have a positive attitude versus those who have a negative attitude is statistically insignificant for p>0.05. No significant association was registered between gender, age (above and below 40 years), level of education and ethnicity on the one hand and the answer given by the surveyed patients to question no. 12 (Table 4) on the other hand.

We registered a significant association between the place of residence and the positive attitude of the surveyed patients that they should know that they can report adverse drug reactions (Pearson Chi-square: 5.9813, df=1, p=.0144585).

Chart 1: What will you do if you have an adverse drug reaction?



The percentage difference between those who answered that they will inform the doctor/pharmacist who prescribed/dispensed the drug and that they will stop using the drug and inform the doctor/pharmacist versus those who answered otherwise is statistically significant for p<0, 05 (Difference test, p=.0000) (Chart 1).

DISCUSSION

In order to assess the respondents' knowledge of the pharmacovigilance system, the questionnaire asked whether they had ever heard of the term pharmacovigilance. For the most part, that is, 76.0% stated that they had not heard of the pharmacovigilance system, 16.0% did not give an answer, and only 8.0% (16 respondents) of those surveyed had heard of the term (Table 1). The percentage difference between those who have not heard or do not know about the term pharmacovigilance versus those who have heard is statistically significant for p<0.05 (Difference test, p=.0000). The data that were available to us in the reviewed literature are in accordance with our results, that is, other researches also show that the number of patients who have heard of the term pharmacovigilance is low. Thus, in a study conducted in Nigeria, the percentage of patients who had heard of this term was 8.6% [8], while in another study conducted in the same country, this percentage was 4.1% [9], Sales et al. [10] in the research they have conducted in Saudi Arabia, determined that 15.1% of the examined patients had heard of the term pharmacovigilance. In a survey conducted in Portugal, 44.1% of the respondents had never heard of the pharmacovigilance system. However, the authors concluded that young people with at least secondary education have significantly greater opportunities to become aware of the existence of this system[11]. In Brazil, the percentage of respondents who have not heard of this term is 65%[12]. According to a large number of authors, the degree of knowledge of patients in developing countries as well as in developed countries is low[13,14].

To the question "Has a pharmacovigilance system been established in the Republic of North Macedonia", only four respondents (2.0%) gave the correct answer, while 196 respondents gave an incorrect answer (Table 1). The percentage difference between those who gave a correct answer versus those who gave an incorrect answer is statistically significant for p<0.05 (Difference test, p=.0000). Of these, only two respondents knew that the Agency for Medicines and Medical Devices is the regulatory body where adverse events are reported. The data we received is worrying. Namely, although the literature talks about a lack of knowledge about the pharmacovigilance system[10,13-15], we did not find any data with this level of knowledge. Unfortunately, only 9% of the respondents knew the purpose of the pharmacovigilance system - increasing patients' safety. Unlike our respondents, in

a study conducted in Nepal, 52.17% of respondents knew the purpose of pharmacovigilance[15].

In our research, when asked who can report an adverse drug reaction, only 64 respondents (32.0%) gave the correct answer, while 136 respondents gave an incorrect answer (Table 2). The percentage difference between those who gave a correct answer versus those who gave an incorrect answer is statistically significant for $p<0.05$ (Difference test, p=.0000). In our opinion, this is due to insufficient knowledge of the pharmacovigilance system, the purpose of this system and who should participate in it.

To the question "Do you know that drugs can cause adverse reactions?", most of the respondents - 69.0% answered affirmatively, 14.0% answered negatively, while 17.0% of the respondents did not give an answer (Table 1). The percentage difference between those who know versus those who do not know is statistically significant at $p<0.05$. The results are similar in other researches. A survey conducted in India indicated that 78.6% of patients are aware that the drug may cause an adverse reaction[16]. In another study in this country, it was determined that 32.2% of patients are not aware that drugs can have adverse effects[17]. An interesting study was conducted in the USA by Shrank et al. (2009), in which 10% of patients believe that generic drugs can cause more adverse reactions than originator drugs[18].

In order to assess patients' experience of experiencing an adverse drug reaction, we asked them in the survey questionnaire whether they had experienced an adverse drug reaction or had seen someone else experience an adverse drug reaction. To the question "Have you ever had an adverse reaction to any drug you have taken?", most of the respondents - 35.0% gave a negative answer, 27.0% of the respondents gave a negative answer, while 38.0% of the patients did not answer at all (Table 3). The percentage difference between those who answered negatively versus those who answered positively is statistically insignificant for $p>0.05$ (Difference test, p=.0837).

To the question "Have you ever seen an adverse drug reaction that happened to someone else?", most of the respondents answered negatively - 40.0%, 26.0% of the respondents answered positively, while 34.0% did not answer at all (Table 3). The percentage difference between those who gave a negative answer versus those who gave a positive answer is statistically significant for $p<0.05$ (Difference test, p=.0029). The results obtained in other researches are similar. In a study by Joshi A et al.[16] 33% of respondents stated that they had an adverse drug reaction, while 39.3% stated that they had seen an adverse drug reaction in other people. Similar are the results obtained in the research in Malaysia[19]. In Adisa's study[8], this percentage is 24.7%. In another study conducted in India, the percentage of patients who reported an adverse drug reaction was 29.4%[20]. A research conducted in Brazil, among oncology patients, showed that 70% of respondents answered positively to the question about adverse drug reaction[21]. According to a meta-analysis by Miguel A et al. it has been determined that adverse drug reactions can occur in 16.8% of hospitalized patients[22]. The results of our study are not consistent with the results obtained from the study conducted in Poland by Staniszewska et al. [23] in which 92% of respondents answered that no adverse event happened to them.

Since patients have the option of reporting an adverse drug reaction, we asked them if they had ever reported an adverse drug reaction. Most of the respondents, 90.0% of the patients, answered that they did not report such an event, while 10.0% of the respondents gave a positive answer (Table 3). The percentage difference between those who gave a negative answer versus those who gave a positive answer is statistically significant for $p<0.05$ (Difference test, p=.0000). Our results completely coincided with the results obtained in the research by Hazell and Shakir[24] in which it was estimated that more than 90% of adverse drug reactions are not reported. The problem of non-reporting of adverse drug reactions by patients is also present in highly developed countries. Namely, data collected by the WHO for 2013 indicate that in Great Britain, the percentage of patients who reported an adverse drug reaction, considered from the total number of reports of an adverse drug reaction, is 7.3%, in Germany – 6%, in France – 3.1%, in Spain and Italy about 2% (Poland). According to a study conducted in Denmark[25], in the period 2004-2006, 8.6% of the reports of an adverse drug reaction were given by patients. In the Netherlands, in 2005, this percentage was 13%[26]. Unlike Europe, in Canada[27] 10.8% of the reports in 2008 were from patients, while in the USA, for the same year, this percentage was 46%, which is a remarkable increase compared to the 90s[28].

Taking into account the situation we have established, that the majority of adverse drug reactions remain unreported by patients, it was of interest to us to find

out whether patients consider it necessary to report adverse drug reactions. Most of the surveyed patients – 45.0% consider that reporting an adverse drug reaction is necessary, 38.0% consider it not necessary, while 17.0% of the surveyed did not answer (Table 4). The percentage difference between those who consider it necessary to report adverse drug reactions versus those who consider it not necessary is statistically insignificant for $p>0.05$ (Difference test, p=.1554).

Regarding the question of whether patients think that the establishment of a system for reporting adverse drug reactions will be useful for the public, we encountered divided opinions. Namely, 41.0% of the surveyed patients think that it will be useful for the public, while 40% - think that it will not be useful for the public (Table 4). The percentage difference between patients with a positive attitude towards this issue and those with a negative attitude is statistically insignificant for $p>0.05$ (Difference test, p=.8386). Our research has shown that the surveyed patients are divided regarding the reporting of adverse drug reactions and the establishment of a reporting system. Of course, it is worrying that the percentage of surveyed patients who do not have a positive attitude towards these serious issues is high. Our results contradict the results obtained in the literature where over 90% of respondents confirmed that reporting is necessary and useful[15,29,30].

Taking into account the previous attitudes of patients about the establishment of the reporting system and the usefulness of reporting, we are not surprised by the fact that the respondents answered that they should not know that they can report an adverse drug reaction. In our research, to the question "Do you think patients should know that they can report adverse drug reactions?", 94.0% of the respondents believe that they should not know that, only 2.0% of the respondents think they should know that, and 4.0% of the respondents did not answer this question (Table 4). The percentage difference between patients who think they should know about the possibility of reporting adverse drug reactions versus those who think they should not know is statistically significant for $p<0.05$ (Difference test, p=.0000). These results show that our patients find the responsibility for reporting adverse drug reactions with healthcare professionals. This attitude of ours should certainly be confirmed by further research. In addition to this attitude of our respondents, the data in the literature indicate that the inclusion of patients in the pharmacovigilance system can have a number of advantages[31,32].

WHO states that the number of countries that encourage patients to report adverse drug reactions through the spontaneous reporting system (e.g. Australia, Canada, Denmark, Netherlands, Sweden, Great Britain, USA) is increasing. WHO and the European Commission have recognized the role of users in spontaneous reporting. Users, patients and their associations are increasingly involved in the pharmacovigilance system, especially in the risk communication process. [33].

However, when asked what will you do if you experience an adverse drug reaction, most of the respondents - 40.0% answered that they would stop taking the drug and inform the doctor/pharmacist, 38.0% of the respondents answered that they would inform the doctor/pharmacist who prescribed/dispensed the drug, 12.0% answered that they will continue taking the drug and will not inform anyone and 7.0% answered that they will stop taking the drug and will not inform anyone. However, the lowest percentage of them (3%) answered that they would file a complaint about an adverse drug reaction (Chart 1). The obtained data are not in accordance with the data we found in the literature where the percentage of patients who answered that they would stop taking the drug and inform the doctor/pharmacist was high [8].

CONCLUSION

The patients in our study had minimal knowledge of the pharmacovigilance system and their negative attitude towards reporting adverse reactions caused by drugs is a concern.

BIBLIOGRAPHY

1. World Health Organization. WHO Policy Perspectives on Medicines, Pharmacovigilance: ensuring the safe use of medicines. Geneva, 2004.
2. Pharmaceutical Research and Manufacturers of America. Drug Discovery and Development Process Brochure. Understanding the R&D Process 2007. Available at: http://cmidd.northwestern.edu/ files/2015/10/Drug_RD_Brochure-12e7vs6.pdf. Accessed on: 20.6.2020
3. Petronijević M. Farmakoepidemiološka studija spontano prijavljenih hepatotoksičnih reakcija na lekove i biljne dijetetske suplemente (doktorska disertacija). Univerzitet u Beogradu, Farmaceutski fakultet. Beograd, 2013.

4. Ivetić Tkalčević V, Letinić Klier G, Lazarić Bošnjak P, Marijanović Barać K. Farmakovigilancija – uvijek budni čuvari sigurnosti pacijenata. Medicus 2017;26(1):53-58.
5. Mandić I, Krajnović D. Talidomidska tragedija - lekcija iz prošlosti. Timočki medicinski glasnik 2009; 34 (2): 126-134.
6. Van Grootheest K: The dawn of pharmacovigilance. Int J Pharm Med. 2003;17(5–6):195–200.
7. Wild RN. Micturin and torsades de pointes. во: Mann RD, Andrews EB (editor). Pharmacovigilance. 1st edition. John Wiley & Sons, 2002.
8. Adisa, R., Omitogun, T.I. Awareness, knowledge, attitude and practice of adverse drug reaction reporting among health workers and patients in selected primary healthcare centres in Ibadan, southwestern Nigeria. BMC Health Serv Res 2019; 19: 926
9. Adisa R, Adeniyi OR, Fakeye TO. Knowledge, awareness, perception and reporting of experienced adverse drug reactions among outpatients in Nigeria. Int J Clin Pharm. 2019; 41(4):1062-1073.
10. Sales I, Aljadhey H, Albogami Y, Mahmoud MA. Public awareness and perception toward Adverse Drug Reactions reporting in Riyadh, Saudi Arabia, Saudi Pharmaceutical Journal, 2017; 25 (6): 868-872.
11. Matos C, van Hunsel F, Joaquim J. Are consumers ready to take part in the Pharmacovigilance System? -a Portuguese preliminary study concerning ADR reporting. Eur J Clin Pharmacol. 2015; 71(7): 883–890.
12. Julian GS, Oliveira RW, Minowa E, Cecilio L, Barros LHC. Pharmacovigilance knowledge in Brazil: perception of participants of oncology patient advocacy group on adverse events reporting. Braz J Oncol. 2018;14:1-11.
13. Aziz Z, Siang TC, Badarudin NS. Reporting of adverse drug reactions: predictors of under-reporting in Malaysia. Pharmacoepidemiol Drug Saf. 2007;16:223–8.
14. Robertson J, Newby DA. Low awareness of adverse drug reaction reporting systems: a consumer-survey. Med J Austr. 2013; 199: 684–6.
15. Jha N, Rathore DS, Shankar PR, Gyawali S. Pharmacovigilance Knowledge among Patients at a Teaching Hospital in Lalitpur District, Nepal. J Clin Diagn Res. 2014;8(3):32-34.
16. Joshi A, Shah N, Mistry M, Gor A. Evaluation of knowledge and perception toward adverse drug reactions among patients visiting tertiary-care teaching hospital. Natl J Physiol Pharm Pharmacol. 2015; 5(4): 280-284.
17. Patel JJ et al. Knowledge, attitude and practice among consumers about adverse drug reaction reporting. Int J Basic Clin Pharmacol. 2019; 8 (8):1776-1782.
18. Shrank WH, Cadarette SM, Cox E, Fischer MA, Mehta J, Brookhart AM, et al. Is there a relationship between patient beliefs or communication about generic drugs and medication utilization? Med Care. 2009;47(3):319-25.
19. Elkalmi R, Hassali MA, Al-Lela OQ, Jawad Awadh AI, Al-Shami AK, Jamshed SQ. Adverse drug reactions reporting: knowledge and opinion of general public in Penang, Malaysia. J Pharm Bioallied Sci. 2013;5(3):224–8.
20. Pahuja et al. Awareness on Adverse Drug Reaction Reporting System in India: A Consumer Survey. AJPCT 2014; 12 (2):1361-1369.
21. Julian GS, Oliveira RW, Minowa E, Cecilio L, Barros LHC. Pharmacovigilance knowledge in Brazil: perception of participants of oncology patient advocacy group on adverse events reporting. Braz J Oncol. 2018;14:1-11.
22. Miguel A, Azevedo LF, Araújo M, Pereira AC. Frequency of adverse drug reactions in hospitalized patients: A systematic review and meta-analysis. Pharmacoepidemiol Drug Saf 2012;21:1139-54
23. Staniszewska A, Dąbrowska-Bender M, Olejniczak D, Duda-Zalewska A, Bujalska-Zadrożny M. Patient knowledge on reporting adverse drug reactions in Poland. Patient Prefer Adherence. 2016;11:47-53.
24. Hazell L, Shakir SAW. Under-reporting of adverse drug reactions. Drug Saf.2006; 29:385–396.
25. Aagaard L, Nielsen LH, Hansen EH. Consumer reporting of adverse drug reactions: a retrospective analysis of the Danish adverse drug reaction database from 2004 to 2006. Drug Saf. 2009; 32(11):1067-74.
26. Netherlands Pharmacovigilance Centre (Lareb) Annual Report from Netherlands Pharmacovigilance Centre. Hertogenbosch: Lareb; 2005. Available from: www.lareb.nl.
27. Health Canada Adverse Reaction and Medical Device Problem Reporting. Available from: http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php. Accessed on 16 May 2021.
28. Food and Drug Administration (FDA) Annual Adverse Drug Experience Report: 1996. Silver Spring, MD: FDA; 1997.
29. Kim, S., Yu, Y., You, M. et al. A cross-sectional survey of knowledge, attitude, and willingness to engage in spontaneous reporting of adverse drug reactions by Korean consumers. BMC Public Health 2020; 20: 1527.

30. Seungyeon K., Yun Mi Y., Myoungsoon Y, Kyeong HJ, Euni L. A cross-sectional survey of knowledge, attitude, and willingness to engage in spontaneous reporting of adverse drug reactions by Korean consumers. BMC Public Health 2020; 20:1527.
31. Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2009;32:19–31.
32. Fernandopulle RB, Weerasuriya K. What can consumer adverse drug reaction reporting add to existing health professional-based systems? Focus on the developing world. Drug Saf. 2003;26:219-25.
33. WHO. Safety monitoring of medicinal products: reporting system for the general public. WHO, 2012.

Profesional paper

VARIABILITY OF MCV ACCORDING TO THE QUARTER IN PREGNANT WOMEN IN RURAL COUNTRIES COMPARED WITH PREGNANT WOMEN IN RURAL COUNTRIES

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ABSTRACT

Anemias can be classified according to different schemes, but in medical practice it is used: Morphological (Cytometric) Classification of Anemia, based on the size of erythrocytes (MCV) and Hb content parameters (MCH). The types of anemia due to MCV deficiency are: 1. Hypochromic Microcytic Anemia: decreased hemoglobin, MCV < 80 fl, MCH < 27 pg; 2. Normochromic anemia Normocytic: decreased hemoglobin, MCV 80 - 100 fl, MCH 29.5 ± 2.5 pg; Macrocytic Anemia: decreased hemoglobin, MCV > 100 fl, MCH > 32 pg. Clinic of anemic syndrome,presence or absence of clinical signs of anemia are determined by 4 factors: 1. Speed of installation of anemia. A rapidly installed anemia (post hemorrhagic, hemolysis) has a more pronounced clinical condition than when it is installed gradually (the Cardiovascular System has more time to adapt).2. Anemia rate. The more profound the anemia, the more pronounced the clinic. The clinic of anemia appears when Hb is less than 9-10gr/dl. But there are cases that the reduction of Hb is pronounced and again there are no signs or they are very few if it was installed gradually and the person was healthy and at a young age (as in anemia due to iron deficiency). 3. The patient's age and general condition. The elderly bear anemia harder than the young, and this is related to the cardiovascular system and associated cardiopulmonary diseases. 4. The curve of dissociation of Hb from oxygen. Anemia is associated with greater ease to release oxygen from Hb to the tissues.

Purpose of the study: the purpose of the work was to identify the variability of MCV according to trimester of pregnancy in pregnant women in urban countries compared to pregnant women in rural countries.

MATERIALS AND METHODS: The study included a total of 200 pregnant women with identical average age of 25.60 ± 12.00 years. The work is prospectively carried out during the checking of the documentation of pregnant women according to residence (rural and urban areas) in the period January-October-2018. In each pregnant patient, we examined the concentrations of MCV, in each trimester of pregnancy.

RESULTS: Of the 200 women surveyed in the first trimester MCV values ≤80.0 fL/erythrocyte were verified in 40.0%, while in the second in 45.0% and in the third in 35.0%.In the first trimester, the second trimester and the third trimester, MCV values of 81.0-88.0 fL/erythrocyte were manifested unchanged and were presented in 50.0% of cases, which means there was no statistically significant change . Concentrations of MCV of ≥89.00 in the first trimester were verified in 10.0% of the respondents, in the second in 5.0% and in the third trimester in 15.0% of the surveyed women. According to the index of dynamics in the first trimester of pregnancy in 60.0% of the patients, the MCV was within the reference values, reduced values were evident in 40.0% of the surveyed women and the difference is more statistically significant for p<0.005 according to the difference test (Difference test, p=0.001).

CONCLUSION: in our paper, we verified that women in urban residence had higher concentrations of the examined parameters (MCV) with a significant difference for p=0.0001 compared to pregnant women in rural areas. The awareness of anemia among rural women was lower compared to urban women. Anemia among these women of the two groups can be attributed to inadequate intake of diet, poor access to health services, illiteracy, lack of knowledge on the effects and consequences of anemia on the baby, lifestyle, etc. We prefer that through lectures,

more frequent checks, brochures to raise the awareness of rural women on the consequences of anemia, which we think would significantly affect the reduction of anemia among women in rural settlements.

Key words: gravid anemia, urban and rural areas.

HYRJE

Anemitë mund të klasifikohen sipas skemave të ndryshme, por në praktikën mjekësore përdoret: Klasifikimi Morfologjik (Citometrik) i Anemisë, që mbështetet në përmasat e eritrociteve (MCV) dhe parametrave të përmbajtjes së Hb (MCH). Llojet e anemive nga mungesa MCV jane : 1.Anemia Hipokrome Mikrocitare: hemoglobina e ulur, MCV < 80 fl, MCH < 27 pg;2. Anemia Normokrome Normocitare: hemoglobina e ulur, MCV 80 - 100 fl, MCH 29,5 ± 2,5 pg; Anemia Makrocitare: hemoglobina e ulur, MCV > 100 fl, MCH > 32 pg.Klinika e sindromit anemic, prania ose mungesa e shenjave klinike të anemisë përcaktohen nga 4 faktorë:1. Shpejtësia e instalimit të anemisë. Një anemi e instaluar shpejt (post hemorragjike, hemolizë) ka klinikë më të shprehur se kur instalohet gradualisht (Sistemi Kardiovaskular ka më shumë kohë për t'u përshtatur).2. Shkalla e anemisë. Sa më e thellë të jetë anemia, aq më e theksuar është klinika. Klinika e anemisë shfaqet kur Hb është më pak se 9-10gr/dl. Por ka raste që pakësimi i Hb të jetë e theksuar dhe përsëri të mos ketë shenja ose të jenë shumë të pakta nëse ajo është instaluar gradualisht dhe personi ka qenë i shëndetshëm dhe në moshë të re (si tek anemia nga mungesa e hekurit). 3. Mosha dhe gjendja e përgjithshme e pacientit. Moshat e vjetra e suportojnë aneminë më vështirë se sa mosha e re dhe kjo lidhet me sistemin kardiovaskular dhe sëmundjet shoqëruese kardiopulmonare.4. Kurba e disocimit të Hb nga oksigjeni. Anemia shoqërohet me lehtësi më të madhe për të çliruar oksigjenin nga Hb tek indet. . Deri në 40-48 % të grave në mbarë botën gjate shtatezanise kanë depo shume te ulta te MCV i cili dukshen ndikon ne anemi. Anemia gjatë shtatëzanisë nuk është vetëm një problem në vendet me të ardhura të ulëta dhe të mesme,por edhe në vendet me të ardhura të larta (5,6). Rreth 40-48 % e grave shtatzëna në shoqëritë perëndimore vlerësohet të kenë anemi gravidare dhe ky problem është më i theksuar në shtetet me standard socio-ekonomik më të ulët. Ushqimi joadekuat i nenes gjatë periudhes se graviditetit mund të ndryshojë funksionet fiziologjike që shpiejne në një rrezik të rritur të sëmundjeve kronike dhe semundjeve kardiovaskulare në jetën dhe zhvillimin e fetusit. Rritja dhe zhvillimi i fetusit eshte tejet i ndjeshëme ndaj mungeses te ushqimeve pa MCV e cila eshte dukuri me e shpeshte te grate shtazena ne vendet rurale(7,8,9). Nje numer i konsiderueshem i grave shtatezene te zonave rurale ishin shtëpiake dhe pa arsimim te mesem (75%) gje qe konsiston me pandergjegjesimin dhe painformin e tyre mbi pasojate a anemise, krahasuar me 90 % te grave në zonen urabe te cilat ishin me edukim arsimor te mesem dhe te larte dhe ishin shume te informuara mbi anemine gravidare. Një pjesë shume e vogel e grave rurale (25 %) kishin njohuri mbi oasojat e anemise dhe ishin te ndërgjegjëshme mbi pasojat,shkaqet dhe efektet e anemisë ndaj zhvillimit te fetusit. Sipas OBSH si anemi gravidare konsiderohet cdo anemi kur vlerat e Hb<110g/l. Lindja e parakohshme,pesha e ulët e fetusit gjithmone konsistojn me aneminë në shtatëzani (10,11).

QËLLIMI I PUNIMIT: punimi kishte për qëllim te indetifikoj variabilitetin e MCV sipsas tremujorshit te gestacionit tek grate shtatezne në vendet urbane krahasuar me grate shtaëzënë në vendet raruale.

MATERIALI DHE METODAT

Në studim u përfshinë gjithsej -200 gra shtatzëna me moshë mesatare identike 25,60±12,00 vjeçare. Punimi është prospektiv i realizuar gjatë kontrollimit të dokumentacionit të grave shtatzëne sipas vendbanimit në periudhën Janar-Tetor-2018.

Tab.nr.1: Paraqitja e përqëndrimeve të fituara të vëllimit mesatar eritrocitar (MCV) sipas trimestrit të gestacionit

MCV 80,0 – 99,0 fL/ eritrocit	Tremujori i parë		Tremujori i dytë		Tremujori i tretë	
	N	%	N	%	N	%
≤80,0 fL/eritrocit	80	40,0	90	45,0	70	35,0
81,0 – 88,0 fL/ eritrocit	100	50,0	100	50,0	100	50,0
≥89,00 fL/eritrocit	20	10,0	10	5,0	30	15,0
Total	200	100,0	200	100,0	200	100,0

REZULTATET

Tabela numer 2 paraqet vlera mesatare dhe devijuese standarde tek gratë rurale dhe urbane. Në zonën rurale, anemia ishte prezente te 76 gra ndersa te grate me vendebanim urban anemia ishte prezente te 40 gra. Rezulatet e fituara nga parametrat e ekzaminuar per MCV dhe Fe++ jane te paraqitura ne tabelen numer 2.

Tabela numer 2: vlerat e firuara nga parametrat e ekzaminuar (MCV) te pacienteve nga zona rurale dhe zona urbane para trajtimit me preparate të hekurit

MCV 1,54 – 1,82 fmol/ eritrocit	Tremujori i parë		Tremujori i dytë		Tremujori i tretë	
	N	%	N	%	N	%
≤1,54 fmol/ eritrocit	100	50,0	90	45,0	80	40,0
1,54 – 1,82 fmol/ eritrocit	70	30,0	80	40,0	100	50,0
≥1,82 fmol/ eritrocit	30	15,0	30	15,0	20	10,0
Total	200	100,0	200	100,0	200	100,0

Nga vete tabela dhe grafikoni numre 2 verehet se gratë rurale kishin një prevalencë më të lartë të anemisë krahasuar me gratë urbane.me nje dallim sinjifikant statistikor per p=0,0001. Rezultatet e fituara për parametrat e ekzaminuar pas trajtimit medikamnetoz me 30-40 mg Fe++ çdo ditë,acid folik dhe vit. B12) treguan një efekt të lartë pozitiv në korrigjimin e anemisë te gratë anemike.

Shume studime kan verifikuar se anemia midis këtyre dy subjekteve mund t'i atribuohet marrjes jo adekuate të ushqimeve te pasura me hekur, me vitamin C,analfabetizmit dhe qasjes së dobët në informacionete mbi pasojat e anemise ndaj rritjes se fetusit.

Nga vetë tabela numër 3 vërehet se pas trajtimit me 30-40 mg preparate të Fe ++ çdo ditë,u vërejtë një dallim sinjifikant në korrigjimin e hemogramit me rrtije të vlerave të Er,Hb,Htc dhe hekurit per tek dy grupet e grave shtatzane.

DISKUTIMI

Në përcaktimin profilit hematologjik të grave shtatzëna rëndësi të madhe kanë indekset eeritrociteve: MCV (MeanCorposcular Volume-Vëllimi Mesatar Eritrocitar. MCV-ja është një faktor i rëndësishëm që përcakton ndarjen morfologjike të anemive. Në mostra të gjakut në tre tremujorët e shtatzënisë u vërejtën ndryshimetë vogla të MCV-së në tremujorin e dytë. Nga 200 gratë anketuara në tremujorin e parë vlera të MCV-së ≤80,0 fL/eritrocit u verifikuan te 40,0 %, ndërsa në të dytin në 45,0 % dhe në të tretin në 35,0 %. Në tremujorin e parë, tremujorshin e dytë dhe tremujorshin e tretë vlerat e MCV-së prej 81,0-88,0 fL/eritrocit u manifestuan të pandryshuara dhe u paraqitën te 50,0 % e rasteve që do të thotë nuk kishte ndonjë ndryshim sinjifikant statsistikor. Përqëndrime të MCV-së prej ≥89,00në tremujorin e parë u verifikuan te 10,0% të të anketuarave,në të dytin në 5,0% dhe në tremujorin e tret te 15,0 % e grave të anketuara (tab.19,graf.15). Sipas indeksit të dinamikës në tremujorin e parë të shtatzënisë te 60,0 % e pacienteve MCV-ja ishte në kufitë e vlerave referente, vlera të zvogëluara janë evidentuar te 40,0 % e grave të anketuara dhe dallimi është më një sinjifikant statistikore për p<0,005 sipas testit të diferencës (Difference test, p=0,001). Në tremujorin e dytë të shtatzënisë te 55,0 % e pacienteve përqëndrimet e MCV-së ishin në kufi të vlerave referente, përqëndrime të zvogëluar u verifikuan te 45,0 %, dhe diferenca në përqindje është me sinjifikancë statistikore për p<0,005 sipas testit të dallimit (Difference test, p=0,0445). Në tremujorin e tretë të graviditetit te 50,0% e të anketuarave vlerat e MCV-së ishin në kufi te vlerave referente, përqëndrime të zvogëluara u evidentuan te 35,0 %, dhe diferenca në përqindje ishte me sinjifikancë statistikore për p<0,005 sipas testit të dallimit (Difference test, p =0,0000).

PËRFUNDIMI

Parandalimi i anemisë gjatë shtatëzanisë fillimisht duhet korrigjuar me anë të konsumimit të ushqimeve të pasura me Fe++.Ndërsa në rastet e anemisë më të shprehur rekomandohet trajtimi me 30-40 mg Fe++/ditë.Efekte më pozitive edhe në përvojën tonë kemi kur terapia me Fe plotësohej edhe me acid folik dhe vit. B12.Terapia me preparate të Fe++ te pacientet tona shtatzëne tregoi efekte te larta positive ne korigjimin e anemise.

LITERATURA

1. https://sq-al.facebook.com/Hygeia.Hospital.Tirana.HHT/posts/882781958503372/
2. Janz TG, Johnson RL, Rubenstein SD / "Anemia in the emergency department: evaluation and treatment". Emergency Medicine Practice. 15 (11): 1–15, quiz 15–6 Archived from the original on 2016-10-18.
3. «What Is Anemia? -NHLBI, NIH». www.nhlbi.nih.gov. Archived from the original on 2016-01-20. Retrieved 2016-01-31.
4. Haggaz AD, Radi EA, Adam I. Anemia and low birth weight in western Sudan. Trans R Soc Trop Med Hyg. 2010;104:234–6
5. World Health Organization. Geneva; 2011. Serum Ferritin Concentrations for the Assessment of Iron Status and Iron Deficiency in Populations.
6. Gunawardena S, Dunlap ME. Anemia and iron deficiency

in heart failure. Curr Heart Fail Rep 2012;9:319-27.

7. Winter WE, Bazydlo LA, Harris NS. The molecular biology of human iron metabolism. Lab Med 2014;45:92-102.
8. Saito H, Hayashi H, et al. Increasing and decreasing phases of ferritin and hemosiderin iron determined by serum ferritin kinetics. Nagoya J Med Sci 2013;75:213
9. Harvey L, Boksa P. Additive effects of maternal iron deficiency and prenatal iiDinune activation on adult behaviors in rat offspring. Brain Behav Immun. 2014;40:27-37.
10. Barker D J, et al. Weight in infancy and death from ischaemic heart disease. Lancet. 1989;2(8663):577-580.
11. Bastian T W, Anderson J A, et al. Fetal and neonatal iron deficiency reduces thyroid hormone-responsive gene mRNA levels in the neonatal rat hippocampus and cerebralcortex. Endocrinology. 2012;153(11):5668- 5680.
12. Levy A, Fraser D, et al. Maternal anemia during pregnancy is an independent risk factor for low birthweight and preterm delivery. Eur J Obstet Gynecol Reprod Biol. 2005;122:182–186.
13. Bondevik GT, Lie RT, et al. Maternal hematological status and risk of low birth weight and preterm delivery in Nepal. Acta Obstet Gynecol Scand. 2001;80:402–408.
14. Beaton GH, Corey PN & Steel C (1989). Conceptual and methodological issues regarding the epidemiology of iron deficiency. Ann Clin Nutr 50: 575-585
15. Mitrache C, Passweg JR,Libura J,Petrikkos L, Seiler WO, Gratwohl A, Stahelin HB & Tichelli A (2001). Anemia : an indicator for malnutrition in the elderly. Ann Hematol May 80(5): 295 -298.
16. Milman N. Iron and pregnancy-a delicate balance. Ann Hematol. 2006;85(9):559-565.
17. London: Department of Health; 2011. Scientific Advisory Committee on Nutrition. Iron and Health.

Profesional paper

КОМОРБИДНИ СОСТОЈБИ КАЈ НОВОДИЈАГНОСТИЦИРАНИ ПАЦИЕНТИ СО НАРУШЕНА КОГНИЦИЈА ВО УНИВЕРЗИТЕТСКАТА КЛИНИКА ЗА НЕВРОЛОГИЈА ВО 2019 ГОДИНА

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АПСТРАКТ

Вовед: Оптималното когнитивно функционирање е неопходно за успешно комуницирање со околината, но медицинските состојби може да го попречат и нарушат здравјето на мозокот, а со тоа и негативно да влијаат на когнитивното функционирање. Таквите коморбидитети вклучуваат, хипертензија, дијабетес, срцеви заболувања, мозочен удар.

Цел: Целта на научниот труд е да ја опише, анализира и прикаже поврзаноста на коморбидните состојби врз когнитивното нарушување кај вкупниот број на пациенти дијагностицирани во текот на 2019 - та година во ЈЗУ Универзитетска клиника за неврологија – Скопје.

Методи: За потребите на истражувањето користени се податоци од програмата Hospital Information System (HIS - софтвер за амбулантско и болничко работење при ЈЗУ Универзитетска клиника за неврологија - Скопје) за: вкупниот број на реализирани прегледи во текот на 2019 - та година, вкупниот број на прегледи на пациенти над 55 годишна возраст, бројот на пациенти со когнитивни нарушувања, половата застапеност и возраста на пациентите. Направена е статистичка анализа на податоците.

Резултати: Од истражувањето добиени се следните резултати: од вкупно прегледани 10856 пациенти во текот на 2019 - та година како статистички примерок се избрани пациенти над 55 годишна возраст, вкупно 5449 пациенти (50.2%). Од нив, со нарушена когницијa биле дијагностицирани 177 пациенти (3,2%), од кои 96 жени и 81 мажи. Просечната возраст на пациентите со нарушена когниција е 74,9 години. Со коморбидни состојби се дијагностицирани 117 пациенти (66,1%), од кои со хипертензија 102 (57,6%), со дијабет 35 пациенти (19.8%), со прележан мозочен удар 10 пациенти (5.6%) и со паркинсонизам 9 пациенти (5,1%). Кај 60 пациенти (33,9%) не се забележани коморбидни состојби.

Заклучок: Врз основа на прикажаните резултати може да се заклучи дека од коморбидните состојби најзастапена е хипертензијата и воедно претставува најзначаен ризик фактор.

Клучни зборови: когнитивни нарушувања, коморбидни состојби, хипертензија.

ВОВЕД

Нарушената когниција или деменција може да се манифестира кога постои оштетена мозочна функција кај невродегенеративните нарушувања како што се Алцхајмерова болест (АБ), васкуларно когнитивно нарушување (ВКН), мозочен удар, траума на мозокот и други. Деменцијата претставува нарушување кое се карактеризира со когнитивно и/или нарушување во однесувањето што значително влијае на активностите во секојдневниот живот. Во 2010 година, е проценето дека деменцијата ги зафаќа 35,7 милиони луѓе ширум светот. АБ претставува најчест вид на деменција кај

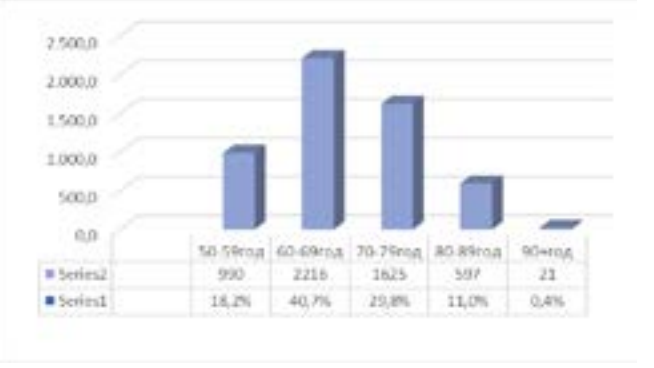
луѓето постари од 65 години, но сепак патологијата на АБ е често придружена со васкуларна болест или Lewy тела. ВКН и АБ се главни пречки за постигнување на здраво стареење и главни причини за хронична попреченост и намален квалитет на живот кај постарите луѓе во индустријализираниот свет. Најчести коморбидни состојби кои се јавуваат кај пациенти со нарушена когницијa предизвикана од различна етиологија се артериската хипертензија, Дијабетес мелитус, состојба после мозочен удар и Паркинсоновата болест (ПБ). Хипертензијата како дефиниција претставува систолен крвен притисок ≥140 mmHg или дијастолен крвен притисок ≥90mmHg, која ги зафаќа една милијарда луѓе ширум светот, со преваленца која значително се зголемува со возраста. Артериската хипертензија е опишана да биде поврзана со двата вида на причинители за деменција, односно АБ и васкуларна деменција. Рапортирано е дека хипертензијата влијае на повеќе од 60% од пациентите на возраст над 65 години и повеќе од 80% од пациентите на возраст над 85 години. Дополнително, хипертензивната васкуларна лезија може да се манифестира како болест на церебралните мали крвни садови (БЦМКС) која претставува главен причинител за појавување на когнитивно нарушување и деменција. Досегашните студии имаат потврдено дека мултипните хипертензивни васкуларопатии и промените во воспалителниот статус играат клучна улога во основните патолошките механизми на БЦКМС. Дијабетес мелитус тип 2 (ДМ) е асоциран со двојно зголемен ризик за појавување на деменција и АБ деменција, претставувајќи важен модифициран фактор на ризик за намалување на појавата на деменцијата во населението, односно ДМ често е асоциран со зголемен ризик за деменција во неколку студии. Една метаанализа која вклучува девет проспективни студии покажа релативен ризик од 1.39 за АД и од 1.47 за деменција од сите причинители кај дијабетичарите, додека друга метаанализа која вклучува осум проспективни студии откри релативен ризик од 1,54 за деменција од сите причинители кај дијабетичарите. Многу досегашни студии ја имаат истакнато поврзаноста помеѓу мозочниот удар и развојот на деменција. Рапортирано е дека околу 10% од пациентите имаат деменција пред нивниот прв мозочен удар, 10% развиваат деменција кратко време по нивниот прв мозочен удар и околу 33% развиваат деменција по повторен мозочен удар. Поранешните студии имаат рапортирано дека просечното време за појава на деменција по поставувањето на дијагнозата на ПБ е приближно 10 години. Оваа бројка е поддржана од поновите студии, вклучително и некои кои ги следеле пациентите од времето на дијагнозата на ПБ и кои рапортирале преваленца на деменција од 15-20% после 5 години и 46% на 10 години. Сепак, пониски стапки на деменција (5% по 4 години) се пријавени од друго студија, додека друга студија која избра само пациенти со ПБ со нормална когницијa, има рапортирано дека кај скоро 50% од пацеинтите дошло до когнитивно нарушување после 6 години.

МАТЕРИЈАЛИ И МЕТОДИ

Податоците се добиени од Болнички информативен систем (ХИС – софтвер за амбулантски и болнички пациенти на Универзитетската клиника за неврологија – Скопје). Во нашата студија вклучивме податоци од сите болнички и амбулантски пациенти, на кои за прв пат им беше дијагностицирано когнитивно нарушување во текот на 2019 година. Систематското пребарување на HIS ги идентификуваше сите субјекти со дијагностички код на когнитивни нарушувања, имено, ICD-10 кодови G30 , F00, F01, F03 во периодот од 1 јануари 2019 година до 31 декември 2019 година.

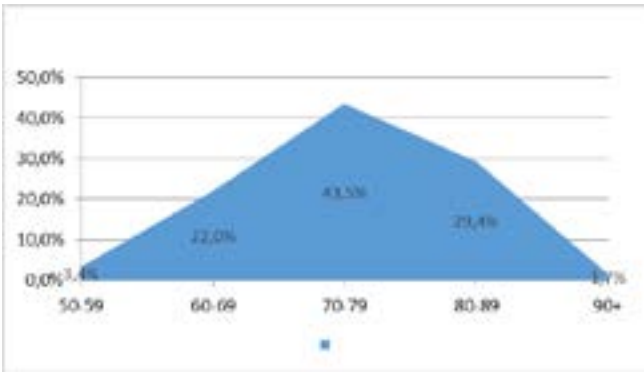
РЕЗУЛТАТИ

Во текот на 2019 година вкупно биле прегледани 5449 пациенти над 55 годишна возраст. Од 55 до 60 годишна возраст биле 18.2% односно 990 пациенти, 60 до 69 годишна возраст биле 2216 пациенти односно 40.7%, од 70 до 79 годишна возраст биле 1625 пациенти односно 29.8%, од 80 до 89 годишна возраст биле 597 пациенти односно 11% и над 90 год. биле 21 пациент односно 0.4% од вкупниот број на прегледани пациенти, табела 1.



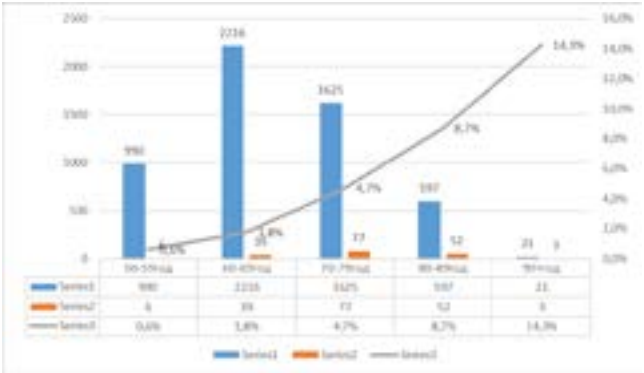
Табела 1: Процентуална застапеност на бројот на прегледани пациенти врз основа на возрасна поделеност.

Со когнитивни нарушувања биле дијагностицирани 177 пациенти или 3.2% од вкупниот број прегледи над 55 годишна возраст, од кои 96 биле жени и 81 биле мажи. Од 55 до 60 годишна возраст со когнитивни нарушувања биле дијагностицирани 6 пациенти, од 60 до 69 годишна возраст биле 39 пациенти, од 70 до 79 годишна возраст биле 77 пациенти, од 80 до 89 годишна возраст биле 52 пациенти и над 90 биле дијагностицирани 3 пациенти, табела 2.



Табела 2. Процентуална застапеност на пациенти дијагностицирани со нарушена когниција распределени врз основа на нивната возраст.

Од вкупниот број прегледи во 2019 година во возрасната група од 55-59 годишна возраст биле дијагностицирани 6 пациенти односно само 0.6%, од 60-69год. 39 или 1.8%, од 70-79 год. 77 или 4.7%, од 80-89 години 52 или 8.7% и над 90 години 3 или 14.3%, табела 3.



Табела 3. Процентуалната застапеност на новодијагностицирани пациенти со нарушена когниција во текот на 2019 година од вкупниот број прегледи распределени во соодветна возрасна група.

Од коморбидните состојби најчесто застапена беше хипертензијата и тоа кај 102 пациенти или 57.6%, диајбетес мелитус кај 35 пациенти или 19.8%, состојба после прележан мозочен удар кај 10 пациенти или 5.6%, паркинсонова болест кај 9 пациенти или 5.1% додека кај 60 пациенти односно 33.9% не беше дијагностицирана друга коморбидна состојба, табела 4.

Табела 4. Коморбидни состојби прикажани во процентуална застапеност.

ЗАКЛУЧОК

Добиените резултати од нашата студија ги потврдуваат досегашните рапортирани резултати од светски студии и метаанализи, и се показател дека артериската хипертензијата и дијабетот се најзастапени коморбидни состојби кај пациентите со нарушена когниција. Додатно, истите се и најсериозен ризик фактор за настанување на когнитивно нарушување кај популацијата, особено кај возрасната група од населението.

Голем број на докази кои укажуваат дека васкуларната деменција и АД имаат заеднички патогени механизми посредувани од васкуларни ризик фактори, ја нагласуваат итноста за проучување и истражување на основните механизми на хипертензијата индуцирана од цереброваскуларните компликации кои истовремено доведуваат до БЦМКС, и се поврзани со когнитивните нарушувања, со цел да се идентификуваат и изолираат ефективни терапевтски цели кои можат да го превернираат и спречуваат когнитивното нарушување предизвикано од хипертензијата.

ЛИТЕРАТУРА

1. Gorelick PB, Furie KL, Iadecola C, Smith EE, Waddy SP, Lloyd-Jones DM, Bae HJ, Bauman MA, Dichgans M, Duncan PW, Girgus M, Howard VJ, Lazar RM, Seshadri S, Testai FD, van Gaal S, Yaffe K, Wasiak H, Zerna C; American Heart Association/American Stroke Association. Defining Optimal Brain Health in Adults: A Presidential Advisory From the American Heart Association/American Stroke Association. Stroke. 2017 Oct;48(10):e284-e303.

2. Dementia, First Edition. Edited by Joseph F. Quinn. © 2014 John Wiley & Sons, Ltd. Published 2014 by John Wiley & Sons, Ltd.
3. Ungvari Z, Toth P, Tarantini S, Prodan CI, Sorond F, Merkely B, Csiszar A. Hypertension-induced cognitive impairment: from pathophysiology to public health. Nat Rev Nephrol. 2021 Oct;17(10):639-654. doi: 10.1038/s41581-021-00430-6. Epub 2021 Jun 14. PMID: 34127835; PMCID: PMC8202227.
4. Banegas JR, Graciani A, de la Cruz-Troca JJ, León-Muñoz LM, Guallar-Castillón P, Coca A, et al. Achievement of cardiometabolic goals in aware hypertensive patients in Spain: A nationwide population-based study. Hypertension. 2012;60:898–905.
5. Fryar, C. D., Ostchega, Y., Hales, C. M., Zhang, G. & Kruszon-Moran, D. Hypertension Prevalence and Control among Adults: United States 2015-1026. NCHS data brief, no 289 (National Center for Health Statistics, 2017).
6. Rouhl RP, Mertens AE, van Oostenbrugge RJ, Damoiseaux JG, Debrus-Palmans LL, Henskens LH, et al. Angiogenic T-cells and putative endothelial progenitor cells in hypertension-related cerebral small vessel disease. Stroke. 2012;43:256–8.
7. Liu Y, Dong YH, Lyu PY, Chen WH, Li R. Hypertension-Induced Cerebral Small Vessel Disease Leading to Cognitive Impairment. Chin Med J (Engl). 2018 Mar 5;131(5):615-619.
8. Moran C, Beare R, Wang W, Callisaya M, Srikanth V; Alzheimer's Disease Neuroimaging Initiative (ADNI). Type 2 diabetes mellitus, brain atrophy, and cognitive decline. Neurology. 2019 Feb 19;92(8):e823-e830.
9. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol 2009;8(11):1006–1018.
10. Williams-Gray CH, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain. 2009;132:2958–2969
11. Williams-Gray CH, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. J. Neurol. Neurosurg. Psychiatry. 2013;84:1258–1264.
12. Aarsland D, Creese B, Politis M, Chaudhuri KR, Ffytche DH, Weintraub D, Ballard C. Cognitive decline in Parkinson disease. Nat Rev Neurol. 2017 Apr;13(4):217-231. doi: 10.1038/nrneurol.2017.27. Epub 2017 Mar 3. PMID: 28257128; PMCID: PMC5643027.
13. Santangelo G, et al. Mild cognitive impairment in newly diagnosed Parkinson's disease: a longitudinal prospective study. Parkinsonism Relat. Disord. 2015;21:1219–1226.
14. Pigott K, et al. Longitudinal study of normal cognition in Parkinson disease. Neurology. 2015;85:1276–1282.
15. Abner EL, Kryscio RJ, Schmitt FA, Fardo DW, Moga DC, Ighodaro ET, et al. Outcomes after diagnosis of mild cognitive impairment in a large autopsy series. Ann Neurol 2017; 81: 549–59.
16. Pantoni L, Garcia JH. The significance of cerebral white matter abnormalities 100 years after Binswanger's report. A review. Stroke. 1995;26:1293–301.
17. Scott JA, Braskie MN, Tosun D, Thompson PM, Weiner M, DeCarli C, et al. Cerebral amyloid and hypertension are independently associated with white matter lesions in elderly. Front Aging Neurosci.
18. Kety S, Hafkenschiel J, Jeffers W, Leopold I, Shenkin H. The blood flow, vascular resistance, and oxygen consumption of the brain in essential hypertension. J. CLin. Invest 1948;27:511–514
19. Gottesman RF, Rawlings AM, Sharrett AR, Albert M, Alonso A, Bandeen-Roche K, Coker LH, Coresh J, Couper DJ, Griswold ME, Heiss G, Knopman DS, Patel MD, Penman AD, Power MC, Selnes OA, Schneider ALC, Wagenknecht LE, Windham BG, Wruck LM, Mosley TH Jr.. Impact of differential attrition in the association of education with cognitive change over 20 years of follow-up: The aric-neurocognitive study. American Journal of Epidemiology.

Profesional paper

COVID-19 PANDEMIC - EXPERIENCES AND CHALLENGES IN NORTH MACEDONIA

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ABSTRACT

Introduction: Over the last two decades, three coronaviruses have periodically crossed animal species such as bats, transmitted to human populations, and caused an ever-increasing outbreak of a large-scale pandemic. In December 2019, the Chinese city of Wuhan experienced an outbreak of a severe form of pneumonia of unknown cause. By January 7, the pathogen had been identified as a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It causes an acute and deadly disease with a 2% mortality rate. However, this novel coronavirus is usually associated with a mild to severe respiratory disease in humans. The virus spread around the globe, and COVID-19 was declared a global pandemic on March 11, 2020. The aim of the study is to investigate the effect of the COVID-19 pandemic on the health system in North Macedonia and to show the experiences and challenges in North Macedonia.

Materials and methods: The study is a descriptive retrospective study. Communicable diseases data, laboratory reporting microbiological isolates data, influenza data, routine immunization data in North Macedonia will be included and compared to 2020/2021 data. The data will be provided by the registries of the Institute of Public Health and the Electronic Health Directorate. Comparative analysis of case management, clinical activities and therapy and coordination, planning, financing and monitoring will be conducted.

Results: The first registered COVID-19 case in N. Macedonia on 26.02.2020. In the period 2020-2021, in N. Macedonia, a total of 225.474 patients were registered with COVID-19 (10.896,8/100.000), 8.108 deaths associated with COVID-19 (391,8/100.000) and a CFR of 3,6%. If we compare the two periods, the ten-year period before the beginning of the COVID-19 pandemic (2010-2019) and the period 2020-2021, a decrease of 82,5% is registered in the number of reported patients with acute communicable disease. There is a statistically significant decrease in the incidence in the COVID-19 period (RR=5,7, p<0,05). Additionally, a decrease of 90,9% was registered in the number of reported deaths from acute communicable disease. If we compare the two periods, season 2010/11 to season 2018/19 before the start of the COVID-19 pandemic and the period 2019/20 to 2021/22, a decrease of 63.9% is registered in the number of reported ILI cases. There is a statistically significant decrease in the incidence in the COVID-19 period (RR=2,7, p<0,05). Additionally, a decrease of 95.5% was registered in the number of reported deaths associated with influenza. If we compare the two periods, the eight-year period before the beginning of the COVID-19 pandemic (2011-2019) and the period 2020-2021, a decrease of 30,5% is registered in the number of pathogens from microbiological laboratories. During the COVID-19 pandemic, the laboratories in North Macedonia performed a total of 1.353.635 COVID-19 PCR and Rapid antigen tests which is 654.192 test per one million population. If we compare the two periods in relation to the primary vaccination and revaccination, there is a decrease in the coverage in the pandemic year in all vaccines with an average decrease of 10,4% and 16,3% respectively. At the beginning of the pandemic, the infectious disease wards in the general hospitals together with the UC for infectious diseases and febrile conditions had a total capacity of 304 hospital beds. During the pandemic, the capacity of the hospitals for treatment of patients with COVID-19 was increased to 922 hospital beds, and during the biggest peaks of infected and hospitalized, 7 university clinics for internal diseases were engaged as COVID 19

center, as well as part of university surgical clinics, bringing the number of hospital beds for COVID-19 to 1.789.

Conclusion: During the pandemic period, a significantly lower number of people infected with communicable diseases and influenza were reported compared to the previous period. In fact, this is the lowest number of reported cases of infectious diseases in the last 70 years and the COVID-19 pandemic that has hit the health system hard may be one of the reasons. Also, a decreased immunization coverage is registered, especially for the MMR vaccine. The pandemic contributed to the disruption of the infectious disease surveillance system in North Macedonia, because of the engagement of all stakeholders in the health sector in response to the pandemic. In order to strengthen the system for monitoring of communicable diseases and achieving a high coverage with immunization, it is necessary to strengthen prevention as part of the public health system in the country.

INTRODUCTION

Over the last two decades, three coronaviruses have periodically crossed animal species such as bats, transmitted to human populations, and caused an ever-increasing outbreak of a large-scale pandemic. The previously reported viral zoonotic pathogens include SARS-CoV (severe acute respiratory syndrome coronavirus) and MERS (Middle East respiratory syndrome coronavirus) that can cause severe respiratory disease in human. [1] In December 2019, the Chinese city of Wuhan experienced an outbreak of a severe form of pneumonia of unknown cause. By January 7, the pathogen had been identified as a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. This virus has the ability of jumping between species and causing a variety of diseases as a strange and complex pathogen. Due to the frequent interaction between humans and animals, a virus is a common source of zoonotic infection. COVID-19, due to its human-to-human transmission, has become a health emergency of global concern. [14] The disease was later designated coronavirus disease 2019 (COVID-19) by the World Health Organization [2]. It causes an acute and deadly disease with a 2% mortality rate. [1] However, this novel coronavirus is usually associated with a mild to severe respiratory disease in humans. Although a travel bans in and out of Wuhan was imposed [4], the virus spread around the globe, and COVID-19 was declared a global pandemic on March 11, 2020 [3]. It is now a pandemic affecting various countries globally. [5]

The COVID-19 pandemic has had both negative and positive impacts on infectious diseases of public health importance. Shifting public health resources to COVID-19 detection, control and prevention has negatively impacted STD control efforts. While COVID-19 mitigation strategies, particularly mask wearing, physical distancing, school closures and limiting travel and economic activity, have resulted in a significant decline in 2 of the most clinically important endemic respiratory viruses—influenza and respiratory syncytial virus (RSV). Collectively, the pandemic has had a profound impact on the public-health profession. [6]

The reporting of communicable diseases in the Republic of North Macedonia is paper-based and conducted by law and sub-law regulation. The Law on population protection of communicable diseases (Official Gazette 66/2004) establishes the measures for prevention of the appearance, early detection and stopping the spread of communicable diseases and obligations of health care institutions, legal entities, and individuals, as well as monitoring the implementation of measures for protection of people for communicable diseases. The last version of the form and the Manual for reporting (Official Gazette 46/2009) were published in 2009. One notification form is used for all 64 notifiable communicable diseases. Microbiological laboratories are obligated (according to the Law and sub-law regulations - Official Gazette 46/2009) to report 56 infectious diseases pathogens.

Influenza is mandatory notifiable diseases in Macedonia, and influenza surveillance is part of the universal system for surveillance of communicable diseases. The network of reporting includes GPs and clinicians. Surveillance system is paper-based and medical doctors are required to report case-based data during out of the influenza season (weeks 21-39) while during the season, they are required to report weekly aggregated data.

The SARS-CoV-2 pandemic has scarcely left any corner of the world untouched, with millions of lives lost as a direct result of the virus. Equally important are the indirect effects of the pandemic. Disruptions of routine health services are likely to increase morbidity and mortality, leaving women and children particularly vulnerable. Systems for routine childhood immunization have been greatly impacted globally, and in May 2020, WHO announced there were at least 80 million children

younger than 1 year of age who were at risk of missing life-saving vaccinations. [7]

Pandemic-related disturbances have jeopardized previous gains in immunization services, with major implications on vaccine-preventable disease eradication and elimination efforts. Immense challenges abound in obtaining accurate and systematic measurements of these changes in immunization status globally.

The aim of the study is to investigate the effect of the COVID-19 pandemic on the health system in North Macedonia and to show the experiences and challenges in North Macedonia.

MATERIALS AND METHODS

The study is a descriptive retrospective study. Communicable diseases data in North Macedonia in the period from 2010-2019 will be included and compared to 2020-2021 data. Laboratory reporting microbiological isolates data in North Macedonia in the period from 2012-2019 will be included and compared to 2020-2021 data. Influenza data in North Macedonia in the period from season 2010/2011-2018/2019 will be included and compared to 2019/2020-2021/2022 data. Routine immunization data on coverage in North Macedonia in the period from 2015-2019 will be included and compared to 2020 data. The data will be provided by the registries of the Institute of Public Health and the Electronic Health Directorate. Comparative analysis of case management, clinical activities and therapy and coordination, planning, financing and monitoring will be conducted.

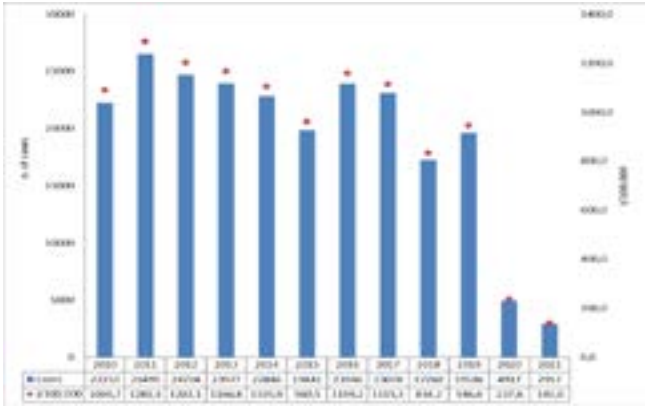
RESULTS

The effect of the COVID-19 pandemic on the surveillance systems

In the ten-year period before the start of the COVID-19 pandemic (2010-2019), a total of 223.986 patients with acute communicable diseases were registered (excluding influenza, tuberculosis, HIV/AIDS, chronic hepatitis, carriers of infectious diseases). On average, annually in this period, 22,399 infected persons were reported with an average incidence of 1.087,1/100,000 inhabitants. The highest number of patients (n=26.495, I=1.289,3/100,000) were registered in 2011, while the lowest number (n=17.260, I=834,2/100,000) in 2018 (Figure 1).

In the period 2010-2019, a decreasing trend of the number of reported infected persons with acute communicable disease was registered in North Macedonia. During this period, a total of 114 deaths from acute communicable diseases were reported (excluding influenza, tuberculosis, HIV/AIDS, chronic hepatitis, carriers of infectious diseases), an average of 11 with an average mortality of 0,5/100.000 inhabitants.

Figure 1. Distribution of infected persons and incidence per 100.000 inhabitants, acute communicable disease, North Macedonia, 2010-2021



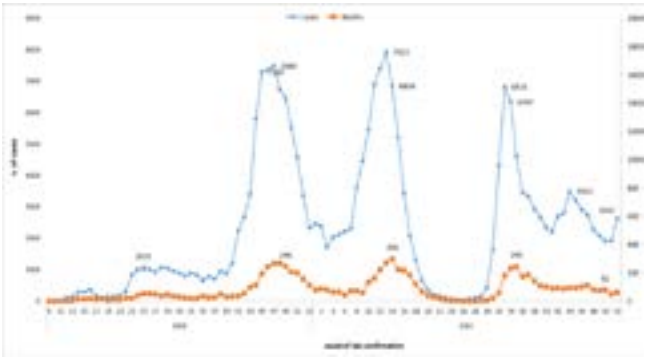
In the two years after the onset of the COVID-19 pandemic, a total of 7.834 infected persons were registered with acute communicable disease (excluding COVID-19, influenza, tuberculosis, HIV/AIDS, chronic hepatitis, carriers of infectious diseases). On average, annually in this period, 3.917 infected persons were reported with an average incidence of 189,3/100.000 inhabitants (Figure 1).

During this period, a total of 2 deaths from acute communicable diseases were reported (excluding COVID-19, influenza, tuberculosis, HIV/AIDS, chronic hepatitis, carriers of infectious diseases), with an average mortality of 0,05/100.000 inhabitants.

The first registered COVID-19 case in North Macedonia on 26.02.2020. In the period 2020-2021, in North Macedonia, a total of 225.474 patients were registered with COVID-19 with an incidence of 10.896,8/100.000 inhabitants, 8.108 deaths associated with COVID-19 with a mortality of 391,8/100.000 inhabitants and a CFR of 3,6% (Figure 2). Most of the COVID-19 associated deaths are registered in people over 60 years old (n=6.648; 82,0%) with the highest specific mortality – 1.510,5 / 100.000 inhabitants. 4.800 (59,2%) deaths were registered in males and 3.308 (40,8%) in females. Comorbidities were registered in 6.216 (81,7%), most often cardiovascular (n=5.137), diabetes (n=2.100) and pulmonary (n=963) diseases. Of the reinfections, 10 ended in death. Eight deaths were registered in pregnant women and 27 deaths in health-care workers. Of the

deaths, 7.489 (92,4%) were hospitalized.

Figure 2. Distribution of infected persons and incidence per 100.000 inhabitants, COVID-19, North Macedonia, 2010-2021



If we compare the two periods, the ten-year period before the beginning of the COVID-19 pandemic (2010-2019) and the period 2020-2021, a decrease of 82,5% is registered in the number of reported patients with acute communicable disease. There is a statistically significant decrease in the incidence in the COVID-19 period (RR=5,7, p<0,05). Additionally, a decrease of 90,9% was registered in the number of reported deaths from acute communicable disease.

If we analze the difference between the incidence in the two examined periods, by group of diseases, it is noticed that the largest decrease is in Food and water borne diseases and Air borne diseases (Table 1).

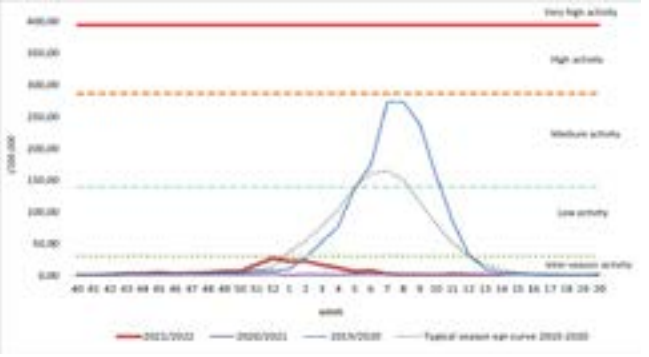
Table 1. Incidence per 100,000 inhabitants, acute communicable disease by group of diseases and difference, North Macedonia, 2010-2019 and 2020-2021

	2010-2019	2020-2021	Difference
Air borne diseases	418,0	90,0	78,5%
Food and water borne diseases	615,4	84,1	86,3%
Zoonoses	5,2	1,2	76,9%
STD and blood transmitted diseases	24,6	6,1	75,2%
Other	34,0	9,8	71,2%

Regarding the reporting of inluenza, we analyzed the period from season 2010/11 to season 2018/19 before the start of the COVID-19 pandemic. A total of 234.179 patients with influenza-like illnesses (ILI) were registered. On average, seasonally, 26.020 ILI cases were reported with an average incidence of 1.257,5/100.000 inhabitants. The highest number of ILI cases (n=35.079, I=1.695,3/100.000) were registered in the 2016/17 influenza season, while the lowest number (n=9.685, I=468,1/100.000) in the 2011/12 influenza season (Figure 3). During this period, a total of 67 deaths associated with influenza were reported, an average of 7 with an average mortality of 0,3/100.000 inhabitants.

We also analyzed the influenza seasons after the start of the COVID-19 pandemic (2019/20 to 2021/22). A total of 37.977 ILI patients were registered. On average, seasonally, 12.659 ILI cases were reported with an average incidence of 611,8/100.000 inhabitants (Figure 3). During this period, a total of 3 deaths associated with influenza were reported, with mortality of 0,1/100.000 inhabitants.

Figure 3. Incidence per 100.000 inhabitants, ILI, North Macedonia, 2010/11-2021/22



If we compare the two periods, season 2010/11 to season 2018/19 before the start of the COVID-19 pandemic and the period 2019/20 to 2021/22, a decrease of 63.9% is registered in the number of reported ILI cases. There is a statistically significant decrease in the incidence in the COVID-19 period (RR=2,7, p<0,05). Additionally, a decrease of 95.5% was registered in the number of reported deaths associated with influenza.

Regarding the reporting of pathogens from microbiological laboratories, we analyzed the period from 2012 to 2019 before the start of the COVID-19 pandemic. A total of 45.416 reports were registered. On average, annually, 5.677 reports were reported. The highest number (n=8.083) was registered in the 2019, while the lowest number (1.027) in 2011.

In the two years after the onset of the COVID-19 pandemic, a total of 7.891 reports were registered (excluding SARS-CoV-2). On average, annually in this period, 3.946 reports were reported.

If we compare the two periods, the eight-year period before the beginning of the COVID-19 pandemic (2011-2019) and the period 2020-2021, a decrease of 30,5% is registered in the number of pathogens from

microbiological laboratories.

During the COVID-19 pandemic, the laboratories in North Macedonia performed a total of 1.353.635 COVID-19 PCR and Rapid antigen tests which is 654.192 test per one million population (Table 2).

Out of the total number of performed tests, 525.460 were performed in public health laboratories, 38,8% of the performed PCR tests, while 828.175 were performed in private laboratories, 61,2% of the performed PCR tests (Table 2).

Of the public health laboratories, most of the PCR tests were performed at the National Institute of Public Health, 316.017 or 60,1%. The highest positivity rate of 40,8% is registered at the Institute for microbiology Skopje, while the lowest (3,5%) at the Gynecology clinic (Table 2).

Of the private laboratories, most of the PCR tests were performed at the private laboratory Biotek, 149.160 or 18,0%. The highest positivity rate of 43,9% is registered at the private laboratory Spektra-MM, while the lowest (2,5%) at the private laboratory Eli Medika Plus (Table 2).

Table 2. Covid-19 testing and positivity rate, North Macedonia, 2020-2022

		N of tests	N of positive cases	% of positivity
	Total	1994827	308507	15,5%
Public health laboratories	Institute of Public Health Skopje	316017	69900	22,1%
	Centar for Public Health Skopje	38096	12108	31,8%
	Centar for Public Health Bitola	40698	11132	27,4%
	Centar for Public Health Prilep	13080	2641	20,2%
	Centar for Public Health Tetovo	9152	3312	36,2%
	Centar for Public Health Kumanovo	17712	4334	24,5%
	Infectious diseases clinic	1879	526	28,0%
	Forensic medicine institute	2945	328	11,1%
	Pulmonary institute for children Kozle	3102	1236	39,8%
	Pulmology clinic	932	219	23,5%
	Citi general hospital 8-mi Septemvri	1125	54	4,8%
	Institute for microbiology Skopje	36475	14899	40,8%
	Macedonian Academy of Sciences and Arts	41690	11164	26,8%
	Gynecology clinic	1802	63	3,5%
	Faculty of Veterinary Medicine	755	81	10,7%
Private laboratories	Zhan Mitrev Clinic	96639	12341	12,8%
	Avicena	140481	20796	14,8%
	Biotek	149160	20009	13,4%
	Sistina	99014	11627	11,7%
	Laor	103005	3555	3,5%
	Sinlab	22734	3608	15,9%
	Remedika	9955	634	6,4%
	Plodnost	16751	3277	19,6%
	Genea	4911	498	10,1%
	Nikob Lab	139958	16082	11,5%
	VFV Medical	16687	818	4,9%
	Eli Medika Plus	12841	318	2,5%
	Royal Medika	6246	547	8,8%
	Spektra-MM	2453	1076	43,9%
	Rapid Lab	2712	481	17,7%
	Zhan Mitrev Strumica	1742	189	10,8%
	Nova Lab	968	29	3,0%
	Ramus	1918	790	41,2%
	Total PCR	1353635	228672	16,9%
	Public health laboratories	525460	131997	25,1%
	Private laboratories	828175	96675	11,7%
	Rapid antigen tests (public and private)	641192	79835	12,5%

The effect of the COVID-19 pandemic on the immunization

Regarding the routine immunization in North Macedonia, we analyzed the 5-year period before the start of the COVID-19 pandemic (2015-2019) and the first pandemic year (2020).

Regarding the primary vaccination, in the period 2015-19, a coverage of over 95% for any vaccine was not registered. The registered coverage for the primary vaccination is below 90% for the MMR and HPV vaccine. HPV vaccination has the lowest coverage of all vaccines in the country (Table 3).

Regarding the primary vaccination in 2020, no coverage of over 90% for any vaccine was registered (Table 3).

If we compare the two periods in relation to the primary vaccination, there is a decrease in the coverage in the pandemic year in all vaccines with an average decrease of 10,4%. The largest decrease in coverage was registered for the MMR vaccine (21,3%) (Table 3).

Table 3. Vaccination coverage (primary vaccination), North Macedonia, 2015-2019 and 2020

			2015	2016	2017	2018	2019	Average 2015-2019	2020	
vaccine	dose	age	%	%	%	%	%	%	%	Difference %
Hepatitis B*	III	0,2,6 m	91,8	93,8	91,3	92,3	90,7	92,0	83,6	-8,4
Heamophilus influenza type B**	III	2,4,6 m	88,6	94	91,1	92,5	90,7	91,4	83,9	-7,5
Di-Te-Per	III	2,4,6 m	91,3	95,3	91,1	92,5	90,7	92,2	83,9	-8,3
OPV/IPV	III	2,4,6 m	92,1	95,3	91,1	92,5	90,7	92,3	83,9	-8,3
MMR	I	12 m	88,8	82,1	82,6	74,8	93,1	84,3	63	-21,3
HPV***	III	12 y	42,2	53,3	48	54,6	57,8	51,2	42,5	-8.7

Regarding the revaccination, no coverage above the recommended 95% was realized for any revaccination in the period 2015-19. The registered coverage for revaccination with all vaccines is below 90% except the MMR (94,2%) and the last Tetanus dose (90,2%) (Table 4).

Regarding the revaccination in 2020, no coverage of over 90% for any vaccine was registered (Table 4).

If we compare the two periods in relation to the revaccination, there is a decrease in the coverage in the pandemic year in seven of the nine vaccines with an average decrease of 16,3%. The largest decrease in coverage was registered for the MMR vaccine (25,7%) (Table 4).

Table 4. Vaccination coverage (revaccination), North Macedonia, 2015-2019 and 2020

		2015	2016	2017	2018	2019	Average 2015-2019	2020	
vaccine	age	%	%	%	%	%	%	%	Difference %
Heamophilus influenza type B**	18 m	89,1	87,4	82,9	80,2	88,2	85,6	66	-19,6
Di-Te-Per I	18 m	91,0	88,9	83,3	80,2	88,2	86,3	66	-20,3
Di-Te II	7 y	91,2	89,9	91,1	75,3	68,9	83,3	87,3	+4,0
Di-Te III	14 y	91,2	93,4	93,1	87,2	73,1	87,6	80,3	-7,3
Te IV	18 y	92,2	92,3	90,7	90,2	85,4	90,2	72,5	-17,7
OPV/IPV I	18 m	91,2	88,3	83,3	80,2	88,2	86,2	66	-20,2
OPV/IPV II	7 y	96,3	90,3	92,5	70	63,7	82,6	87,3	+4,7
OPV/IPV III	14 y	91,2	92,7	92,9	73,5	68,4	83,7	80,3	-3,4
MMR	6 y	93,4	93,3	97	93,8	93,4	94,2	68,5	-25,7

On 17.02.2021, North Macedonia has started vaccination against COVID-19.

As of March 19, 2022, a total of 872.183 people have been vaccinated with at least one dose of COVID-19 vaccine in the country and abroad. A total of 852.319 people were completely vaccinated (with two doses), and 149.793 people were vaccinated with the third dose (Table 5).

Table 5. Vaccinated persons, COVID-19, North Macedonia, by vaccine type / dose

Vaccine	First dose	Second dose	Third dose	Total
Pfizer/Biontech	372.946	362.714	149.790	885.450
Sinovac	251.105	245.386	-	496.491
Sinopharm	153.307	152.595	-	305.902
AstraZeneca	71.204	68.519	-	139.723
Sputnik V	23.272	22.958	-	46.230
Moderna*	141	124	3	268
Janssen*	208	23	-	231
Total	872.183	852.319	149.793	1.874.295

* vaccinated only abroad

With one dose of COVID-19 vaccine, in the country and abroad, 52.3% of the population over 18 years of age were vaccinated, 48.3% of the population over 12 years of age, and 42.2% of the total population.

The coverage with two doses of COVID-19 vaccine in the population over 18 years of age is 51.1%, 47.2% in the population over 12 years of age. The coverage with two doses in the total population is 41.2%.

The effect of the COVID-19 pandemic on the case management, clinical activities and therapy

The adjustment of the health sector to provide conditions for the treatment of patients with COVID-19 was going very fast. The University Clinic for Infectious Diseases and Febrile Conditions in Skopje was designated to be a reference clinic for the treatment of patients infected with COVID-19. Regular communication has been established between the public health centers and the regional hospitals / departments for infectious diseases.

According to the scenarios determined for case management, the wards for infectious diseases were activated in all Clinical Hospitals (CH), General Hospitals (GH) and Special Hospitals (SH), and in case of increased need for hospitalization, other wards are activated and repurposed in all CH , GH and SH, as well as University Clinics (UC).

In order to respond in a timely manner to the increased need for hospitalizations, 19 modular facilities have been set up in the Republic of North Macedonia. 15 modular facilities have hospital beds for the treatment of COVID-19 patients. Additionally, with the amendments to the Law on Health Care, it was possible for the private health institutions that perform services for intensive care and therapy to be included in the treatment of patients at the personal choice of the patient.

At the beginning of the pandemic, the infectious disease wards in the general hospitals together with the UC for infectious diseases and febrile conditions had a total capacity of 304 hospital beds. During the pandemic, the capacity of the hospitals for treatment of patients with COVID-19 was increased to 922 hospital beds, and during the biggest peaks of infected and hospitalized, 7 university clinics for internal diseases were engaged as COVID 19 center, as well as part of University surgical clinics, bringing the number of hospital beds for COVID-19 to 1789 (highest number of hospitalized persons on 12.04.2021).

Special pathways were established in all hospitals, with so-called red and green zones, and hospital coordination bodies were established. Employees over the age of 60 with chronic diseases were assigned to work with patients with pathology other than COVID-19. In addition to infectologists, the care of patients with COVID 19 specialist pulmonologists, internists and interns were included.

The effect of the COVID-19 pandemic on the coordination, planning, financing and monitoring

The Ministry of Health is coordinating the response during the outbreak.

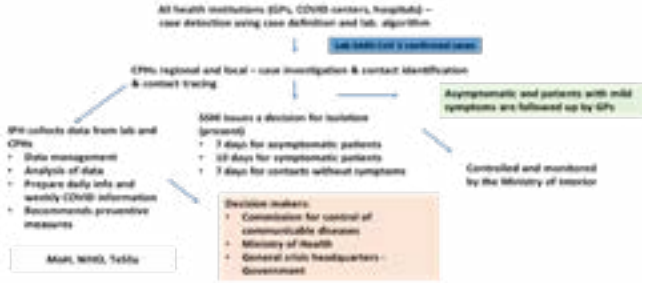
Additionally, in March 2020, the Government of the Republic of North Macedonia established the Main Coordination Crisis Headquarter as an operational body for ensuring complete coordination of state administration bodies, legal entities established by the state, as well as local self-government units, regarding prevention, introduction and spread of COVID-19. The Main Coordination Crisis Headquarter, based on the recommendations of the Commission for communicable diseases, prepares conclusions, measures and recommendations for state administration bodies,

legal entities established by the state, as well as for local self-government and monitors the implementation of conclusions, measures and recommendations adopted by the Government of the Republic of North Macedonia regarding the prevention, introduction and spread of COVID-19.

The Commission on communicable Diseases (CCD) is an advisory body to the Minister of Health. The members of the commission are experienced experts from: the Ministry of Health, the Institute of Public Health, the Centers for Public Health, the Food and Veterinary Agency, the State Sanitary and Health Inspectorate, the University Clinic for Infectious Diseases and Febrile Conditions, the University Clinic for Pediatrics, representative from the Center for crisis management and from WHO office in Skopje, and other experts - laboratory, pediatricians, as well as additional members, depending on the identified risk.

At the national level, the Ministry of Health coordinates response to the situation with COVID- 19. At the local level, the Institute of Public Health coordinates the response provided by the ten regional centers for public health (CPH) and 21 regional units of the CPH in the municipalities. At the regional level, according to the division of the 10 CPHs, there are rapid response teams in case of an epidemic of infectious disease that work in cooperation with the IPH and local authorities.

Figure 4. Coordination of roles and responsibilities for investigation and response, North Macedonia, 2010/11-2021/22



CONCLUSION, DISCUSSION AND RECOMMENDATIONS

During the pandemic period, a significantly lower number of people infected with communicable diseases and influenza were reported compared to the previous period. In fact, this is the lowest number of reported cases of infectious diseases in the last 70 years and the COVID-19 pandemic that has hit the health system hard may be one of the reasons. Also, a decreased immunization coverage is registered, especially for the MMR vaccine.

Additionally, microbiological laboratories were also overburdened by COVID-19 testing so a lower number of reports were registered regarding other pathogens.

The pandemic contributed to the disruption of the infectious disease surveillance system in North Macedonia, because of the engagement of all stakeholders in the health sector in response to the pandemic.

In order to strengthen the system for monitoring of communicable diseases and achieving a high coverage with immunization, it is necessary to strengthen prevention as part of the public health system in the country.

Equipping the epidemiological services with human, but also technological capacities is the first and essential step. The COVID-19 pandemic showed the weaknesses in this part, but also the possibility of involving other staff in the epidemiological research of positive cases and the contact tracing.

Digitizing and linking infectious disease and pathogen surveillance systems to avoid paper reporting and thus reporting delays is also critical. Paper reporting of all diseases is an outdated model and requires digitization. The COVID-19 pandemic and the COVID-19 (laboratory based) surveillance system implemented in North Macedonia have shown that it is much more appropriate to operate with this type of real-time surveillance. Additionally, replacing the old with a new, digitized ALERT system enables real-time detection of clusters and possible epidemics.

Although during the pandemic, routine immunization was never stopped, quarantines and restrictions on the movement of people (curfews), as well as the large number of positive people, but also the involvement of vaccination teams in COVID-19 vaccination, significantly reduced the coverage in 2020. Therefore, it is crucial to equip the vaccination teams with trained staff that will function in normal but also in times of crisis, as well as to complete the process of digitalization of immunization surveillance, which is run as a pilot project at the moment in North Macedonia.

Law and sub law change processes must be implemented as soon as possible to address the previous recommendations.

Implementation of experiences (lessons learned) during the COVID-19 pandemic in the existing and new

developed documents regarding pandemic preparedness and response is a step forward. North Macedonia should revise these documents and use them in time of crisis.

REFERENCES

1. Seyed Hosseini E, Riahi Kashani N, Nikzad H, Azadbakht J, Hassani Bafrani H, Haddad Kashani H. The novel coronavirus Disease-2019 (COVID-19): Mechanism of action, detection and recent therapeutic strategies. Virology. 2020 Dec;551:1-9. doi: 10.1016/j.virol.2020.08.011. Epub 2020 Sep 24. PMID: 33010669; PMCID: PMC7513802.
2. Phelan AL, Katz R, Gostin LO. The novel coronavirus originating in Wuhan, China: challenges for global health governance. JAMA. 2020;323:709–10.
3. World Health Organization. Listings of WHO's response to COVID-19. https ://www.who.int/news/item/29-06-2020-covid timel ine. Accessed 21 Dec 2020.
4. Tian H, Liu Y, Li Y, et al. An investigation of transmission control measures during the first 50 days of the COVID-19 epidemic in China. Science. 2020;368:638–42.
5. Matta S, Chopra KK, Arora VK. Morbidity and mortality trends of Covid 19 in top 10 countries. Indian J Tuberc. 2020 Dec;67(4S):S167-S172. doi: 10.1016/j.ijtb.2020.09.031. Epub 2020 Oct 8. PMID: 33308665; PMCID: PMC7543896.
6. Gilligan P. Impact of COVID-19 on Infectious Diseases and Public Health. American Society for Microbiology. 2022 February https://asm.org/Articles/2022/February/Impact-of-COVID-19-on-Infectious-Diseases-and-Publ
7. WHO, At least 80 million children under one at risk of diseases such as diphtheria, measles and polio as COVID-19 disrupts routine vaccination efforts, warn Gavi, WHO and UNICEF. https://www.who.int/news/item/22-05-2020-at-least-80-million-children-under-one-at-risk-of-diseases-such-as-diphtheria-measles-and-polio-as-covid-19-disrupts-routine-vaccination-efforts-warn-gavi-who-and-unicef

Profesional paper

FAKTORËT ETIOLOGJIK DHE METODAT DIAGNOSTIKE TË OSTEOPOROZËS

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ABSTRAKTI

Hyrje: Osteoporoza është një çrregullim skeletor sistemik që karakterizohet me ulje të masës kockore, përkeqësim mikro-arkitektonik i indit kockor që çon në rrallim kockor dhe si pasojë, rritje të rrezikut për fraktura. Është arsyeja më e zakonshme për thyerjen e kockave tek të moshuarit.

Qëllimi: Qëllimi i këtij punimi ishte që të analizohen faktorët etiologjik që luajnë rol në shfaqjen e Osteoporozës. Në kuadër të faktorëve të rrezikut per paraqitjen e sëmundjes, do të analizohen veq e veq të gjithë shkaktarët e mundshëm që kanë luajtur rol negativ. Poashtu do të analizohen metodat bashkëkohore diagnostikuese të sëmundjes.

Materiali dhe metodat: Materiali është mblledhur në librat e protokolit si dhe në historitë e sëmundjeve të pacientëve të shtruar në spital. Gjithsej janë analizuar 57 paciente të gjinisë femërore, pra nuk e kemi asnjë mashkull. Punimi është i tipit të kombinuar, pra retro dhe prospektiv dhe analitik. Të dhënat janë përpunuar me metodat statistikore aktuale duke perdorur madhësitë mesatare të nevojshme. Rezultatet janë paraqutur në tabela dhe grafikone të përshtatshme sipas nevojes.

Rezultatet: Grupmosha më e atakuar nga osteoporoza është ajo 50-59 dhe 60-69 vjeçë, me nga 21 raste ose 36.84 % të tyre, pasuar nga grupmosha 70-79 vjeçë me 9 raste ose 15.78 %, dhe grupmosha 40-49 vjeçë me vetëm 6 raste ose 10.52% të tyre. Faktori më i shpeshtë rreziku për osteoporozë është inaktiviteti fizik me 57 raste ose 100% e rastëve, pasuar nga Hipovitaminoza D me 54 raste ose 94.73% të rastëve, postmenopauza me 53 raste ose 92.98 % të tyre, si dhe duhanpirja me 12 raste ose 21.05% të rastëve. Nga matjet me DEXA score, shihet se më së shumti pacient ishin me vlera të T score nga -3.0 deri -3.9 me gjithsej 27 pacient ose 47.36 % të tyre, pasuar nga ata me T score nga -2.5 deri -2.9 me 21 pacient ose 36.84% të tyre, ata me vlerat e T score nga -4.0 deri -4.9 me 6 pacient ose 10.52% të tyre dhe në fund ata me vlerat e T score nga -5.0 deri -5.9 me gjithsej 3 pacient ose 5.26% të tyre. Më së shumti kishte pacient me pamjaftueshmëri të vitaminës D në gjak dhe atë 42 pacient ose 73.68% të tyre, pasuar nga ata që kishin mungesë të vitaminës D gjithsej 12 raste ose 21.05% të tyre, ndërsa vetëm 3 raste ose 5.26% të tyre ishin me vlera optimale të vitaminës D në gjak.

Përfundimi: Ekzistojnë shumë faktorë etiologjik për të shkaktuar osteoporozë, andaj kjo sëmundje është shumë faktoriale dhe si rrjedhoje edhe multidiciplinare. Shumica dërmuese e pacientëve ishin në fazën e postmenopauzës, që do të thotë se ky faktorë etiologjik është kyq në paraqitjen e sëmundjes. Grupmosha më e atakuar ishte ajo nga 50 deri 7 vjeçë. Nivelet e ulëta të vitaminës D u gjetën në shumicën dërmuese të pacientëve që paraqet faktor rreziku me rëndësi në paraqitjen e osteoporozës. Mos aktiviteti fizik poashtu është gjetur tek të gjitha rastet në studim. Duahnpirja dhe përdorimi i kortizonit u gjetën në shume pak raste, megjithatë vlen të theksohet përdorimi i kortizonit pikërisht në rastet që ende nuk ishin në postmenopauzë, gjë që me gjasë ky medikament ishte shkaku i osteoporozës tek këto raste. Metoda e artë dhe kryesore për diagnostikimin e Osteoporozës mbetet metoda e Osteodensitometrisë (DEXA-scan).

Fjalët kyç: Osteoporoza, postmenopauza, vitamina D, kortizoni, mosaktiviteti fizik.

HYRJE

Osteoporoza është një çrregullim skeletor sistemik që karakterizohet me ulje të masës kockore, përkeqësim mikro-arkitektonik i indit kockor që çon në rrallim kockor dhe si pasojë, rritje të rrezikut për fraktura. Është arsyeja më e zakonshme për thyerjen e kockave tek të moshuarit. (1) Kockat që thyhen zakonisht përfshijnë shtyllën kurrizore, kockat e parakrahut, kyçin e dorës dhe nyjen coxo femurale.(2,3) Derisa nuk ndodhë thyerje kockore, sëmundja zakonisht nuk ka simptoma. Kockat mund të dobësohen në një shkallë të tillë që mund të ndodhë thyerje nga një traumë e vogël ose thyerje spontane. Pas shërimit të kockës së thyer, personi mund të ketë dhimbje kronike dhe aftësi të zvogëluar për të kryer aktivitete normale.(1)

Humbja e masës kockore rritet pas menopauzës për shkak të niveleve më të ulëta të estrogjenit, dhe pas 'andropauzës' për shkak të niveleve më të ulëta të testosteronit.(4) Osteoporoza mund të ndodhë gjithashtu edhe për shkaqe tjera duke përfshirë alkoolizmin, anoreksinë, hipertiroidizmin, sëmundjet e veshkave dhe heqjen kirurgjikale të vezoreve. Përdorimi i disa barnave gjithashtu rrisin shkallën e humbjes së masës kockore, duke përfshirë disa barna kundër konvulsioneve, disa kimioterapeutik, frenuesit e pompës së protonit, frenuesit selektivë të rimarrjes së serotoninës dhe glukokortikoidet. Pirja e duhanit dhe mos aktiviteti fizik janë gjithashtu faktorë rreziku.(1) Osteoporoza përkufizohet si një densitet kockor prej 2,5 devijime standarde nën atë të një të rrituri të ri. Kjo matet zakonisht me anë të absorbimit me rreze X me energji të dyfishtë (DXA ose DEXA), metodë e cila quhet Osteodensitometri ndërsa aparatura quhet Osteodensitometër. Kjo metodë aktualisht është standard i artë në diagnostikimin e Osteoporozës vlerat e së cilës janë: T score ≥ -1.0 normal, T score -1 deri -2.5 osteopeni, T score ≤ -2.5 osteoporozë. (5)

Parandalimi i osteoporozës përfshinë dietën e duhur dhe të balancuar gjatë fëmijërisë, terapinë zëvendësuese hormonale për gratë në menopauzë dhe përpjekjet për të shmangur medikamentet që rrisin shkallën e humbjes së masës kockore. Përpjekjet për të parandaluar thyerjen e kockave tek pacientët me osteoporozë përfshijnë dietën e pasur me minerale dhe vitamina, stërvitjet dhe parandalimin e traumave dhe sforcimeve. Ndryshimet e stilit të jetesës si ndërprerja e duhanit dhe mos konsumimi i alkoolit gjithashtu mund të ndihmojnë. (1) Medikamentet bisfosfonate janë të dobishme për të ulur rrezikun e thyerjes së kockave në të ardhmen tek pacientët që në të kaluarën kishin thyerje kockore për shkak të osteoporozës. Te pacientët me osteoporozë, por pa thyrje kockore në të kaluaren, ato janë më pak efektive.(6,7,8)

Osteoporoza bëhet më e zakonshme me kalimin e moshës. Rreth 15% e kaukazianëve në të 50-at e tyre dhe 70% e atyre mbi 80 vjeç, janë të prekur nga osteoporoza.(9) Është më e zakonshme tek femrat se sa tek meshkujt.(1) Në botën e zhvilluar, në varësi të metodës së diagnostikimit, preken 2% deri në 8% të meshkujve dhe 9% deri në 38% të femrave.(10) Rreth 22 milion gra dhe 5.5 milionë burra në Bashkimin Evropian kishin osteoporozë në vitin 2010. (11) Në Shtetet e Bashkuara në vitin 2010, rreth 8 milion gra dhe midis 1 dhe 2 milion burra kishin osteoporozë. (12) Njerëzit e bardhë dhe aziatikët janë më të rrezikuar. (3) Fjala "osteoporozë" rrjedh nga greqishtja që bëhet fjalë pra për "kockat poroze".(13)

QËLLIMI I PUNIMIT

Qëllimi i këtij punimi ishte që të analizohen faktorët etiologjik që luajnë rol në shfaqjen e Osteoporozës. Në kuadër të faktorëve të rrezikut per paraqitjen e sëmundjes, do të analizohen veq e veq të gjithë shkaktarët e mundshëm që kanë luajtur rol negativ. Poashtu do të analizohen metodat bashkëkohore diagnostikuese të sëmundjes.

MATERIALI DHE METODAT

Te dhenat jane mbledhur nga historite e pacienteve me semundje reumatizmale, te hospitalizuar ne Kliniken e Reumatologjise, te Qendres Klinike Universitare te Kosoves, në Prishtine, gjatë periudhës kohore gjashte muojore, Janar – Qershor, te vitit 2023! Nga keto histori, eshte analizuar anamneza si dhe markeret laboratorik dhe imazherik te hulumtuar gjate spitalizimit te tyre! Gjithsej janë analizuar 57 paciente të gjinisë femërore, pra nuk e kemi asnjë mashkull. Punimi është i tipit të kombinuar, pra retro dhe prospektiv dhe analitik. Të dhënat janë përpunuar me metodat statistikore aktuale duke perdorur madhësitë mesatare të nevojshme. Rezultatet janë paraqutur në tabela dhe grafikone të përshtatshme sipas nevojes.

REZULTATET

Pas analizës dhe përpunimit te të dhënave, janë përfituar rezultatet si vijon:

Të gjitha pacientet e analizuara, i takojne gjinisë femërore, pra nuk kemi asnjë mashkull.

Tabela 1. Numri i pacientëve sipas grupmoshës

Grupmosha	Nr.	%
40-49	6	10.52
50-59	21	36.84
60-69	21	36.84
70-79	9	15.78
Gjithsej	57	100

Grupmosha më e atakuar nga osteoporoza është ajo 50-59 dhe 60-69 vjeçë, me nga 21 raste ose 36.84 % të tyre, pasuar nga grupmosha 70-79 vjeçë me 9 raste ose 15.78 %, dhe grupmosha 40-49 vjeçë me vetëm 6 raste ose 10.52% të tyre.

Grafiku 1. Paraqitja grafike e pacientëve sipas grupmoshës

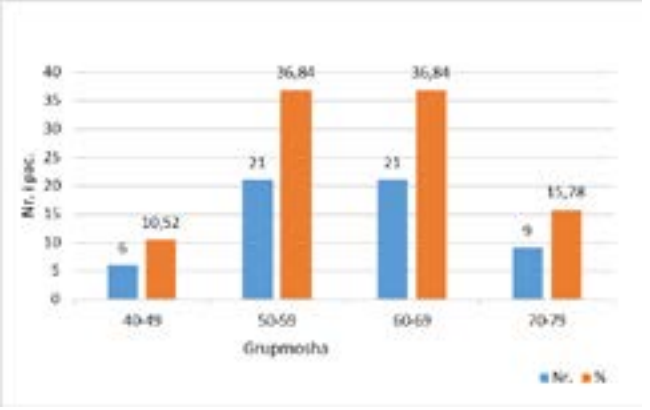


Tabela 2. Numri i pacientëve sipas faktorëve etiologjik

Faktorët etiologjik	Nr.	%
Post menopauza	53	92.98
Vit. D e ulët	54	94.73
Inaktiviteti fizik	57	100
Duhanpirja	12	21.05
Përdorimi i kortizonit	4	7.01

Faktori më i shpeshtë rreziku për osteoporozë është inaktiviteti fizik me 57 raste ose 100% e rastëve, pasuar nga Hipovitaminoza D me 54 raste ose 94.73% të rastëve, post menopauza me 53 raste ose 92.98 % të tyre, si dhe duhanpirja me 12 raste ose 21.05% të rastëve.

Grafiku 2. Paraqitja grafike e efaktorëve etiologjik

Tabela 3. Numri i pacientëve sipas vlerave të T score

DEXA (T score)	Nr.	%
-2.5 deri -2.9	21	36.84
-3.0 deri -3.9	27	47.36
-4.0 deri -4.9	6	10.52
-5.0 deri -5.9	3	5.26
Gjithsej	57	100

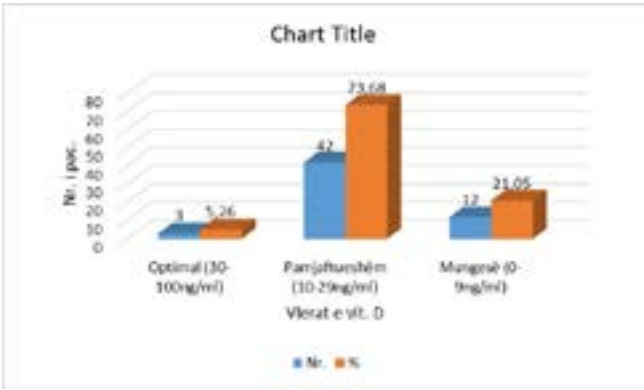
Nga matjet me DEXA score, shihet se më së shumti pacient ishin me vlera të T score nga -3.0 deri -3.9 me gjithsej 27 pacient ose 47.36 % të tyre, pasuar nga ata me T score nga -2.5 deri -2.9 me 21 pacient ose 36.84% të tyre, ata me vlerat e T score nga -4.0 deri -4.9 me 6 pacient ose 10.52% të tyre dhe në fund ata me vlerat e T score nga -5.0 deri -5.9 me gjithsej 3 pacient ose 5.26% të tyre.

Tabela 4. Numri i pacientëve sipas vlerave te vitaminës D

Vlerat e vit. D	Nr.	%
Optimal (30-100ng/ml)	3	5.26
Pamjaftueshëm (10-29ng/ml)	42	73.68
Mungesë (0-9ng/ml)	12	21.05
Gjithsej	57	100

Më së shumti kishte pacient me pamjaftueshmëri të vitaminës D në gjak dhe atë 42 pacient ose 73.68% të tyre, pasuar nga ata që kishin mungesë të vitaminës D gjithsej 12 raste ose 21.05% të tyre, ndërsa vetëm 3 raste ose 5.26% të tyre ishin me vlera optimale të vitaminës D në gjak.

Grafiku 3. Paraqitja grafike e pcientëve sipas vlerave të vitaminës D



DISKUTIMI

Osteoporoza, një problem i madh i shëndetit publik, po bëhet gjithnjë e më e përhapur me plakjen e popullsisë botërore. Osteoporoza është një çrregullim skeletor i karakterizuar nga kompromet imi i forcës së kockave, i cili e predispozon individin për një rrezik të shtuar të frakturave të kofshës, shtyllës kurrizore dhe zonave të tjera skeletore. Pasojat klinike dhe barra ekonomike e kësaj sëmundjeje kërkojnë masa për të vlerësuar individët që janë në rrezik të lartë dhe për të lejuar ndërhyrjen e duhur. Shumë faktorë rreziku ndërlidhen me osteoporozën, duke përfshirë faktorët hormonalë, përdorimin e barnave të caktuara (p.sh., glukokortikoidet), tymosjen e duhanit, aktivitetin e ulët fizik, marrjen e ulët të kalciumit dhe vitaminës D, racën, përmasat e vogla të trupit, dhe një histori personale ose familjare për frakturës. Për shkak se rreziku i frakturave osteoporotike është më i lartë tek gratë e moshuara sesa tek burrat e moshuar, të gjitha gratë në postmenopauzë duhet të vlerësohen për shenja të osteoporozës gjatë ekzaminimeve fizikale rutinore.(14)

Vitamina D (VD) është thelbësore për homeostazën e kockave, por është gjithashtu e përfshirë në efektet pleiotropike në organe dhe inde të ndryshme. Tek të rriturit, mungesa e VD mund të shkaktojë ose përkeqësojë osteoporozën dhe të shkaktojë osteomalaci. Në fakt, mungesa e VD rrit rrezikun e osteoporozës dhe disa sëmundjeve dhe komplikimeve të tjera të karakterizuara nga metabolizmi i dëmtuar i kockave, të tilla si sëmundjet autoimune, sëmundjet inflamatore të zorrëve, alergjitë, sëmundjet endokrinologjike, tumoret malinje hematologjike dhe transplantimi i palcës kockore. (15)

Shëndeti i dobët i kockave ka një ndikim tejet negativ në Britaninë e Madhe, si për sa i përket sëmundshmërisë ashtu edhe vdekshmërisë si dhe kostot financiare. Pirja e duhanit është pranuar prej kohësh si një faktor rreziku për shëndetin e dobët të kockave pasi ndikon në metabolizmin e hormoneve, peshën trupore, nivelet e vitaminës D, përthithjen e kalciumit, qarkullimin e gjakut dhe rrit stresin oksidativ duke prishur kështu resorbimin dhe formimin e shëndetshëm të kockave, dhe duke çuar te osteoporoza. Rrjedhimisht, duhanpirësit kanë një rritje prej 25% të rrezikut të frakturave dhe kanë gati dy herë më shumë gjasa për të përjetuar fraktura të ijeve. Tymosja e duhanit gjithashtu vonon shërimin e kockave pas operacioneve për riparimin e frakturave. Megjithatë, ndërprerja e duhanpirjes, është treguar se e kthen pjesërisht rrezikun e pësimit të frakturave, Prandaj, në udhëzimet kombëtare për parandalimin dhe trajtimin e osteoporozës, këshillohet ndërprerja e duhanpirjes. (16)

Osteoporoza dhe frakturat e lidhura me të, shkaktojnë sëmundshmëri dhe vdekshmëri të konsiderueshme në mbarë botën dhe rezultojnë në kosto të mëdha për individët dhe shoqërinë e prekur. Zgjedhjet e stilit të jetesës përgjatë jetëgjatësisë, ndikojnë në osteoporozë dhe rrezikun e frakturave. Aktiviteti fizik është një strategji e zbatueshme për parandalimin dhe trajtimin e masës së ulët kockore. Pra, është tashmë e vërtetuar dhe e provuar se aktiviteti fizik, shton masën muskulore dhe atë kockore.(17)

Osteoporoza e induktuar nga kortikosteroidet është forma më e zakonshme e osteoporozës dytësore dhe shkaktari i parë tek të rinjtë. Humbja e kockave dhe rritja e shkallës së frakturave, ndodhin herët pas fillimit të terapisë me kortikosteroide, dhe më pas lidhen me dozën dhe kohëzgjatjen e trajtimit.(18)

Nga të gjitha rastet e studjuara në punimin tone, shumica prej tyre, ose 92.98% të rastëve ishin në fazën e postmenopauzës. Kjo do të thotë se kjo faze e jetës tek femrat është pothuajse faktor kryesore rreziku për të shkaktuar osteoporozë.

Mosha e pacientëve është poashtu faktorë rreziku. Sa më e madhe mosha, aq më e madhe është gjasa per osteoporozë. Në rastin tone gupmosha më e atakuar ishte ajo 50 deri 70 vjeç me mbi 73% të rstëve.

Faktor tjetër rreziku që vlen të theksohet është nivelet e ulëta të vitaminës D të cilat u gjetën në masë shumë të madhe. Prej të gjitha pacienteve në studim, 94.73 % të tyrë kishin nivele të ulëta të vitaminës D në gjak. Kjo situatë na inkurajon që me urgjencë duhet të përpiqemi

që të bëjmë të pamundurën që në popullatë të ndryshohet stili i të ushqyerit, që sa më shumë të promovohen dietat me shumë vitamina e minerale, e sa më pak ushqime të njëllojta dhe të këqija.

Një ndër faktorët e rrezikut për osteoporozë ishte edhe mosaktiviteti fizik i cili në pacientet e studjuara nga ne u gjet 100% të rastëve. Asnjë paciente nuk ka theksuar që merret me ndonjë aktivitet fizik, madje nuk ka bëre as edhe 1 kilometer ecje gjatë 24 orëve, gjë që është mjaft shqetësuese, dhe ku shtohet nevoja të punohet ndoshta më së shumti që të ndryshohet kjo veti e të jetuarit në mbarë popullatën tonë, sidomos me grupet e rrezikuara siq janë femrat në kohën e postmenopauzës.

Duhanpirja dhe perdorimi i kortikoideve u gjeten në pak raste, andaj nuk kishin ndonjë rëndësi sinjifikante në studimin tone. Sa i përket përdorimit të kortizonit, vlen të theksohet se në këtë studim, ky medikamnet është përdorur nga pacientet të cilat ende nuk ishin në fazën e postmenopauzës, andaj me gjasë faji për osteoporozë tek këto paciente ishte pikërisht perdërimi për kohë te gjatë i këtij preparati, i shoqëruar edhe me disa faktorë tjerë rreziku.

PËRFUNDIMI

Ekzistojnë shumë faktorë etiologjik për të shkaktuar osteoporozë, andaj kjo sëmundje është shumë faktoriale, dhe si rrjedhoje edhe multidiciplinare.

Shumica dërmuese e pacienteve ishin në fazën e postmenopauzës, që do të thotë se ky faktor etiologjik është kyq në paraqitjen e sëmundjes.

Grupmosha më e atakuar ishte ajo nga 50 deri 70 vjeç.

Nivelet e ulëta të vitaminës D u gjetën në shumicën dërmuese të pacienteve që paraqet faktor rreziku me rëndësi në paraqitjen e osteoporozës.

Mosaktiviteti fizik poashtu është gjetur tek të gjitha rastet në studim.

Duhanpirja dhe përdorimi i kortizonit u gjetën në shumë pak raste, megjithate vlen të theksohet përdorimi i kortizonit pikërisht në rastet që ende nuk ishin në postmenopauzë, gjë që me gjasë ky medikament ishte shkaku kryesorë i osteoporozës tek këto raste.

Metoda e artë dhe kryesore për diagnostikimin e Osteoporozës mbetet Osteodensitometria (DEXA-scan).

LITERATURA

1. "Handout on Health: Osteoporosis". NIAMS. August 2014. Archived from the original on 18 May 2015. Retrieved 16 May 2015.
2. Golob AL, Laya MB (May 2015). "Osteoporosis: screening, prevention, and management". The Medical Clinics of North America. 99 (3): 587–606. doi:10.1016/j.mcna.2015.01.010. PMID 25841602.
3. Branch, NIAMS Science Communications and Outreach (7 April 2017). "Osteoporosis". National Institute of Arthritis and Musculoskeletal and Skin Diseases. Retrieved 16 September 2023.
4. "Clinical Challenges: Managing Osteoporosis in Male Hypogonadism". www.medpagetoday.com. 4 June 2018. Retrieved 22 March 2022.
5. WHO Scientific Group on the Prevention and Management of Osteoporosis (2000 : Geneva, Switzerland) (2003).
6. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P (January 2008). "Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women". The Cochrane Database of Systematic Reviews (1): CD001155. doi:10.1002/14651858.CD001155.pub2. PMID 18253985.
7. Wells GA, Hsieh SC, Zheng C, Peterson J, Tugwell P, Liu W (May 2022). "Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women". The Cochrane Database of Systematic Reviews. 2022 (7): CD004523. doi:10.1002/14651858.CD004523.pub4. PMC 9062986. PMID 35502787.
8. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P (January 2008). "Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women". The Cochrane Database of Systematic Reviews. 2008 (1): CD003376. doi:10.1002/14651858.CD003376.pub3. PMC 6999803. PMID 18254018.
9. "Chronic rheumatic conditions". World Health Organization. Archived from the original on 27 April 2015. Retrieved 18 May 2015.
10. Wade SW, Strader C, Fitzpatrick LA, Anthony MS, O'Malley CD (2014). "Estimating prevalence of osteoporosis: examples from industrialized countries". Archives of Osteoporosis. 9 (1): 182. doi:10.1007/s11657-014-0182-3. PMID 24847682. S2CID 19534928.
11. Svedbom A, Hernlund E, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jönsson B, Kanis JA (2013).

"Osteoporosis in the European Union: a compendium of country-specific reports". Archives of Osteoporosis. 8 (1–2): 137. doi:10.1007/s11657-013-0137-0. PMC 3880492. PMID 24113838.

12. Willson T, Nelson SD, Newbold J, Nelson RE, LaFleur J (2015). "The clinical epidemiology of male osteoporosis: a review of the recent literature". Clinical Epidemiology. 7: 65–76. doi:10.2147/CLEP.S40966. PMC 4295898. PMID 25657593.
13. Gerald N. Grob (2014). Aging Bones: A Short History of Osteoporosis. Johns Hopkins UP. p. 5. ISBN 9781421413181. Archived from the original on 23 July 2014.
14. Nancy E. Lane, MD*. Epidemiology, etiology, and diagnosis of osteoporosis. Aging Center, Medicine and Rheumatology, University of California at Davis Medical Center, Sacramento, CA Received for publication April 20, 2005.
15. Massimo De Martinis, Alessandro Allegra, Maria Maddalena Sirufo. Vitamin D Deficiency, Osteoporosis and Effect on Autoimmune Diseases and Hematopoiesis: A Review. Int J Mol Sci. 2021 Aug; 22(16): 8855.
16. Lion Shahab. Smoking and bone health. 2012 National Centre for Smoking Cessation and Training (NCSCT) UK.
17. Melissa I. Carter, Pamela S. Hinton. Physical Activity and Bone Health. Mo Med. 2014 Jan-Feb; 111(1): 59–64.
18. Karine Briot, Christian Roux. Glucocorticoid-induced osteoporosis. Rheumatic and Musculoskeletal diseases. 2015; 1(1): e000014.

РЕФРАКТИВНИ ГРЕШКИ КАЈ ДЕЦАТА ОД УЧИЛИШНА ВОЗРАСТ: ПРЕГЛЕД НА ЛИТЕРАТУРА

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АБСТРАКТ

На глобално ниво, се проценува дека има 36 милиони луѓе кои се слепи, 216,6 милиони со умерено до тешко оштетување на видот и 188,5 милиони имаат мало оштетување на видот. Една од најчестите причини за оштетување на видот е некорегираната рефрактивна грешка. Истражувањата покажуваат дека приближно 2,3 милијарди луѓе во светот имаат рефрактивно оштетување, но само 1,8 милијарди луѓе имаат пристап до офталмолошки преглед и ефективен третман.

Со цел да се анализира застапеноста на рефрактивните грешки кај децата на училишна возраст, во ова истражување беа формулирани следните истражувачки прашања: Каква е застапеноста на рефрактивните грешки, кои рефрактивни грешки се најзастапени и дали постои семејна историја кај децата со рефрактивни грешки?

Рефрактивната грешка е важна причина за оштетување на видот и слепило ширум светот што може да се спречи. Во моментов, преваленцијата на миопија го привлекува светско внимание бидејќи многу студии известуваат за драматично зголемување во последните 20 години. Раното откривање и лекување на рефрактивните грешки е важно за да се спречи трајно оштетување на видот кај децата. Дијагнозата и третманот на овие грешки е релативно едноставна и е еден од најлесните начини за намалување на оштетениот вид.

ВОВЕД

На глобално ниво, се проценува дека има 36 милиони луѓе кои се слепи, 216,6 милиони со умерено до тешко оштетување на видот и 188,5 милиони имаат мало оштетување на видот [1]. Една од најчестите причини за оштетување на видот е некорегираната рефрактивна грешка [2, 3, 4]. Истражувањата покажуваат дека приближно 2,3 милијарди луѓе во светот имаат рефрактивно оштетување, но само 1,8 милијарди луѓе имаат пристап до офталмолошки преглед и ефективен третман [5].

Рефрактивните грешки, најчесто поради должината на очното јаболко, доведуваат до проблеми во фокусирање на светлосните зраци на мрежницата. Поради тоа се јавува нејасна слика и за јасно гледање потребна е соодветна корекција. Овие грешки можат да се поделат на миопија (кратковидност), хиперметропија (далековидност) и астигматизам (нема

единствена точка на фокус во окото). Кај миопијата како резултат на прекумерна рефракција на рожницата или леќата, или, многу почесто, зголемена должина на окото (‹аксијална миопија›) зраците се фокусираат пред мрежницата. Спротивно од миопијата, кај хиперметропијата зраците се фокусираат позади мрежницата како резултат на неадекватна рефракција или поради кратка аксијална должина на окото. Кај астигматизмот, рефрактивната сила во различни меридијани на окото е нерамномерна [6].

Рефрактивните грешки се поврзани со одредени фактори - на пример, позитивна историја на носење очила во семејството, читање многу блиску до очите, долго гледање компјутери/телевизори, итн. [7]. Некои студии укажуваат и на генетски причини [8].

Оштетувањето на видот во детството поради рефрактивни грешки е еден од најчестите проблеми кај децата на училишна возраст и е втора водечка причина за слепило што може да се лекува. Во изминатите две децении, од голем интерес на сите држави е токму застапеноста на рефрактивните грешки кај децата. Во светот, се проценува дека 19 милиони деца се со оштетен вид, од кои 12 милиони се должат на рефрактивни грешки кои можат лесно да се коригираат. Токму поради тоа, во глобалната иницијатива „VISION 2020 The Right to Sight“, детското оштетување на видот и рефрактивната грешка се нагласени како приоритетна област [9].

Примарната цел на офталмолошкиот скрининг на видот е да се детектираат деца со оштетување на видот кај кои може да се корегира, да се спроведе ран третман и да се намали влијанието што секоја нетретирана состојба може да го има врз нивниот образовен и социјален напредок [10]. Раното откривање на проблемите со видот е важна бидејќи околу 85% од информациите од надворешниот свет се добиваат првенствено преку видот; оштетувањето на видот може да го попречат учењето и социјализацијата на децата [11].

Во 2000 година, во извештајот на Негрел за рефрактивните грешки предложен е протокол за одредување на рефрактивните грешки кај децата [12]. Според овој протокол, кај децата на 5-15 години рефрактивните грешки треба да се мерат со циклоплегија. Оттогаш, бројни студии ширум светот ги базираат своите истражувања на овој протокол за да ја проценат преваленцијата на рефрактивните грешки кај децата. Со цел да се намали појавата на оштетување на видот предизвикано од рефрактивни грешки, многу автори истакнуваат дека е потребно итно да се направат епидемиолошки истражувања за рефрактивните грешки и други очни болести кај децата на училишна возраст.

Неоткриените и некорегираните рефрактивни грешки се особено значаен проблем кај училишните деца. Децата обично никогаш не се жалат на дефектен вид. Општо земено, тие не се свесни за нивниот проблем или може да се прилагодат на нивниот слаб вид. Дури и некое време избегнуваа работа за која е потребна визуелна концентрација. Некорегираната рефрактивна грешка може да предизвика негативно влијание врз процесот на учење и образовниот капацитет.

МЕТОДОЛОГИЈА

Со цел да се анализира застапеноста на рефрактивните грешки кај децата на училишна возраст, во ова истражување беа формулирани следните истражувачки прашања: Каква е застапеноста на рефрактивните грешки, кои рефрактивни грешки се најзастапени и дали постои семејна историја кај децата со рефрактивни грешки?

Постапка за пребарување на литература

Спроведено е систематско пребарување и преглед на литература во согласност со процедурите за систематски прегледи и мета-анализи (PRISMA). Повеќе национални и меѓународни електронски научни бази на податоци, како што се MEDLINE/PubMed, Web of Science, Scopus, Google Scholar и академските репозиториуми беа систематски пребарувани за да се анализираат сите потенцијално релевантни публикации на епидемиолошки студии за преваленцата и инциденцата на рефрактивните грешки кај децата на училишна возраст. Беше спроведена сеопфатна стратегија за пребарување, комбинирајќи ги термините поврзани со епидемиологија (преваленца, инциденца, епидемиологија, фреквенција), термини поврзани со интерес на ова анализа (рефрактивна грешка, миопија, хиперопија, астигматизам, семејна историја) и возраст (од 5 до 15 години) комбинирани со Булови оператори (ИЛИ, И) или не. Не е дефиниран временски интервал на објавувањето на публикациите. Барајќи дополнителни студии или податоци, беше истражувана и библиографијата на секој труд.

Публикациите беа избрани врз основа на следните

критериуми за вклучување: истражување на преваленцата, инциденцата или други епидемиолошки податоци за различната рефрактивна грешка (миопија, хиперопија и астигматизам) на англиски јазик. Секој труд беше прегледан, информациите/податоци беа извлечени врз основа на следните карактеристики: име на авторот, наслов, година, формат на објавување (академска теза или научна публикација), тип на студија, големина на примерок, возраст, семејна историја, преваленца на рефрактивна грешка и, доколку е применливо, преваленца на миопија, хиперопија и астигматизам.

РЕЗУЛТАТИ

Во Табела 1 се сумирани 11-те студии вклучени во ова анализа. Годините на студии се движат од 2002 до 2021 година. Непосредната анализа покажува висока хетерогеност помеѓу студиите во однос на големината на примерокот и опсегот на возраст.

Табела 1. Рефрактивни грешки

Автор/и	Земја	%
Мути и сор. [13]	Америка	26
Али и сор. [14]	Пакистан	19,8
Алем и Гебру [15]	Етиопија	12,9
Фарахата и сор. [8]	Египет	30,1
Сандја [16]	Индија	44,9
Галиб и сор. [17]	Судан	27%
Исмаил и Сукумаран [18]	Малезија	47,8
Димитрова-Радојичиќ и Тасевска [19]	С. Македонија	42,6
Гонзалес-Мејоме и сор. [20]	Португалија	38
Танг и сор. [21]	Кина	38
Јинјанг [22]	Тајланд	25,2

Преваленцата на рефрактивните грешки кај училишните деца се движи помеѓу 12,0% и 47,8%. Овие варијации во распространетоста на рефрактивните грешки меѓу различните студии може да се должат на разликите во големината на примерокот, дефинициите на рефрактивните грешки, методологијата, етничките, еколошките, начинот на живот и генетските фактори во испитуваните популации. Генерално, овие наоди потврдуваат дека рефрактивните грешки се една од најчестите окуларни состојби кои се јавуваат кај оваа возрасна група ширум светот.

Неоткриените и некорегираните рефрактивни грешки се особено значаен проблем кај училишните деца. Децата обично никогаш не се жалат на дефектен вид. Општо земено, тие не се свесни за нивниот проблем или може да се прилагодат на нивниот слаб вид. Дури и некое време избегнуваа работа за која е потребна визуелна концентрација. Непоправената рефрактивна грешка може да предизвика негативно влијание врз процесот на учење и образовниот капацитет.

Табела 2. Вид на рефрактивни грешки

Автор/и	миоп.	хипер.	атигм.
Мути и сор. [13]	70,5%	29,5%	/
Али и сор. [14]	45%	24%	31%
Алем и Гебру [15]	76,5%	8,8%	14,7%
Фарахата и сор. [8]	40,4%	13,8%	45,8%
Сандја [16]	82%	2,3%	15,7%
Галиб и сор. [17]	25,3%	23,2%	51,6%
Исмаил и Сукумаран [18]	30,2%	/	/
Танг и сор. [21]	38%	/	/
Јинјанг [22]	67,4%	32,6%	/

Резултатите од табела 2 покажуваат дека миопијата е најчеста рефрактивна грешка. Глобално, преваленцијата на миопија се зголемува. Мета-анализите сугерираат дека речиси половина од светската популација може да развие миопија до 2050 година, а 10% развиваат висока миопија [23]. Интересно е дека децата со миопија имаат тенденција да имаат повисоки резултати на тестовите за интелигенција, имаат подобар речник и оценки на училиште, отколку немиопите. Неколку клинички студии ја документирале поврзаноста помеѓу миопијата и времето поминато на блиска работа кај децата. Во текот на изминатите две децении, зголемена е употребата на електронски уреди и се повеќе се анализираат можните ефекти на електронските уреди (времето) врз развојот на миопија кај децата. Особено паметните телефони и таблетите поради нивното невообичаено блиско работно растојание [24]. Докажано е дека времето на отворено е конзистентен еколошки фактор кој може да го одложи почетокот на миопијата. Најновите студии покажуваат дека престојувањето повеќе време на отворено го превенира развојот на миопија (независно од типот на активност на отворено) [25]. Дополнително, констатирани се разлики во преваленцата на миопија помеѓу урбаните и руралните области. Децата кои живеат во урбани средини имаат 2,6 пати поголем ризик за развој на миопија во споредба со децата кои живеат во рурални средини [26].

Табела 3. Семејна историја

Автор/и	да
Аиоуб и сор.	57%
Фарахата и сор.	47%
Галиб и сор.	25,3%
Јинјанг [19]	29,5%

Од вкупно 11 студии, кај четри е истражувано и присуството на семејна историја кај децата кои имаат рефракциони грешки (Табела 3). Овие студии покажа значајна врска помеѓу преваленцата на рефрактивни грешки и семејната историја на носење очила (од 25,3% до 57%). Исто така, во други студии констатиран е поголем процент на кратковидни деца меѓу семејствата со двајца родители со кратковидост во споредба со семејствата со еден родител и родители без миопија.

ЗАКЛУЧОК

Рефрактивната грешка е важна причина за оштетување на видот и слепило ширум светот што може да се спречи. Во моментов, преваленцијата на миопија го привлекува светско внимание бидејќи многу студии известуваат за драматично зголемување во последните 20 години. Раното откривање и лекување на рефрактивните грешки е важно за да се спречи трајно оштетување на видот кај децата. Дијагнозата и третманот на овие грешки е релативно едноставна и е еден од најлесните начини за намалување на оштетениот вид.

ЛИТЕРАТУРА

1. Abdi Ahmed Z, Alrasheed SH, Alghamdi W. Prevalence of refractive error and visual impairment among school-age children of Hargesia, Somaliland, Somalia. East Mediterr Health J. 2020;26(11):1362-1370. doi: 10.26719/emhj.20.077
2. Bourne RRA, Flaxman SR, Braithwaite T, Cicinelli MV, Das A, Jonas JB et al. Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis. Lancet Glob Health. 2017;5(9):e888–97. doi: 10.1016/S2214-109X(17)30293-0 PMID:28779882 2.
3. Flaxman SR, Bourne RRA, Resnikoff S, Ackland P, Braithwaite T, Cicinelli MV et al. Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. Lancet Glob Health. 2017;5(12):e1221–34. doi: 10.1016/S2214-109X(17)30393-5 PMID:29032195
4. He M, Zeng J, Liu Y, Xu J, Pokharel GP, Ellwein LB. Refractive error and visual impairment in urban children in Southern China. Invest Ophthalmol Vis Sci. 2004;45:793–799. doi: 10.1167/iovs.03-1051
5. Holden BA, Sulaiman S, Knox K. The challenge of providing spectacles in the developing world. Community Eye Health 2000;13(33):9-10.
6. Williams KM, Verhoeven VJ, et al. Prevalence of refractive error in Europe: the European eye epidemiology. Eur J Epidemiol. 2015;30:305–315. doi: 10.1007/s10654-015-0010-0
7. Pokharel A, Pokharel P, Das H, Adhikari S. The patterns of refractive errors among the school children of rural and urban settings in Nepal. Nepal J Ophthalmol 2010;2:114–120.
8. Farahata HG, G. Marey HM, Badawi NM, Allam HK, M. Issa MM. Prevalence of occult refractive errors in primary school students. Menoufia Med J 2018;31:267-272.
9. Gilbert C, Foster A. Childhood blindness in the context o fVISION 2020—the right to sight. Bull World Health Organ.2001;79(3):227–232.
10. Solebo AL, Rahi JS. Vision in children aged 4-5. External review against program appraisal criteria for the United Kingdom Screening Committee 2013.
11. Lopes CLR, Barbosa MA, Marques ES, Lino AIA, Morais NHF. O trabalho da enfermagem na detecção de problemas visuais em crianças/adolescentes. Rev Eletrônica Enferm 2003; 5:45-49.
12. Negrel AD, Maul E, Pokharel GP, Zhao J, Ellwein LB. Refractive Error Study in Children: sampling and measurement methods for a multi-country survey. Am J Ophthalmol. 2000 Apr;129(4):421-6. doi: 10.1016/s0002-9394(99)00455-9
13. Mutti DO, Mitchell GL, Moeschberger ML, Jones LA, Zadnik K. Parental myopia, near work, school achievement, and children's refractive error. Invest Ophthalmol Vis Sci. 2002 Dec;43 (12): 3633-3640.
14. Ali A, Imran A, Ayub S. Prevalence of uncorrected refractive errors among school children, E: /Biomedica. 2007;23.
15. Alem KD, Gebru EA. A cross-sectional analysis of refractive error prevalence and associated factors among elementary school children in Hawassa, Ethiopia. J Int Med Res. 2021 Mar;49(3):300060521998894. doi: 10.1177/0300060521998894

16. Sandhya RN, A Study on Refractive Errors among the School Children of Kothapatnam Manual, Parkas District. IOSR Journal of Dental and Medical Sciences 2018;17(7):29-32. doi:10.9790/0853-1707152932
17. Ghalib NM, Ibrahim SM, Bahakim N. Prevalence of Refractive Errors among Primary School Children (6-15 Yrs) in Al-Khartoum- Sudan. Systematic Reviews in Pharmacy. 2020;11(10):674-678. doi: 10.31838/srp.2020.10.99
18. Ismail LA, Sukumaran S. Prevalence of refractive errors among school children in Wangsa Maju, Kuala Lumpur, Malaysia. Med Hypothesis Discov Innov Optom.2022 Fall; 3(3): 106-112. doi: 10.51329/mehdioptometry158
19. Dimitrova-Radojichikj D, Tasevska D. Causes of visual impairment:a retrospective study in Macedonian children. Journal of Ophthalmology (Ukraine) 2020; 3 (494):29-30.
20. González-Méijome J, Faria-Correia F, Marques C, et al. Two-year change in refractive error prevalence in a school population from 6 to 13 years of age in portugal: longitudinal pilot study. Investigative Ophthalmology & Visual Science 2018 July, Vol.59, 3384.
21. Tang Y, Chen A, Zou M, Liu Z, Xoung CA, Zheng D, Jin G. Prevalence and time trends of refractive error in Chinese children: A systematic review and meta-analysis. J Glob Health 2021;11:08006. doi: 10.7189/jogh.11.08006
22. Yingyong P. Risk factors for refractive errors in primary school children (6-12 years old) in Nakhon Pathom Province. J Med Assoc Thai. 2010 Nov;93(11):1288-93.
23. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, Wong TY, Naduvilath TJ, Resnikoff S. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. Ophthalmology. 2016 May;123(5):1036-42. doi: 10.1016/j.ophtha.2016.01.006
24. Miranda AM, Nunes-Pereira EJ, Baskaran K, Macedo AF. Eye movements, convergence distance and pupil-size when reading from smartphone, computer, print and tablet. Scand J Optom Vis Sci. 2018;11(1):1-5. doi:10.5384/sjovs.vol11i1p1-5
25. Dhakal R, Shah R, Huntjens B, Verkicharla PK, Lawrenson JG. Time spent outdoors as an intervention for myopia prevention and control in children: an overview of systematic reviews. Ophthalmic Physiol Opt. 2022 May;42(3):545-558. doi: 10.1111/opo.12945
26. Rudnicka AR, Kapetanakis VV, Wathern AK, Logan NS, Gilmartin B, Whincup PH, Cook DG, Owen CG. Global variations and time trends in the prevalence of childhood myopia, a systematic review and quantitative meta-analysis: implications for aetiology and early prevention. Br J Ophthalmol. 2016 Jul;100(7):882-890. doi: 10.1136/bjophthalmol-2015-307724

CHALLENGES WITH PARENTERAL FEEDING IN SHORT BOWEL SYNDROME PATIENTS:A CASE REPORT

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ABSTRACT

Intestinal failure (IF) is a clinical condition that occurs as a result of intestinal resection or disease-related malabsorption or dysmotility. Intestinal failure causes malabsorption, which can lead to malnutrition, diarrhoea, weight loss, steatorrhea, electrolyte imbalance, and vitamin deficiencies. To avoid the many problems of SBS, the patient requires long-term therapy and mineral and electrolyte supplements.

Necrotising enterocolitis is responsible for about one-third of all reported cases. Malrotation leading to midgut volvulus, abdominal wall defects (gastroschisis), and intestinal atresia are the most common causes of SBS (short bowel syndrome) in children, while long segment involved Hirschsprung's disease and extensive aganglionosis are more rare causes.

We represent a case of Hirschsprung's disease in a one-month-old boy who developed short bowel syndrome after substantial resection of the small and large intestines. Low potassium was one of our patient's key issues prior to admission to our department for parenteral nourishment. The patient has idiopathic arthritis and a low red blood cell count.

Intestinal failure causes malabsorption, which can lead to malnutrition, diarrhoea, weight loss, steatorrhea, electrolyte imbalance, and vitamin deficiencies. To avoid the many problems of SBS, the patient requires long-term therapy and mineral and electrolyte supplements.

Key words: Short Bowel Syndrome,Intestinal failure,Hirschprung's disease, parenteral nutrition

INTRODUCTION

Intestinal failure (IF) is a clinical condition that occurs as a result of intestinal resection or disease-related malabsorption or dysmotility. It is distinguished by a decrease in functional gut capacity below the bare minimum required for optimal digestion and nutrition absorption. It is defined by the failure to maintain protein-energy, fluid, electrolyte, or micronutrient balance after intestinal resection or disease-associated malabsorption or dysmotility. The objective of care is to maintain appropriate nutritional and metabolic support until intestinal adaptation is complete. (Li & Chen, 2022)

Congenital and perinatal diseases such as necrotising enterocolitis (NEC), malrotation leading to midgut volvulus, abdominal wall defects (gastroschisis), and intestinal atresia are the most common causes of SBS (short bowel syndrome) in children, while long segment involved Hirschsprung's disease and extensive aganglionosis are more rare causes.However, NEC is responsible for about one-third of all reported cases. (Chiara Caporilli, Giuliana Giannì, Grassi, & Esposito, 2023)

Many of the impacts are most likely caused by changes in the gut microbiota, which alters important signalling

pathways. Recent research has revealed that changes in gut shape have ramifications for the microbiota. (Carter et al., 2023)

Intestinal failure causes malabsorption, which can lead to malnutrition, diarrhoea, weight loss, steatorrhea, electrolyte imbalance, and vitamin deficiencies. To avoid the many problems of SBS, the patient requires long-term therapy and mineral and electrolyte supplements. Among these consequences include intestinal failure-related liver disease and hepatic cholestasis. Oral feeding is required to avoid this problem. Hyponatremia, dehydration, nephrolithiasis (from hyperoxaluria), and chronic renal failure are all reduced by IV fluids. Regular hydration and maintaining a urine output of 800 mL/d and a urine sodium level more than 20 mmol/L are appropriate interventions for these individuals. Magnesium deficiency should be addressed with > 1.5 mg/dL supplementation. Hydration and thiamine supplementation should also be considered. (Lakkasani, Seth, Khokhar, Touza, & Dacosta, 2022)

CASE REPORT

This is a patient with short bowel syndrome as a result of extensive resection of the small and large intestine at the age of one month, on several past occasions he was hospitalised at UC for GEH for enteral and parenteral nutritional support. Enteral and parenteral nutrition supplemented with infusion solutions, electrolytes and vitamin therapy is prescribed , with the last adjusted body weight of 43 kg.

A percutaneous endoscopic gastrostomy was placed 4 years ago, and it was reimplanted 2 months ago. On several occasions he was hospitalised at UC for GEH for parenteral nutrition, last hospitalised until 02.12.2022 for changing the previously placed percutaneous endoscopic gastrostomy Figure 2.Currently, the patient complains of occasional numbness of the fingers on the palms.

A CT evaluation of the abdomen and small pelvis was performed. The tomogram is dominated by distinct intestinal distension along the length of the colon.Into the rectum,a narrower segment is observed, and proximally present distension of the colon along its entire length, due to which it compresses the parenchymal organs, as well as the small intestines. A percutaneously placed catheter is seen in the left hemiabdomen. There is no free fluid in the abdomen and small pelvis.Figure 3

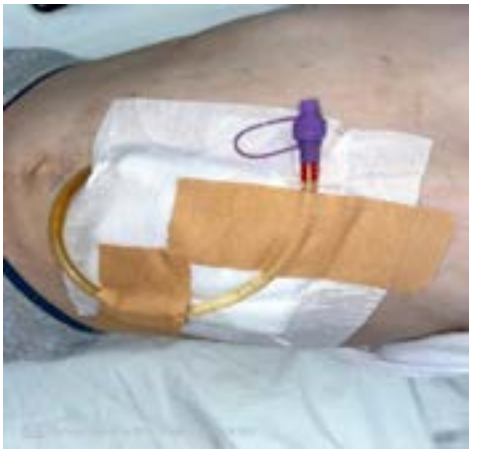
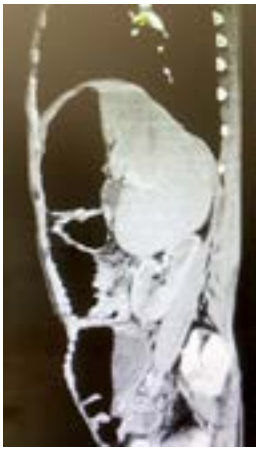


Figure 2.Percutaneous endoscopic gastrostomy in our patient



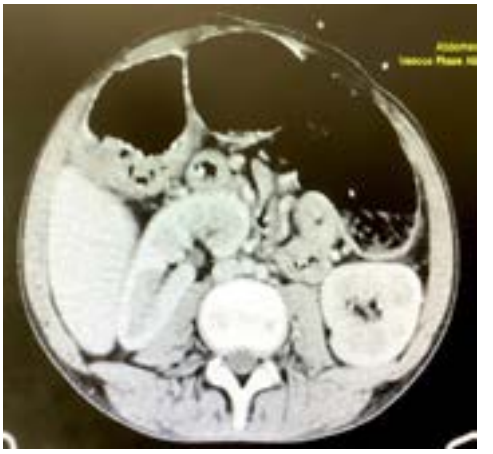


Figure 3. Distension of the colon

Laboratory tests were performed on a regular basis during hospitalisations, and the results are as follows.Table 1Last hospitalisation in February 2023 for parenteral nutrition, echo finding during hospitalisation. Liver with a rounded edge slightly increased echogenicity of the parenchyma, no focal changes. The spleen with a diameter of 12 cm. There was no ascitic fluid the abdomen and no dilatation

of biliary stem. The two kidneys are somewhat larger, larger the left, there is no stagnation in the channel systems. The patient is 43 kg.

	RBC	HGB	WBC	PLT	AP	AA-S	LDH	Sodium	Iron-S
06.10.2022	4.12	96	4.1	241	102	145	923		
10.10.2022	4.85	121	1.8	55	140	97	823		
17.10.2022	4.74	119	8.2	543	121	143	351	137	5.5
24.01.2023	4.31	107	7.2	277	176	158	202	139	3.1
01.02.2023	4.56	117	5.9	318		166	158	142	5.1
02.10.2023	4.90	99	6.7	288	116	192	190		

Table 1. Lab reports during hospitalisations * (RBC-red blood cells normal ranges 4,20-5,50 10^12\L,HGB-hemoglobin 120-180 g\L,WBC-white blood cells 4,00-9,00 10^12\L,PLT-platelets 150-450 10^9\L,AP-alkaline phosphatases 36-126 U\L,AA-S-alfa amylase serum 30-110 U\L,LDH-lactate dehydrogenase borderline 248).

DISCUSSION

Estimating the length of the small intestine in a single patient is still challenging. The average length of the adult human small intestine has been determined as 600 cm based on cadaver research. Any condition that results in fewer than 200 cm of viable small intestine puts a patient at risk of developing short bowel syndrome (SBS). Estimating the incidence and prevalence of SBS is difficult. According to one data from the United Kingdom, published in 1990 by Lennard-Jones, the incidence of SBS needing parenteral nutrition (PN) in the United Kingdom was two patients per million in the population.According to a European survey conducted in 1997, the prevalence of home PN (HPN), of which SBS was the most common indicator, was little over four per million.

The residual small bowel length required to avoid PN dependency is around 100 cm in the absence of an intact and functional colon or 60 cm in the presence of a totally functional colon.The degree of intestinal adaption and eventual PN dependency is extremely unique. The gut adjusts to enable better absorption. Villus diameter and height rise, as does small bowel lengthening, resulting in an increase in absorptive surface. This procedure may take years to complete. Bacterial overgrowth, which is typically attributable to ileocecal valve resection and intestinal denervation following surgery, is a prominent factor that may impact absorption and nutritional assimilation in these individuals. The mobility of the intestines may also have an impact on a patient's capacity to tolerate enteral feeding following a small intestinal removal. (DeLegge et al., 2007)

This disorder can cause deficiencies in fat-soluble vitamins, which can lead to complications including bleeding diathesis. Myeloproliferative Syndrome was found in our patient. A bone biopsy was performed, and the results are listed below.

(Microscopically, the sections show rich cellular debris due to the proliferation of cells of the myeloid and myelomonocytic lineage (lysozim+, CD15+ and D68+) which suppress the CD235+ erythroid lineage. Cells with myeloblastic morphology are seen but CD34 and CD117 are negative. The finding is consistent with SYNDROMA MEYLOPROLIFERATIVUM).

In babies, oral feeding is the recommended method, and breast milk (BM) is the first milk of choice. In the absence of maternal BM, donor BM or conventional preterm or term formula are options. When they are not accepted, extensively hydrolyzed or amino acid-based diets are utilised. As soon as clinically acceptable, solids should be offered. To avoid oral aversion, children are encouraged to eat by mouth and experiment with diverse tastes and textures. Aggressive PN weaning and tube (over-)feeding are no longer recommended. (Puoti & Köglmeier, 2022)

Complications of parenteral nutrition

Adults taking PN (parenteral nutrition) had a variety of liver problems, including biochemical (elevated serum aminotransferases and alkaline phosphatase) and histological (steatosis, steatohepatitis, lipidosis and phospholipidosis, cholestasis, fibrosis, and cirrhosis) changes. Although most of these anomalies are harmless and temporary, a tiny percentage of people acquire more significant and progressive illness.

When potassium falls below the usual threshold of 3.5

mEq/L, the body has already lost a significant amount of potassium due to the majority of potassium being stored intracellularly.

substantial electrolyte imbalances can occur in patients with short bowel syndrome, resulting in substantial morbidity. (Sobash, Vedala, McClain, & Oster, 2020)

One of our patient's primary difficulties prior to admission to our department for parenteral nutrition was low potassium, as seen in the chart below.Figure 1

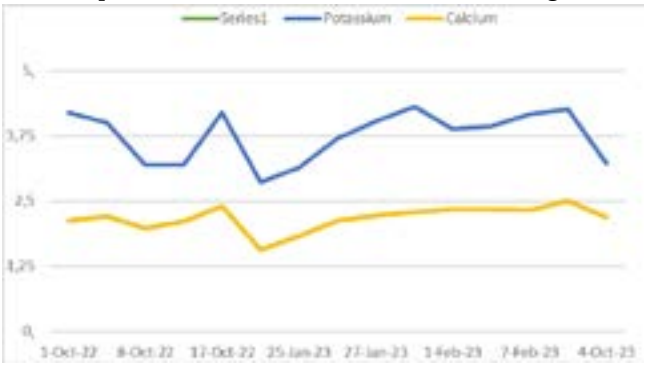


Figure 1. Progression of selected laboratory parameters:Potassium (normal ranges 3.8-5.5 mmol\L),Calcium (normal ranges 2.1-2.6 mmol\L).

Acalculous cholecystitis, gallbladder sludge, and cholelithiasis are biliary problems linked with PN. Sludge and gallstone development can be reduced or even prevented by stimulating gallbladder contraction and emptying by enteral feedings or cholecystokinin injections.

Patients taking long-term PN for more than a few months suffer metabolic bone disorders, including osteomalacia and osteopenia. Asymptomatic bone disease with radiologic evidence of demineralisation to severe bone pain and fracture are all clinical symptoms of bone disease. The origin of metabolic bone disease is unknown, suggested pathways include aluminum toxicity, vitamin D toxicity, and negative calcium balance. (DeLegge et al., 2007)

CONCLUSION

In this study, we presented a case of a 23 years old male with short bowel syndrome with post-implantation of percutaneous endoscopic gastrostomy and arthritis juveniles idiopathic-a. Patients who have had an extensive part of their gut removed typically have particular dietary requirements. They may be unable to absorb enough nutrients and water from the food they consume.

As a result, home PN (HPN) is the basis of therapy for severe SBS. Chronic administration of macronutrients, micronutrients, hydration, and electrolytes via central venous access in the patient's home is required for HPN. HPN necessitates close clinical and biochemical monitoring. (Bielawska & Allard, 2017)

COI Statement:This paper has not been submitted in parallel. It has not been completely or partially presented at a meeting, podium, or conference. It hasn't been published or offered for review in advance.All authors declare that there is no conflict of interest.

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REFERENCE

1. Bielawska, B., & Allard, J. (2017). Parenteral Nutrition and Intestinal Failure. Nutrients, 9(5), 466. https://doi.org/10.3390/nu9050466
2. Carter, J., Bettag, J., Morfin, S., Manithody, C., Nagarapu, A., Jain, A., ... Kurashima, K. (2023). Gut Microbiota Modulation of Short Bowel Syndrome and the Gut–Brain Axis. Nutrients, 15(11), 2581. https://doi.org/10.3390/nu15112581
3. Chiara Caporilli, Giuliana Giannì, Grassi, F., & Esposito, S. (2023). An Overview of Short-Bowel Syndrome in Pediatric Patients: Focus on Clinical Management and Prevention of Complications. Nutrients, 15(10), 2341–2341. https://doi.org/10.3390/nu15102341
4. DeLegge, M., Alsolaiman, M. M., Barbour, E., Bassas, S., Siddiqi, M. F., & Moore, N. M. (2007). Short Bowel Syndrome: Parenteral Nutrition Versus Intestinal Transplantation. Where Are We Today? Digestive Diseases and Sciences, 52(4), 876–892. https://doi.org/10.1007/s10620-006-9416-6
5. Lakkasani, S., Seth, D., Khokhar, I., Touza, M., & Dacosta, T. J. (2022). Concise review on short bowel syndrome: Etiology, pathophysiology, and management. World Journal of Clinical Cases, 10(31), 11273–11282. https://doi.org/10.12998/wjcc.v10.i31.11273
6. Li, R., & Chen, W. (2022). Medical nutrition therapy for adult intestinal failure: A review of current perspectives. PubMed, 31(3), 483–488. https://doi.org/10.6133/apjcn.202209_31(3).0014
7. Merras-Salmio, L., & Pakarinen, M. P. (2022). Infection Prevention and Management in Pediatric Short Bowel Syndrome. Frontiers in Pediatrics, 10, 864397. https://

doi.org/10.3389/fped.2022.864397

8. Puoti, M. G., & Köglmeier, J. (2022). Nutritional Management of Intestinal Failure due to Short Bowel Syndrome in Children. Nutrients, 15(1), 62. https://doi.org/10.3390/nu15010062
9. Sobash, P. T., Vedala, K., McClain, C. M., & Oster, C. (2020). Electrolyte Replacement in Bartter Syndrome With Abnormal Small Bowel: A Case Report. Journal of Investigative Medicine High Impact Case Reports, 8, 232470962098244. https://doi.org/10.1177/2324709620982440

CLINICAL PRESENTATION OF PULMONARY EMBOLISM ASSOCIATED WITH ORAL CONTRACEPTIVES: A CASE REPORT

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ABSTRACT

Pulmonary thromboembolism (PTE) presents a significant challenge in clinical practice due to its nonspecific symptoms and potential for fatal outcomes if not promptly diagnosed and treated.

This case report highlights the presentation, management, and outcomes of a 22-year-old female patient admitted to the Emergency Department with severe dyspnea, tachycardia, pain in the left hemithorax hypotension and loss of consciousness on two occasions. .The key outcome of a pulmonary thromboembolic episode is a hemodynamic instability. Predisposing factors are numerous; in this case, the patient was obese and was on oral contraceptive therapy. Despite initial challenges in diagnosis, comprehensive evaluation, including laboratory analyses, CT angiography, and echocardiography, confirmed the diagnosis of PTE. The patient was admitted to the intensive care unit, where she was placed on continuous heparin therapy, followed by low molecular weight heparin, and on the 7th day of hospitalization switched to NOAC (Novel Oral Anticoagulant). The patient responded well to the therapy. The patient was followed up for a period of 15 months after admission to the hospital. Throughout all follow-up visits, she remained hemodynamically stable with normal vital parameters. She was placed on NOAC therapy. A follow-up echocardiogram revealed normal findings. A genetic panel was performed, showing heterozygous mutations for MTHFR C677T, LTA heterozygous , and beta-fibrinogen homozygot, which are not provocateurs for pulmonary thromboembolism (PTE). NOAC therapy was discontinued due to assessment for provoked VTE and a thrombophilic panel showing no risk of repetitive PTE episodes.

This revised abstract provides a concise summary of the case report, including key details of the patient presentation, diagnostic evaluation, treatment approach, and long-term outcomes.

Key words: Pulmonary embolism, contraceptives

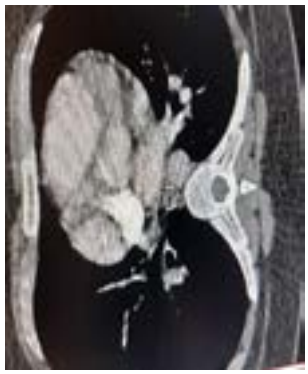
INTRODUCTION

The key outcome of a pulmonary thromboembolic episode is a hemodynamic instability. Big and/or multiple embolises lead to sharp increase of the pulmonary vascular resistance and then result with increased postoverload of the right heart chamber. It is possible to experience a heart syncope and/or systematic hypotension, that can progress up to death because of weakness of the right heart chamber. The paradoxical movement of the valvula leads to disorder of the diastolic function of the left heart chamber and decrease of the systemic cardiac output. A middle hemodynamic destabilization can happen, usually in the first 24 to 48 hours, because of repeated embolism and/or decrease of the function of the right heart chamber. This can appear from the start or because of repeated episodes of PTE, that are quite common with undiagnosed or inadequately treated DVT. The respiratory insufficiency in PTE is usually a consequence of hemodynamic disorders. Small, distal embolization, although they don't affect the hemodynamic, can cause areas of alveolar pulmonary hemorrhage that will result with hemoptysis, pleuritis and mild pleural effusion. The diagnosis of acute and massive pulmonary embolism (PE)

is often apparent, even in the absence of other diseases and presence of risk factors. The diagnosis is easily established in the presence of the following symptoms: hypotension, syncope, shock, anoxia, increased venous pressure. PE presenting as isolated dyspnea is often difficult to diagnose. Initial dyspnea subsides immediately, while dyspnea with an increasing character is more common and nonspecific. In older patients with multiple diseases, even a small embolus can exacerbate symptoms of the underlying disease. Diagnosis becomes challenging when symptoms correspond to the underlying disease, for example, chronic heart failure, exacerbation of coronary artery disease, or even worsening of dementia because of cerebral ischemia.

CASE REPORT

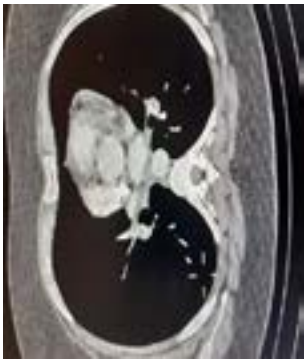
Case presentation: A 22-year-old female patient was brought to the Emergency Department by ambulance due to severe dyspnea, choking sensation, pain in the left hemithorax, tachycardia, hypotension, and loss of consciousness on two occasions. Symptoms started two days before admission; the patient visited the ER service where she was noted to have a heart rate of 140/min and was prescribed Verapamil tablets. Due to worsening symptoms the following day, emergency medical services were called.Personal history: Non-smoker, non-drinker, denies allergy to medications, on regular therapy with contraceptive tablets. Past medical history:Denies relevant diseases. Family history: Denies relevant diseases. Physical examination: Conscious, oriented, afebrile, easily dyspneic, well-developed, skin, and visible mucous membranes appropriately colored, lymph nodes in accessible regions are not palpable, tachycardic, restless, hypotensive. Chest - symmetrical, respiratory movements equally mobile. Lungs - vesicular breath sounds auscultated. Heart - rhythmic action, tachycardic, frequency 140/min, BP 90/60 mmHg. Abdomen - soft, non-tender, liver, and spleen not palpable. Extremities - normal without edema, peripheral pulses palpable. Laboratory analyses, D-dimer test, and CT angiography of the pulmonary trunk were performed at the Emergency Department.Laboratory analyses: Leukocytes (Le) 21.8, Erythrocytes (Er) 4.91, Hemoglobin (Hgb) 125, Hematocrit (Hct) 0.38, Platelets (Tr) 312, Sodium (Na) 136, Potassium (K) 3.2, Glucose (glik) 10, Alanine Aminotransferase (ALT) 18, Aspartate Aminotransferase (AST) 13, Lactate Dehydrogenase (LDH) 214, Urea 4.6, Creatinine (Kreat) 74, Total Bilirubin (Vkup Bili) 10, Amylase (Ami) 48, Lipase (Lip) 86, Creatine Kinase (CK) 47, Creatine Kinase-MB (CK-MB) 28, C-Reactive Protein (CRP) 86.3, troponin negative. Hemostasis and D-dimer: normal hemostasis, D-dimer 4.94 CT angiography of the pulmonary trunk: The cross-sections of the main pulmonary trunk and the right pulmonary artery show no convincing signs of endoluminal changes. In the left pulmonary artery at the bifurcation, there is a recommendation from surrounding structures, but there is no clear demarcation of the wall from the blood vessel, suspicious for an intramural thrombus measuring 17x18mm, correlating with the D-dimer. No enlarged lymph nodes are observed in the mediastinum. No signs of focal changes or pleural effusion are observed in the lung parenchyma.



Echocardiography: LV-d: 44mm, LV-s: 21mm, RV d: 35mm, LA 32mm, Ao 21mm, IVS 10mm, EF% 65%. The aorta is within normal dimensions, AoV trileaflet with a normal appearance and proper opening. MV with a normal appearance and motion consistent with age. E/A fusion due to tachycardia. TV with moderate TR with V. Max 33.4 m/sec and pressure gradient P 44.5 mmHg, SPAP 54.4 mmHg. PV with mild PR and shortened accT 78 milliseconds. VKI 20mm, respiratory collapsibility less than 50%. Cardiac chambers with normal dimensions. Left ventricle with a D-shaped ventricle, indicating right ventricular pressure/volume overload and normal systolic function. Right ventricle with enlarged dimensions. IVS and IAS without defects, pericardium with a 5mm free space ahead of RV.Gas analyses:pH 7.350, pCO2 5.12 kPa, pO2 2.87 kPa, HCO3-act 20.7 mmol/l, HCO3-std 19.6 mmol/l, BE -4.4, sO2 32.9Follow-up gas analyses:pH 7.49, pCO2 3.96 kPa, pO2 15.98 kPa, HCO3-act 22.1 mmol/l, HCO3-std 24.3 mmol/l, BE -0.2, sO2 98.3 Gas analyses:pH 7.350, pCO2 5.12 kPa, pO2 2.87 kPa, HCO3-act 20.7 mmol/l, HCO3-std 19.6 mmol/l, BE -4.4, sO2 32.9Follow-up gas analyses:

pH 7.49, pCO2 3.96 kPa, pO2 15.98 kPa, HCO3-act 22.1

mmol/l, HCO3-std 24.3 mmol/l, BE -0.2, sO2 98.3 Follow-up CT angiography: Regular presentation of the aortic arch. Ascending aorta with a transverse diameter of 26mm, pulmonary trunk with a transverse diameter of 25mm. The pulmonary arteries are filled with extensive thrombotic masses and almost occluded. Thrombotic masses are observed in the segmental branches for the upper and lower lobes bilaterally. Subpleural consolidation with a diameter of 34mm extending towards the mediastinal pleura, which is irregularly thickened, is observed in the subpleural parenchyma in the posterobasal regions. The remaining lung parenchyma shows no focal lesions.



DISCUSSION

Predisposing factors are numerous; in this case, the patient was obese and was on oral contraceptive therapy. The patient was admitted to the intensive care unit, where she was placed on continuous heparin therapy, followed by low molecular weight heparin, and on the 7th day of hospitalization switched to NOAC (Novel Oral Anticoagulant). The patient responded well to the therapy. The patient was followed up for a period of 15 months after admission to the hospital. Throughout all follow-up visits, she remained hemodynamically stable with normal vital parameters. She was placed on NOAC therapy. A follow-up echocardiogram revealed normal findings. A genetic panel was performed, showing heterozygous mutations for MTHFR C677T, LTA, and beta-fibrinogen, which are not provocateurs for pulmonary thromboembolism (PTE). NOAC therapy was discontinued due to assessment for provoked PTE and a thrombophilic panel showing no risk of repetitive PTE episodes. Upon recommendation from a transfusiologist and a cardiologist, the patient was prescribed ASA (aspirin) 100mg tablets.

CONCLUSION

In conclusion, this case underscores the importance of prompt recognition and management of pulmonary thromboembolism (PTE), a potentially life-threatening condition. Through timely intervention and appropriate anticoagulant therapy, the patient demonstrated a favorable response, with sustained hemodynamic stability and resolution of symptoms during the 15-month follow-up period. Additionally, genetic testing revealed mutations that do not predispose to recurrent PTE, informing the decision to discontinue novel oral anticoagulant therapy. This case highlights the critical role of comprehensive evaluation, including genetic analysis, in guiding treatment decisions for PTE patients. Continued vigilance and individualized management strategies are essential to mitigate the risk of recurrent thromboembolic events and optimize patient outcomes.

REFERENCE

1. Konstantinides, S. V., Meyer, G., Becattini, C., Bueno, H., Geersing, G. J., Harjola, V. P., ... & Zamorano, J. L. (2019). 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). European Heart Journal, 41(4), 543-603. DOI: 10.1093/eurheartj/ehz405
2. Goldhaber, S. Z. (2010). Pulmonary embolism. New England Journal of Medicine, 363(3), 266-274. DOI: 10.1056/NEJMra0907731
3. Kline, J. A., Courtney, D. M., Kabrhel, C., Moore, C. L., & Smithline, H. A. (2018). Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. Journal of Thrombosis and Haemostasis, 16(5), 987-994. DOI: 10.1111/jth.14011
4. Böttiger LE, Boman G, Eklund G, Westerholm B. Oral contraceptives and thromboembolic disease: effects of lowering oestrogen content. Lancet 1980
5. 3Stolley PD, Tonascia JA, Tockman MS, Sartwell PE, Rutledge AH, Jacobs MP. Thrombosis with low-estrogen oral contraceptives. Am J Epidemiol 1975;
6. Vandenbroucke P, Rosing J, Bloemenkamp KW, Middeldorp S, Helmerhorst FM, Bouma BN, et al. Oral contraceptives and the risk of venous thrombosis. N Engl J Med. 2001.
7. Gronich N, Lavi I, Rennert G. Higher risk of venous thrombosis associated with drospirenone-containing oral contraceptives: a population-based cohort study. CMAJ. 2011.
8. 8. WHO Collaborative Study, Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study.Lancet. 1995

CASE REPORT: HOUGE TYPE X-LINKED CNKSR2 DELETION: A RARE PRESENTATION OF DEVELOPMENTAL DISORDER AND EPILEPSY

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ABSTRACT

Houge syndrome, also known as Houge type X-linked syndromic mental retardation, is a rare genetic disorder characterized by intellectual disability, developmental delay, distinctive facial features, and other associated abnormalities. In this case report, we identified a microdeletion in the CNKSR2 gene with previously described phenotype, rarely mentioned in literature. Deletions in connector enhancer of kinase suppressor of Ras-2 (CNKSR2) located on the X chromosome (Xp22.12) result in epilepsy phenotype and developmental delay with variable intellectual impairment (Mei D et al. BMC Medical Genetics 2020; 21:69). CNKSR2 gene is highly expressed only in the brain resulting in phenotypic effects restricted to the brain. The child gave favorable therapeutic response to Valproic acid and attends speech and occupational therapy in order to achieve the best possible outcome. This report aims to help clinicians in diagnosis of this rare microdeletion and further genetic counseling and better understanding and improve ability to ordinate adequate treatment in individuals with CNKSR2-related neurodevelopmental disorders and epilepsy.

Keywords: CNKSR2 deletion, epilepsy, X-linked, development delay,aCGH

INTRODUCTION

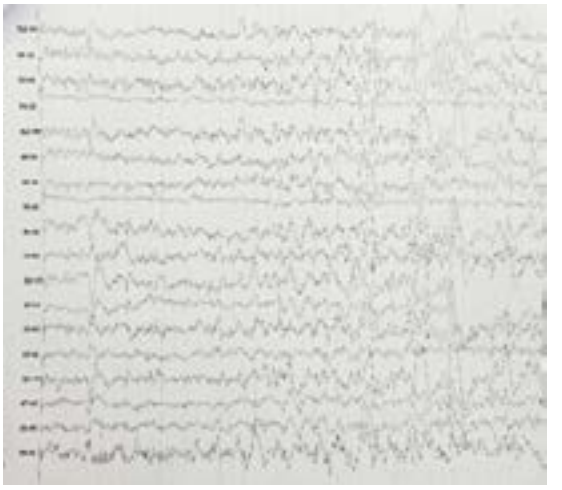
Houge syndrome, also known as Houge type X-linked syndromic mental retardation, is a rare genetic disorder characterized by intellectual disability, developmental delay, distinctive facial features, and other associated abnormalities. It is caused by mutations in the CNKSR2 gene, which is located on the X chromosome [1,2]. This condition is inherited in an X-linked recessive manner, meaning the gene associated with the disorder is located on the X chromosome. It primarily affects males, as they have only one X chromosome, whereas females have two X chromosomes and are often carriers.

The CNKSR2 gene provides instructions for making a protein that is involved in signaling pathways in the brain. Mutations or deletions in this gene can disrupt normal brain development and function, leading to the features associated with Houge syndrome [3,4].The presentation and severity of symptoms can vary widely among affected individuals, even within the same family. Treatment typically focuses on managing symptoms and providing supportive care, such as speech therapy, occupational therapy, and antiepileptic medications to control seizures [5,6]. Symptoms can vary in severity from person to person. Individuals with Houge syndrome typically have some level of intellectual disability, which can range from mild to severe.Distinctive facial features are often present in individuals with Houge syndrome [7,8].. These may include a prominent forehead, wide-set eyes, a broad nasal bridge, and a thin upper lip.

Delayed development is common in individuals with Houge syndrome, affecting milestones such as walking and talking.Some individuals with Houge syndrome may exhibit behavioral problems, such as hyperactivity, impulsivity, or difficulty with social interactions [9,10]. Additional features may include skeletal abnormalities, such as joint hypermobility or abnormalities of the fingers and toes.Some individuals with Houge syndrome may have growth deficiency, resulting in short stature. Delayed speech and language development may be present in individuals with this syndrome [11,12].It's important to note that not all individuals with Houge syndrome will exhibit all of these symptoms, and the severity of symptoms can vary widely [13-15]. Due to its rarity and variable presentation, diagnosis may be challenging and often requires input from specialists in genetics, neurology, and developmental pediatrics. A thorough medical history and physical examination are essential for identifying characteristic features associated with Houge syndrome. These may include distinctive facial features, developmental delays, intellectual disability, skeletal abnormalities, and behavioral issues [16-18]. Genetic testing is crucial for confirming the diagnosis of Houge syndrome. It typically involves molecular genetic testing to identify mutations or alterations in the responsible gene. Houge syndrome is associated with mutations in the NHS gene located on the X chromosome [19-21]. Identification of a pathogenic variant in this gene confirms the diagnosis.Since Houge syndrome is inherited in an X-linked recessive manner, a detailed family history can provide valuable information. It helps identify other affected family members and carriers, assisting in genetic counseling and family planning decisions. Genetic counseling may be recommended for families affected by Houge syndrome to better understand the inheritance pattern and the risk of passing the condition to future generations. Additionally, ongoing research into the underlying genetic mechanisms of the disorder may lead to advancements in diagnosis and treatment in the future [22-24]. We present this case in order to enable a better understanding and improve ability to ordinate adequate treatment in individuals with CNKSR2- related neurodevelopmental disorders and epilepsy. This report aims to help clinicians in diagnosis of this rare microdeletion and further genetic counseling.

CASE DESCRIPTION

We describe a case of a 4-year-old female child born in the 39th week of gestation, from the first regular and orderly controlled pregnancy, she cried immediately after birth and was not blue. Lactation established in a maternity hospital.The baby was delivered spontaneously and her APGAR score was 8/9. Neurological status with stigmata of cerebral palsy, generalized hypotonia of body axis, afebrile, meningeal signs negative. The patient presented seizures with early onset.Neurological examination, cranial magnetic resonance imaging (MRi) and electroencephalography (EEG) were also performed. Her psychomotor development evidently delayed withing the first year of life and further. Neurological examination showed axial hypotonia and underdeveloped expressive speech. Cranial magnetic resonance imaging revealed mild periventricular leukomalacia (PVL) and the EEG recordings showed rare isolated epileptiform discharges. Basic brain activity, the presence of a flattened alpha wave with the appearance of an isolated focus (Fi



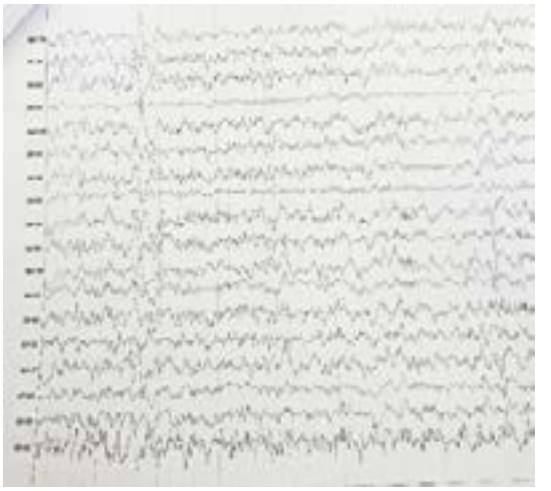


Figure 1,2. EEG demonstrating Basic brain activity, the presence of a flattened alpha wave with the appearance

of an isolated focus

Blood samples were collected for array comparative genomic hybridization (aCGH) analyses from both the parents and the child. Genetic analysis showed the presence of a pathogenic deletion of the xp22.12 chromosomal region. The size of the deletion is about 688 Kb. The CNKSR2 gene and exons 1-11 are included in the deletion. This deletion is inherited from the mother. Pathogenic mutations in the CNKSR2 gene have been described as the cause of X-linked syndromic intellectual developmental disorder, Houge type. This condition is inherited X-linked and in the literature there are data on affected female individuals but with a milder clinical picture than affected male individuals.The child gave favorable therapeutic response to Valproic acid and attends speech and occupational therapy in order to achieve the best possible outcome.

DISCUSSION

In this case report, we identified a microdeletion in the CNKSR2 gene with previously described phenotype, rarely mentioned in literature. Deletions in connector enhancer of kinase suppressor of Ras-2 (CNKSR2) located on the X chromosome (Xp22.12) result in epilepsy phenotype and developmental delay with variable intellectual impairment (Mei D et al. BMC Medical Genetics 2020; 21:69). CNKSR2 gene is highly expressed only in the brain resulting in phenotypic effects restricted to the brain [25-28]. Diagnosis is typically made based on clinical evaluation, including assessment of symptoms and medical history. Genetic testing may be performed to confirm the diagnosis and identify the specific genetic mutation involved. In addition to intellectual disability and developmental delay, individuals with Houge syndrome may have seizures or epilepsy, speech and language difficulties, behavioral problems, and distinctive facial features such as a prominent forehead, wide-spaced eyes, and a broad nasal bridge [29,30]. Given the overlapping features with other genetic syndromes, differential diagnosis is crucial to rule out similar conditions. Conditions such as Coffin-Lowry syndrome, Sotos syndrome, and others may present with intellectual disability and dysmorphic features, requiring careful evaluation to distinguish them from Houge syndrome [31,32]. Additionally, studies focused on the development of targeted therapies or interventions aimed at ameliorating the symptoms and improving outcomes for affected individuals are warranted [33,34]. Collaborative efforts involving clinicians, researchers, and advocacy groups are essential for advancing knowledge and improving the management of this rare genetic disorder [35]. Despite advances in our understanding of the genetic basis and clinical features of Houge syndrome, there are currently no specific targeted treatments for the underlying cause of the disorder. Houge syndrome represents a complex and challenging condition that requires comprehensive care, ongoing support, and continued research to improve outcomes and ultimately enhance the lives of affected individuals and their families.Further research into the molecular mechanisms underlying the syndrome, as well as the development of novel therapeutic interventions, is warranted.

CONCLUSION

Houge syndrome represents a complex and challenging genetic disorder with a wide range of clinical manifestations. Continued research efforts aimed at elucidating its genetic basis, improving diagnostic methods, and exploring potential treatment strategies are essential for advancing our understanding and ultimately improving the lives of affected individuals and their families. If there is suspicion of this condition based on clinical features, consultation with a healthcare professional experienced in genetic disorders is recommended for further evaluation and testing.

REFERENCES

1. Houge G. “Syndromic Mental Retardation due to Mutations in Small GTPase Regulators: Three More Cases and a Review of the Phenotype.” European Journal of Human Genetics, vol. 20, no. 8, 2012, pp. 790–797.
2. Li J, et al. “X-linked Mental Retardation Gene CUL4B Targets Ubiquitylation of H3K4 Methyltransferase Component WDR5 and Regulates Neuronal Gene Expression.” Molecular Cell, vol. 34, no. 3, 2009, pp. 27–33.
3. Kuchenbuch M, et al. “X-linked Intellectual Disability: Characteristics and Molecular Genetics.” Journal of Intellectual Disability Research, vol. 63, no. 8, 2019, pp. 949–960.
4. Field M, et al. “X-linked ID syndromic surveillance study: Results from a 2-year follow-up.” Developmental Medicine & Child Neurology, vol. 54, no. 4, 2012, pp. 396–403.
5. Badura-Stronka M, et al. “A novel nonsense mutation in the NHS gene associated with Nance-Horan syndrome.” Ophthalmic Genetics, vol. 33, no. 2, 2012, pp. 111–116.

6. Lesca G, et al. "Clinical and neurocognitive characterization of a family with a novel MED12 gene frameshift mutation." American Journal of Medical Genetics Part A, vol. 164, no. 11, 2014, pp. 2934–2941.
7. Pichon O, et al. "Dissection of the Nance-Horan syndrome by whole-genome sequencing reveals new insights into its pathogenesis." Genetics in Medicine, vol. 19, no. 6, 2017, pp. 622–628.
8. Neri G, et al. "Expanding the clinical spectrum of the X-linked intellectual disability syndromes." American Journal of Medical Genetics Part A, vol. 170, no. 8, 2016, pp. 1941–1946.
9. Patel S, et al. "Genetic advances in syndromic craniosynostoses." American Journal of Medical Genetics Part A, vol. 176, no. 8, 2018, pp. 1756–1766.
10. Gilissen C, et al. "Genome sequencing identifies major causes of severe intellectual disability." Nature, vol. 511, no. 7509, 2014, pp. 344–347.
11. Al-Dewik N, et al. "Molecular genetics of X-linked intellectual disability syndromes." Journal of Child Neurology, vol. 29, no. 7, 2014, pp. 974–983.
12. Huang L, et al. "The Genetics of Nance-Horan Syndrome: A Review of the Literature." Journal of Ophthalmology, vol. 2017, Article ID 4323746.
13. Tarpey PS, et al. "Mutations in the DLG3 gene cause nonsyndromic X-linked mental retardation." American Journal of Human Genetics, vol. 75, no. 2, 2004, pp. 318–324.
14. Al Chalabi A, et al. "VAMP1 mutation causes dominant hereditary spastic ataxia in Newfoundland families." American Journal of Human Genetics, vol. 57, no. 4, 1995, pp. 767–777.
15. Chiurazzi P, et al. "Recessive loss of function of the neuronal ubiquitin hydrolase UCHL1 leads to early-onset progressive neurodegeneration." Proceedings of the National Academy of Sciences, vol. 115, no. 12, 2018, pp. 3143–3148.
16. Lessel D, et al. "De Novo Missense Mutations in DHX30 Impair Global Translation and Cause a Neurodevelopmental Disorder." American Journal of Human Genetics, vol. 101, no. 4, 2017, pp. 716–724.
17. Jin SC, et al. "Contributions of de novo variants to nonsyndromic neurodevelopmental disorders." Brain, vol. 141, no. 3, 2018, pp. 1–8.
18. Wenger TL, et al. "Genetic causes of syndromic and nonsyndromic autism." Clinical Genetics, vol. 91, no. 2, 2017, pp. 199–210.
19. Stromme P, et al. "X-linked Angelman-like syndrome caused by Slc9a6 knockout in mice exhibits evidence of endosomal-lysosomal dysfunction." Brain, vol. 139, no. 10, 2016, pp. 1–16.
20. Uddin M, et al. "Germline and somatic mutations in STXBP1 with diverse neurodevelopmental phenotypes." Neurology Genetics, vol. 1, no. 1, 2015, pp. 1–7.
21. Koide R, et al. "Molecular pathogenesis of X-linked Nance-Horan syndrome." Ophthalmic Genetics, vol. 41, no. 4, 2020, pp. 1–8.
22. Hu H, et al. "X-exome sequencing of 405 unresolved families identifies seven novel intellectual disability genes." Molecular Psychiatry, vol. 23, no. 1, 2018, pp. 1–11.
23. Richards S, et al. "Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology." Genetics in Medicine, vol. 17, no. 5, 2015, pp. 405–423.
24. Chahrour M, et al. "MeCP2, a key contributor to neurological disease, activates and represses transcription." Science, vol. 320, no. 5880, 2008, pp. 1224–1229.
25. Santos-Cortez RLP, et al. "A novel C-T mutation in the X-linked Nance-Horan syndrome gene (NHS) suggests a role for the NHS protein in transcriptional regulation." Human Genetics, vol. 117, no. 2-3, 2005, pp. 107–113.
26. Kortüm F, et al. "The core FOXG1 syndrome phenotype consists of postnatal microcephaly, severe mental retardation, absent language, dyskinesia, and corpus callosum hypogenesis." Journal of Medical Genetics, vol. 49, no. 6, 2012, pp. 394–406.
27. Ba W, et al. "Epilepsy therapy in clinical development: focus on ezogabine, an activator of KCNQ/K(v)7 channels." Acta Pharmacologica Sinica, vol. 33, no. 9, 2012, pp. 1073–1078.
28. Yuan H, et al. "Expansion of the spectrum of NAA10-related phenotypes: X-linked NAA10-related intellectual disability." American Journal of Medical Genetics Part A, vol. 173, no. 4, 2017, pp. 858–862.
29. Wang T, et al. "An insertion mutation in FAM36A is associated with the Nance-Horan syndrome." Journal of Medical Genetics, vol. 50, no. 12, 2013, pp. 725–729.
30. Hamdan FF, et al. "Mutations in SYNGAP1 in autosomal nonsyndromic mental retardation." New England Journal of Medicine, vol. 360, no. 6, 2009, pp. 599–605.
31. Nguyen L, et al. "Mutations in NRXN1 in a family multiply affected with brain disorders: NRXN1 mutations and

brain disorders." American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, vol. 159B, no. 3, 2012, pp. 354–358.

32. Philippakis AA, et al. "The Matchmaker Exchange: A platform for rare disease gene discovery." Human Mutation, vol. 36, no. 10, 2015, pp. 915–921.
33. Slavotinek AM, et al. "Nance-Horan syndrome: a contiguous gene syndrome involving deletion of the amelogenin gene region at Xp22.13." American Journal of Medical Genetics Part A, vol. 173, no. 6, 2017, pp. 1613–1618.
34. Kalscheuer VM, et al. "Disruption of the serine/threonine kinase 9 gene causes severe X-linked infantile spasms and mental retardation." American Journal of

Case report

ANOMALITE E LINDURA BUZE-QIELLZE

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REZYME

Defektet e lindura buzë-qiellzë, quhen ato të çara ose hapje të buzës, të qiellzës, ose të të dyjave, të cilat vijnë si rezultat i mos bashkimit të strukturave faciale gjatë periudhës intrauterine të jetës së fëmijës[1]. Skiza e buzëve, buzët e lepurit dhe skiza e palatit, janë malformime që lidhen me anomali në zhvillimin e harkut të parë brankial të embrionit[2].

QËLLIMI: defekte të lindura buzë-qiellzë janë një sfidë për mjekun neonatolog pas lindjes së neonatit. Qëllimi i punimit tonë është të paraqesim rastet e izoluara të shfaqjes së kësaj anomalie në spitalin tonë pas një periudhe të gjatë kohore, afërsisht 8 vite.

MATERIALI DHE METODAT: metodë retrospektive, përfshin të dhënat e marrura nga kartelat e lindjes në Repartin e Neonatologjisë pranë Spitalit të Përgjithshëm "Ferid Murad"- Gostivar për vitin 2022. Në vitin 2022 kemi pasur 470 neonat të gjallë, prej të cilëve 236 femra dhe 234 meshkuj.Në dy të porsalindur të seksit mashkull është disgnostifikuar buza e lepurit dhe palatoskiza, pa sindroma tjera shoqëruese. Studimi ynë është bazuar në klinikën e të porsalindurit, konsultimet me ORL dhe specialist maksilofacial të cilët kanë dhënë rekomandimet e tyre të mjekimit.

REZULTATET: Në studimin tonë nga gjithsejt 470 të porsalindur të gjallë, dy të porsalindur kanë qenë me keilopalatoskizë, unilaterale e djathtë, gjinia meshkuj, të lindur në term, eutrofik, Apgar score të mirë.

PËRFUNDIMI: anomalitë e lindura kërkojnë një ndjekje të veçantë menjëherë pas lindjes në repartet neonatologjike. Qasja multidispilinare dhe mjekimi kirurgjikal përbën trajtimin përfundimtar. Është e rëndësishme të bëhet dallimi midis defekteve sindromike dhe atyre të izoluara, pasi kjo ndihmon në menaxhimin klinik dhe kirurgjikal të pacientëve si edhe vlerësimin e riskut familjar përsa i përket shtatzanive të tjera.

FJALËT KYÇE: Neonati; Anomalitë e lindura neonatale; Keilopalatoskiza; Qasja multidisiplinare.

HYRJE

Defektet e lindura buzë-qiellzë, quhen ato të çara ose hapje të buzës, të qiellzës ose të të dyjave, të cilat vijnë si rezultat i mos bashkimit të strukturave faciale gjatë periudhës intrauterine të jetës së fëmijës. Defektet e lindura të buzes dhe qiellzës njihen ndryshe me termin: skiza, klefte, çarje, buzë lepuri, gojë ujku etj[1]. Skizat e buzës dhe të palatumit janë anomalitë kongjenitale më serioze, më të zakonshme që prekin regjionin orofacial. Për shkak të lokalizimit përfshihen në specialitetet dentare[5]. Buza e lepurit dhe palatoskiza janë dy entitete të ndryshme,të cilat janë të lidhura në aspekt embriologjik,funksional dhe gjenetik[11,12].Edhe pse ekzistojnë teori të shumta,mendohet se skiza e buzës ndodh për shkak të hipoplazisë së shtresës mezenkimale,duke rezultuar në dështimin e bashkimit të proceseve mediale të hundës dhe nofullës së sipërme[11].Prindët duhet të marrin informacionin e duhur lidhur me prognozën dhe trajtimin. Mënyra më e saktë e afrimit të prindërve është ajo me shpjegime informuese dhe qetësuese. Ekzistojnë faktorë të shumtë teratogjenë për këtë defekt, të cilët mund të jenë: endogjen-faktorë gjenetikë nga mutacionet e gjeneve dhe

faktorë egzogjen: rrezatimet, metalet e rënda, barnat, hormonale, infeksionet virale, çregullimet ushqimore dhe depresioniβ. Anamneza familjare pozitive për këtë defekt është 12-55 % [1]β. Metodat e vërtetimit të faktorëve të mirëfilltë në të kaluarën kanë qenë më shumë empirike[3]. Çarja mund të jetë vetëm në buzë(cheiloschisis), nofulla e sipërme(gnathoschisis) ose qiellza(palatoschisis), ose mund të kap të gjitha pjesët(cheilognathopalatoschisis)β' β. Incidenca është më shpesh në racën e verdhë, kurse më rrallë te raca e zezëβ.Skiza e buzës me/pa skizë të qiellzës është 1/750 neonat te raca e bardhë, me predominim te meshkujt. Incidenca e çarjes së qiellzës është afërsisht 1/2.500 lindje te raca e bardhë, me e predominim te gjinia femërore. Janë afërsisht 300 sindroma të lidhura me çarjen e buzës dhe qiellzës (Stickler, Apert, Pierre Robin, Treacher-Collins, Van der Woude, DiGeorge etj[1]β. Buza e çarë mund të shoqërohet me anomali të tjera kraniale të fytyrës, ndërsa çarja e qiellzës mund të shoqërohet me anomali të sistemit nervor qendror. Më të shpeshta janë defektet e lindura të anës së majtë të buzës kundrejt anës së djathtëβ'[11'12].Çarjet e qiellzës çojn në çrregullimin e rrenditjes së dhëmbeve, anodonci parciale ose dhëmbë supranumerareβ. Kombinimet mund të jenë të ndryshme, të izoluara, të kombinuara, të njëanshme (më të shpeshta), të dyanshme, të plota dhe jo të plota[11]. Komunikimi i gojës dhe hundës pamundëson krijimin e shtypjes negative në gojë, e nevojshme per thithjeβ. Në keiloskizë nuk vërehet vështirësi në ushqyerjen e fëmijës. Në palatoskizë me inetresim të palatit të fortë, ushqyerja në gji paraqitet e vështirë, kurse ushqyerja me kapsë, lugë, pikatore ose me sondë, duke mbajtur fëmijën në pozicion të përshtatshëm, është e mundshme.Keilopalatoskiza bëhet shkak edhe për çregullime në të folur dhe për infeksion të veshit të mesëm (nga anatomia e muskulaturës së palatumit të butë, të cilat marin fillesën direkt ose afër tubit auditor[2']β. Pacientët me malformime të tilla,paraqesin probleme në të folur, përtypje dhe gëlltitjen e ushqimit si dhe deformime të dukshme të aspektit estetik si edhe të rritjes faciale.Çarjet çojn në vështirësi në të ushqyer (mungon akti i thithjes), del lëngu nga hunda, në të folur veçanërisht në shqiptimin e bashkëtinglloreve grykore G,Kβ. Një diagnozë prenatale me anë të ekografisë është e vështirë që justifikon marrjen e një kariotipi fetal në qoftë se ekzistojnë edhe anomali tjeraβ. Trajtimi i këtyre defekteve të lindura është kirurgjikal nga specialist maksilo-facial. Para se këta fëmijë të futen në operacion zbatohet(rregulli)i 4 dhjetave: (1) mosha-10 javëshe (2, Hb-mbi 10(3), pesha mbi 10 paund (afërsisht 5 kg), (4) Le-nën 10 mijë,për të shmangur praninë e ndonjë infeksioni në organizëmβ'β. Ndërhyrja kirurgjikale e buzës zakonisht kryhet në muajin e tretë të jetës, kur i posalinduri shton në peshë dhe nuk ka infeksione orale, respiratore ose infeksione sistemike.Teknika më e perdorur është teknika e modifikuar e Millard,teknikë me rrotacion;me linjë të suturuar në formë të shkronjës latine Z.Korekcioni i hundës mund të shtyhet deri në adoleshencë.Për arsye se skiza e qiellzës ka variacione në madhësi,formë dhe shkallë deformiteti,momenti kryerjes së intervenimit është individual.Te fëmiu i shëndoshë mbyllja e qiellzës bëhet para se fëmiu të mbush një vit që të mundësohet zhvillimi normal i të folurit.Kujdesi post operator është mjaft i rëndesishëm. Kujdes të madh duhet kushtuar plagës nga infeksionet dhe tensionet ndaj suturave. I posalinduri ushqehet me biberon special, kurse duart fiksohen te bërrylat me përforcues[11'13].Një program i plotë rehabilitimi për femijën me buzë të çarë dhe qiellzë, mund të kërkojë vite trajtim dhe përbëhet nga ekipi multidisiplinar: obstetri, pediatri, kirurgu oral dhe maksilo-facial, ORL, stomatologu, ortodonti, ortopedi, logopedi, audiometristi, gjenetisti, neuropsikiatri, psikologu, punonjës social mjekësor dhe infermier i shëndetit publikβ'[1]β'[11].Numri I specialistëve që nevojiten reflekton numrin dhe kompleksitetin e problemeve me të cilët ballafaqohen individët me skiza orofacialeβ. Trajtimi i këtyre defekteve paraqitet tepër i veçantë pasi duhen zgjidhur disa probleme njëherësh, si p.sh: problemet dentare, psikologjike, të të folurit, të përtypjes, të gëlltitjes, otologjike si dhe ato estetike[1']β.

RASTET TONA

Në repartin e Neonatologjisë pranë Spitalit të Përgjithshëm "Ferid Murad" -Gostivar në vitin 2022 nga gjithsejt 472 lindje,470 neonat të gjallë, dy të vdekur,prej ku dy të porsalindur të gjinisë mashkullore menjëherë pas lindjes me inspeksion kemi vërejtur defektet e lindura buzë-qiellzë. Studimi ynë është bazuar në klinikën e të porsalindurit, konsultimet me ORL dhe specialist maksilo-facial të cilët kanë dhënë rekomandimet e tyre. Kemi bërë përpunimin e të dhënave nga kartelat e lindjes, numrin e të porsalindurve, llojin e defektit, mosha gestacike, pesha e lindjes, gjinia e neonatit si dhe konsultat për ndjekjen e mëtutjeshme nga ekipi multidisiplinar.Rasti i parë: nëna 24 vjeç, fëmija i parë, nuk ka përdorur barna gjatë shtatzanisë, shtatzani spontane, lindje spontane. Pesha e lindjes së neonatit:2950gr, gjatësia:50cm, mosha gestacike 39 javë; lindje cezariane, lëngu amniotik ngjyrë qumështi, placenta pa ndryshime.

Në anamnezën familjare kemi të dhëna për defekte të lindura buzë-qiellzë para dy gjeneratave–nga ana e babait (Foto nr.1).Rasti i dytë: nëna 26 vjeç, fëmija i dytë, gjatë shtatzanisë ka përdorur barna për hipotireozë-Euthyrox dhe vitaminoterapi. Pesha e lindjes- 3200gr, gjatësia:54cm, mosha gestacike 37 javë, lindje spontane, lëngu amniotik ngjyrë qumështi, placenta pa ndryshime. Në historinë familjare nuk kanë pasur defekte të lindura buzë-qiellzë (Foto nr.2).Të dy lindjet janë vlerësuar me anë të Apgar pikësimit mbi 7. Menjëherë pas lindjes është realizuar konsulta me ORL dhe kirurg maksilo-facial të cilët kanë vënë diagnozen–defekt i lindur i buzës dhe qiellzës unilateral i djathtë te të dy rastet. Diferenca kohore midis dy lindjeve ishte afërsisht 2 muaj.Të dy nënat në anamnezë japin të dhëna se kanë kryer kontrole të rregullta gjinekologjike dhe ekografi 3D. Problemi i menjëhershëm te këta të porsalindur ka qenë ushqyerja. Me furnizimin e biberonit special për këto defeke të lindura, infermieret tona kanë bërë monitorimin e veçantë 24 orësh të porsalindurve (Foto nr.3). Qëndrimi disa ditor ka qene pa ndonjë gjë të vecantë, me rekomandim për konsultë me kirurg maksilo-facial pas daljes nga spitali. Në bazë të dhënave të dokumentuara nga prindërit, të dy rastet janë diagnostikuar me Cheilognathopalatoschisis-unilaterale të djathtë.Është realizuar konsult me mjek pediatër pranë Klinikës së Fëmijëve–Shkup, ku janë përjashtuar sindromat shoqëruese tek të dy fëmijët. Në Maqedoninë e Veriut keiloplastika e ashtuquajtur rekonstruim operativ i defektit të lindur të buzës kryhet në muajin e 6 të jetës,nëse fëmija plotëson rregullin e 4 dhjetave.Palatoplastika realizohet në moshën 18 muaj nëse pacienti nuk ka probleme mjekësore dhe si rezultat i të folurit që zhvillohet pas kësaj moshe.Paraprakisht aplikohet pllaka palatine ortodontike pre operatore. Pajisje të disenjuara për ngritjen e palatumit të butë dhe për të obturuar kavitetet orale dhe nazale.Pas konsultave klinike dhe paraklinike,neonati i parë është operuar në moshën 8 mujore;Cheiloplastica sec.Millard-korigjim unilateral I buzës. I është rekomanduar operim I dytë në muajin e 19 të jetës. Ndërkohë me kontrolle të rregullta te mjeku maxilo–facial, duke ndjekur rritjen dhe këshillat, me theks të veçantë ushqyerja dhe masat higjieno-dietetike.Rasti dytë, pas pregaditjes preoperatore dhe konsultave si te rasti i parë, intervenimi është kryer në muajin e 9; Cheiloplastica sec. Stelmach, suturae-korigjim unilateral buzës dhe qiellzës.Me rekomandim që operimi i dytë të kryhet në muajin e 18 të jetës.Akualisht fëmijet gëzojnë shëndet të mirë me perkrahje maksimale nga të dy prindërit.Modifikimi i Millard teknika e rrotullimit–avancimit është teknika më e përdorur. Kirurgjia korrigjuese në hundë mund të shtyhet deri në adoleshencë.Rëndësi të madhe ka kthimi i gjidhënies në normalitet dhe të folurit. Pas operimit duhet kushtuar kujdes higjienës orale.

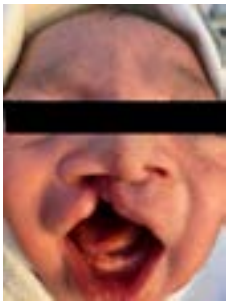

Foto nr.1-defekt unilateral

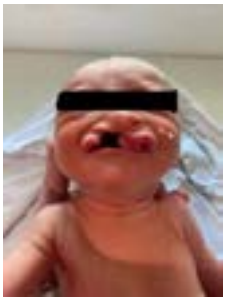

Foto nr.2 – defekt unilateral

Foto nr.3- Biberon

PËRFUNDIMI

skizat oro-faciale shkaktohen nga mekanizma të pashpjeguar plotësisht, si mekanizma gjenetike dhe faktorët e mjedisit.Të dhënat tona tregojnë se te njëri neonat kemi anamnezë familjare për këtë defekt, kurse rasti i dytë nga veprimi teratogjen i barnave. Në mungesë të njohurive të plota të shkaktarëve, për të parandaluar këtë deformim nuk njihen masa parandaluese efikase, përveç atyre prenatale-evitimi i medikamenteve që nuk janë absolutisht të domosdoshme. Suksesi në të folur, i udhëhequr paraprakisht nga intervenimet e sukseshme, mundëson që fëmiu të ndjehet i barabartë në rrethin ku jeton.

REFERENCA

1. Andis Qendro, DEFEKTET E LINDURA BUZE- QIELLZE DHE KORRIGJIMI I PASOJAVE TE TYRE POST OPERATORE,Marrja e grades shkencore DOKTOR,fq.I,II, IX,Tiranë 2020.
2. Prof.Dr. Selaudin Bekteshi PEDIATRIA, Vol.I ,421-2, Tiranë 1974.
3. Акад.Илија Васков, СИНДРОМИ ВО МАКСИЛОФАЦИЈАЛНАТА РЕГИЈА, стр.119, Скопје, 2009.
4. Prof.Asc.R.Isufi,DMD MSc A.Qendro,DMD MSc E.Bardhoshi,Kirurgjia orale dhe maksilofaciale,Vol.II, fq.981,996,Tiranë 2010.
5. Peterson, Ellis, Hupp,Tucker, KIRURGJIA ORALE DHE MAXILO-FACIALE 2 ,Shtëpia botuese U.F.O Press,fq.648,655-2 Tiranë,2006.
6. LAUGIER, F. GOLD; NEONATOLOGIE-MASSON 1991; NEONATOLOGJIA–Perkthyer dhe pershtatur: Eduard Tushe, Tirane.fq.366
7. Grupa na avtori, OTORINOLARINGOLOGIJA, Zagreb 1981; OTORINOLARINGOLOGJIA- Përkthyer: Prof.Dr. T. Pallaska, Prof.Dr.B. Sllamniku, Ass.Dr.R. Ramku, Ass. Dr.H. Jakupi, Ass.Dr.V. Haxhi–Jaha, fq. 245-3, Prishtinë 1983.
8. Dr.D. Savič, Dr.D. Cvejič, Dr.M. Kosanovič- OTORINOLARINGOLOGIJA; Beograd,1986;184-2
9. Željko Bumber,Vladimir Katič,Marija Niksič,Boris Pegan,Vlado Petric,Nikola Šprem I suradnici,OTORINO LARINGOLOGIJA,172-2,Zagreb 2003.
10. 10.C. HENRY KEMPE,HENRY K. SILVER,DONOUGH O' BRIEN;SAVREMENA DIJAGNOSTIKA I LECENJE U PED IJATRIJI;California,1972;Beograd 1974,286-2.
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Case report

SURGICAL TREATMENT OF AN INCARCERATED PESSARY–A SERIES OF TWO CASES

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ABSTRACT

Genital prolapse presents a common concern especially among postmenopausal women, often treated with surgical intervention. However, conservative management with pessaries serves as an alternative for patients averse to surgery or unfit for it. Despite their efficacy and safety profile, rare complications such as pessary incarceration can arise, necessitating surgical removal in severe cases. An incarcerated pessary is the one that has been displaced from its original position and is incorporated into the vaginal mucosa, cervical mucosa or surrounding structures. Regular follow-up and maintenance are crucial to prevent such occurrences. This paper presents two cases of incarcerated pessaries, highlighting the challenges and surgical management of this uncommon complication.

The first case involves a 63-year-old patient presenting with vaginal bleeding secondary to an incarcerated pessary. Surgical removal was performed without damaging surrounding tissue, followed by reapplication of a new pessary. In the second case, a 68-year-old patient exhibited an anterior colpocele and an incarcerated pessary protruding from the vulva and perineum. In both cases,the patients neglected the pessary for a long period of time, resulting in complications requiring surgical intervention.

Incarcerated pessaries pose challenges due to patient age and comorbidities. Preventative measures include proper patient education, maintenance, and estrogen cream application. Neglected pessaries can lead to tissue necrosis and ulcerative changes, underscoring the necessity of timely intervention. Local estrogen cream application aids in inflammation reduction, facilitates pessary removal and helps in epithelization of the vaginal mucosa. Surgical removal as a definitive treatment, is required in rare cases, with techniques tailored to minimize tissue damage and optimize patient outcome. It is done either by excising the surrounding tissue or removing the pessary in parts.

Our paper highlights the significance of regular monitoring and patient compliance in preventing rare complications of conservative genital prolapse management and emphasizes the need for a minimally invasive surgical approach while achieving maximal efficacy in treating incarcerated pessaries.

Key words: genital prolapse, pessary, incarceration

OBJECTIVE

Presentation of a series of two cases of incarcerated pessary as a rare complication in patients treated conservatively for genital prolapse.

INTRODUCTION

Genital prolapse and pelvic floor dysfunctions are relatively common in the female population, especially in the postmenopausal period. Although a common

treatment of these conditions is surgical intervention, as an alternative treatment in patients who refuse surgery or are not suitable candidates for surgical treatment, the application of a pessary (mostly a silicone pessary in the form of a ring) is applied1. The pessary is a safe, effective, inexpensive solution with minimal complications in these patients.2 Prerequisites for minimizing complications are regular visits to the practicing gynecologist, maintenance of the pessary and local application of estrogen creams. Frequent accompanying complaints and findings are vaginal erosions, ulcerations, bleeding, and major and rare complications include an incarcerated pessary, vesico-vaginal and/or recto-vaginal fistulas.2 Severe complications tend to occur in patients who neglect the pessary for an extended period of time after its placement. The pessary requires attention and care from the patient, including periodic removal, cleaning, reapplying, and/or replacement. Routine monitoring in a gynecological clinic is mandatory due to the occurrence of side effects and complications. However, there is no consensus on the optimal monitoring and the frequency of check-ups in literature. Some gynecologists prefer follow-up in 2 weeks, then every 3 months for the first year, and every 6 months thereafter, while others suggest follow-up every 9-12 months until there are no adverse symptoms.3 An incarcerated pessary is the one that has been displaced from its original position and is incorporated into the vaginal mucosa, cervical mucosa or surrounding structures. In this case series, we present an incarcerated pessary as a complication and surgical procedures to resolve it.

PRESENTATION OF THE CASES

The first case refers to a 63-year-old multiparous patient having Hashimoto's thyroiditis as a comorbidity, for which she was not receiving therapy. The patient had a silicone pessary applied several years ago, for the management of subtotal uterine prolapse. She did not attend regular check-ups after the application of the pessary. The patient presented to our clinic with vaginal bleeding as a main concern. Due to the same symptom, diagnostic D&C was previously performed in another hospital, with normal histopathological results. On speculum examination, an incarcerated pessary was visualized in the posterior fornix of the vagina, with a tissue bridge around it and surrounded by local bleeding and decubitus. Laboratory findings were within normal ranges. After the patient underwent pre-operative preparations, the pessary was surgically removed by cutting and removing it, without excision and damage to the surrounding vaginal tissue. (Figure 1, 2, 3). The postoperative course was uneventful. At the post-operative checkup, the local findings were normal with per secundam healing of the changes.

Duplication of the posterior vaginal wall in the posterior fornix was visualized and a new pessary was reapplied.

The second case is a 68-year-old female patient, without comorbidities, who had a silicone pessary applied more than 5 years ago for the management of cystocele. Due to absence of subjective complaints, she did not turn up for follow-up examinations and did not adhere to the instructions for care of the pessary. On speculum examination, an anterior colpocele and a silicone pessary protruding from the vulva was found, with a decubitus wound and bleeding on the left labia majora caused the by pessary that had penetrated the wall of the vulva and the perineum with a depth of at least 2-3 cm. The anterior and posterior walls of the vagina were fused, to the extent that the cervix could not be visualized. The patient underwent pre-operative preparations and laboratory findings were within normal ranges. The pessary was surgically removed by cutting it with a scalpel, was pulled out and removed from the vagina, without intervention on the surrounding tissue. (Picture 4,5,6,7). An opening (defect) of the vaginal wall was observed after the removal of the pessary. A detailed examination of the surrounding structures did not show recto-vaginal or vesico-vaginal fistulas. The postoperative findings were normal, with epithelialized granulations at the site of the vaginal defect and fused anterior and posterior vaginal walls, with no need for additional interventions or pessary reapplication.

DISCUSSION

Incarceration of the pessary in the vaginal and surrounding paravaginal tissue is a rare complication. It is considered that the exact number of such cases is higher than reported.4 To prevent such complications, all patients should be properly advised and trained on pessary maintenance, hygiene, use of local estrogen cream and timed follow-up visits at the gynecologist. However, these patients often belong to an older age group and have comorbidities, and this presents difficulties for outpatient visits and regular follow-up visits after pessary placement. The local application of estrogen creams reduces inflammation, allows easy removal of the embedded pessary and helps in epithelization of the

vaginal mucosa. Surgical removal is required in rare cases, and is the definitive treatment for an incarcerated pessary. It can be achieved by:

- Excision of the surrounding tissue bridges and subsequent reparation.
- Removal of the pessary in parts, without damaging the surrounding tissue.

In our cases, we decided to surgically remove the pessary by cutting it, which was done without accompanying damage to the surrounding tissue. In the first case, due to the formation of a duplication of the vaginal wall at the posterior fornix and persistence of the genital prolapse, it was decided that the patient should continue to be treated conservatively with pessary reapplication. On the contrary, in the second case, post-operatively, a fusion of the anterior and posterior vaginal walls was visualized. Although it is a complication, since the patient was no longer sexually active, it helped prevent genital prolapse with a similar mechanism as in colpocleisis.5

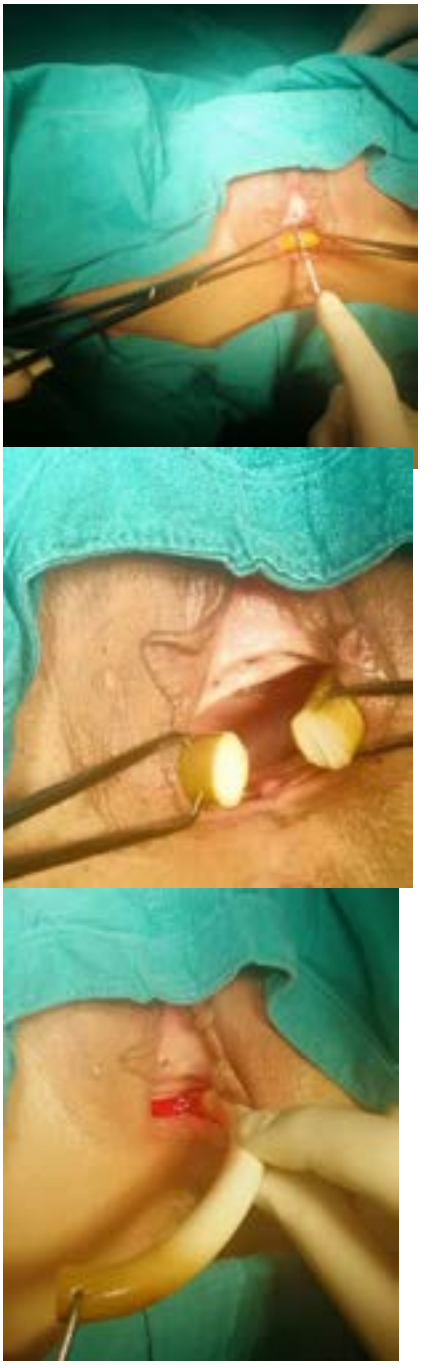
CONCLUSION

Pessary incarceration is a relatively rare occurrence in the conservative treatment of genital prolapse. Usually, the discovery of an incarcerated pessary is either an incidental finding during the examination or the patient presents to the clinic because of vaginal discharge or bleeding. A neglected pessary, due to pressure on the surrounding tissues can cause necrosis and ulcerative changes of the mucosa that heals and overgrows around the pessary leading to impaction and incarceration6. The surgical treatment should be based on the principle of maximally minimal interventions for the prevention of possible complications such as vesico-vaginal or recto-vaginal fistulas whilst achieving maximal efficacy. Regular gynecological follow-ups are required for patients with a vaginal pessary, which would prevent such occurrences.

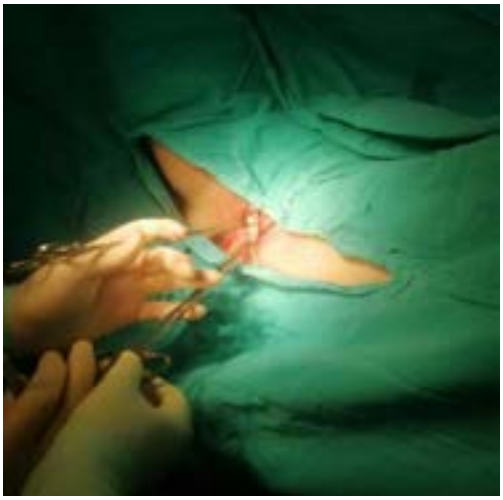
References

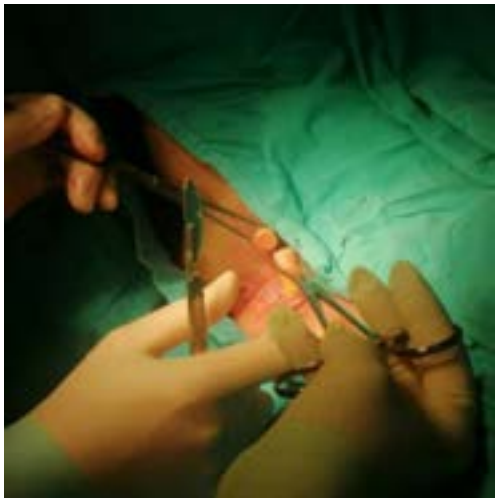
1. Daniyan ABC, Dimejesi IBO, Sunday-Adeoye I, Egwu ND (2017) Incarcerated Vaginal Pessary.
2. So-Jung Liang, Pui-Ki Chow, Szu-Yuan Chou, Chun-Sen Hsu.Incarcerated Vaginal Pessary: A Rare Complication. Taiwanese Journal of Obstetrics and Gynecology,Volume 43,Issue 3.2004
3. Wu V, Farrell SA, Baskett TF, Flowerdew G. A simplified protocol for pessary management. Obstet Gynecol. 1997
4. Foust-Wright CE, Napoe GS, Weinstein MM. (2015). Pessary incarcerated in the bladder: A case presentation of vaginal pessary morcellation.
5. O'Leary, A.J., Vyas, S.K. Le Fort's partial colpocleisis: a review of one surgeon's experience. Gynecol Surg 1, 15–19 (2004).
6. Patel A, Singh S, Mahapatra M.Incarcerated Vaginal Pessary.JCR 2019;9:92-94

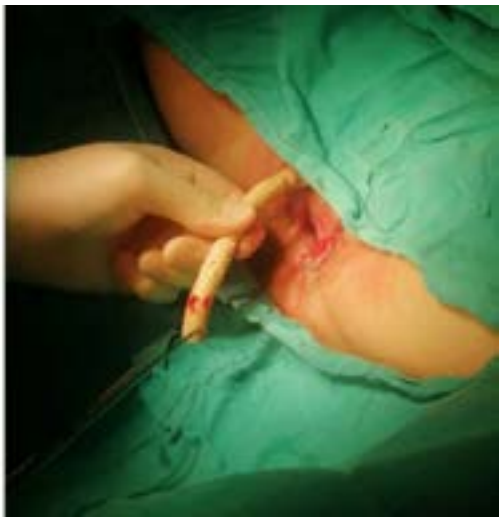
PICTURES

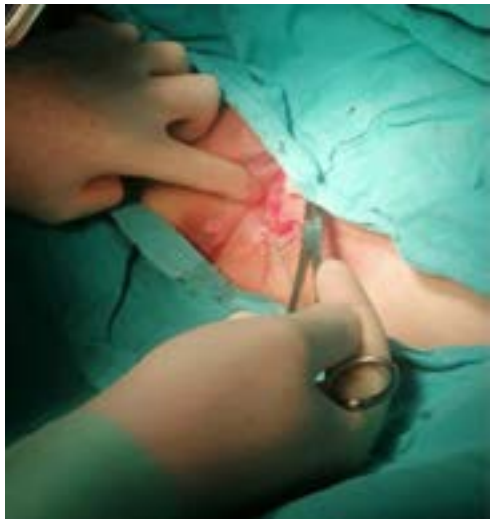


Picture 1,2,3









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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.

Dorëshkrimi i dërguar tek botuesi duhet të shënohet nga autorët , nëse janë në seksionin e "punimeve origjinale shkencore" apo në pjeset tjera përmbajtesore të revistës.

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

Additional Information for Authors

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 vrojtimit gjatë realizimit të studimeve të verbuara. Definoni termet statistikore, 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 përmbledhni 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 probabilitetit (p) dhe të tregoni se është shprehës (sinjifikant 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

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

Interval – 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 mendon 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 afërt 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).
6. Kamberi A, Kondili A, Goda A, dhe bp; *Udhërrëfyes i shkurtër i Shoqatës Shqiptare të Kardiologjisë për parandalimin e Sëmundjes Aterosklerotike Kardiovaskulare në praktikën klinike*, Tiranë, 2006
7. Azemi M, Shala M, dhe bp. *Pediatria sociale dhe mbrojtja shëndetësore e fëmijëve dhe nënave*. Pediatria, Prishtinë 2010; 9-25

Shmangni përdorimin e abstrakteve si referenca; "të dhëna të papublikuara" 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 bërjen 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).

Journal articles:

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.

Books and other monographs:

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).
6. Osler AG. *Complement: mechanisms and functions*. Englewood Cliffs: Prentice-Hall, 1976.

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.

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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).