MEDICUS

ISSN 1409-6366 UDC 61 Vol · 29 (2) · 2024

Original scientific paper

Profesional paper

Review

Case report

Medical Journal

MEDICUS

ISSN 1409-6366 UDC 61 Vol · 29 (2) · 2024

Original scientific paper

Profesional paper

Review

Case report

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

Medical Journal

MEDICUS

ISSN 1409-6366 UDC 61 Vol · 29 (2) · 2024

Revistë Shkencore Nderkombëtare e Shoqatës së Mjekëve Shqiptarë të Maqedonisë
International Journal of Medical Sciences of the Association of the Albanian Doctors from Macedonia

Botues/ Publisher: **SHMSHM / AAMD**
Tel. i Kryeredaktorit / Contact: **+389 (0) 71 240 927**
Zhiro llogaria / drawing account: **200-000031528193**
Numri tatimor / tax number: **4028999123208**
Adresa e Redaksisë-Editorial Board Address: **Mehmed Pashë Deralla nr. 16, Tetovë**
e-mail: **shmshm@live.com**

Shtypur në
Shtypshkronjen "Pruf Print", Shkup
Medicus shtypet në tirazh: 600 ekzemplarë
Revista shperndahet falas

Printed in:
Print House "Pruf Print", Skopje
The Jounal Medicus is printed and distributed free of charge with a circulation of 600 copies.

Original scientific paper

PHI AND MR SPECTROSCOPY AS GUIDELINES TO EARLY DIAGNOSIS AND TREATMENT OF CA PROSTATE IN PATIENTS IN THE GRAY ZONE OF PSA – OUR EXPERIENCES

Minev I[1,2], Ivcev J[1,2], Izairi A[1,2], Markovski D[1,3]

[1]City General Hospital 8th of September Skopje, Republic of North Macedonia
[2]Faculty of Medical Sciences, University Goce Delcev Stip
[3]Medical Faculty , Saint Cyril and Methodius University, Skopje

Medicus 2024, Vol. 29 (2): 117-122

INTRODUCTION

Prostate cancer (CAP) is the most commonly diagnosed type of cancer in men and the second leading cause of cancer death in the world after lung cancer (1). Progress in CAP diagnosis can, in part, be attributed to the discovery of the Prostate Specific Antigen (PSA) in the 1970s. In the 1980s, PSA was primarily approved by the FDA to track patients diagnosed with CAP, and later was approved for CAP diagnostics and introduced as a screening tool for prostate cancer.This wide use of PSAled to a dramatic increase in incidence rates and prostate cancer diagnosis.Today, the prostate cancer mortality rate is approximately 45% lower than in 1992.(2). PSA has low sensitivity and low specificity for CAP. Increased PSA may not be an indicator of clinically significant cancer. The most common cause of a small increase in PSA is Benign Prostate Hyperplasia (BPH). BPH's incidence increases with age. Approximately 25% of 40-year-old men and 80% of 80-year-old men are estimated to have BPH.(3)(4). Differential diagnosis between malignant and benign disease is particularly challenging when considering that the total range of PSA is from 2ng/mL to 10 ng/mL, where there is a significant overlap between patients with benign and malignant conditions. The low specificity of PSA led to excessive diagnosis of indolent disease and excessive treatment, resulting in high costs for treating patients with elevated PSA.

MATERIAL AND METHODS:The study involved 49 patients (observed group) who had TRUS prostate biopsy, based on previousPHI (Prostatic Health Index) and multiparameter MR spectroscopy studies. In patients, an analysis of PathoHistological Postbioptic finding (PHP) from TRUS biopsy (transrectal ultrasound guided biopsy of the prostate) was performed and they were statistically processed and shown through:percentage representation, middle value, table and graphic view of parameters. In the second group of 45 patients (control group) TRUS biopsy was performed only on the basis of PSA findings, physical-digitorectal examination (DRP) and ultrasound examination. The study was conducted for a period of 2 years in patients followed by the Urological department at the City General Hospital 8th of September-Skopje.

GOAL: Determining the degree of specificity of PHI and multiparameter MR spectroscopy in early CAP diagnostics in the observed group, Analysis of postbioptic pathohistological finding according to the Glison classification in the observed group(6), Determination of the correlation of PHI and multiparameter MR spectroscopy with PathoHistological Postbioptic results, Determining the criteria for the use of PHI and multiparameter MR spectroscopy when setting an indication of TRUS biopsy according to the study analysis.

RESULTS: Of the 49 patients in the observed group with PSA valuesbetween 3.11 ngr/ml to 10.99 ngr/ml, in 63% pf the patients the PHI was with value 55+, the multiparameter MR spectroscopy was valued PIRADS 4 and 5 in 38% of patients, and TRUS biopsy had value for BPH in 61% of patients and CAP in 39% of biopsies. In the control group of a total of 45 patients with PSA values between 3.5 ngr/ml to 11.02 ngr/ml and a positive digitorectal examination, in 62% of patients the findings of TRUS prostate biopsy were as follows: BPH in 64% of patients and CAP in 36% of biopsies.

CONCLUSION: Based on the above mentioned results, we can conclude that prebioptic examination gives

better prognostics and refers us to a better treatment of the patients. Patients with negative PHI findings and multiparameter MR spectroscopy do not need to be biopsied immediately, but activlymonitored (multiparameter MR spectroscopy once a year) and just in case of a positive finding the next step is to do a prostate biopsy. These kind of diagnosed patients have a higher degree of positive diagnosis, meaning a positive PHP prostate cancer result. Using PHI and multiparameter MR spectroscopy reduces the percentage of overtreated patients, thereby reducing the cost of hospital days and the cost for TRUS prostate biopsy. With reducing the number of unnecessarily biopsyed patients there is also a reduction in the percentage of postbioptic complications in patients.

Keywords: Prostate cancer, TRUS prostate biopsy, BPH, PHI, multiparameter MR spectroscopy, PSA, PHP

INTRODUCTION

Prostate cancer (CAP) is the most commonly diagnosed type of cancer in men and the second leading cause of cancer death in the world after lung cancer (1).

Progress in CAP diagnosis can, in part, be attributed to the discovery of the Prostate Specific Antigen (PSA) in the 1970s. In the 1980s, PSA was primarily approved by the FDA to track patients diagnosed with CAP, and later was approved for CAP diagnostics and introduced as a screening tool for prostate cancer. This wide use of PSA led to a dramatic increase in incidence rates and prostate cancer diagnosis.Today, the prostate cancer mortality rate is approximately 45% lower than in 1992. (2).

PSA has low sensitivity and low specificity for CAP. Increased PSA may not be an indicator of clinically significant cancer. The most common cause of a small increase in PSA is Benign Prostate Hyperplasia (BPH). BPH's incidence increases with age. Approximately 25% of 40-year-old men and 80% of 80-year-old men are estimated to have BPH.(3)(4).

Differential diagnosis between malignant and benign disease is particularly challenging when considering that the total range of PSA is from 2 ng/mL to 10 ng/mL, where there is a significant overlap between patients with benign and malignant conditions. The low specificity of PSA led to excessive diagnosis of indolent disease and excessive treatment, resulting in high costs for treating patients with elevated PSA.

MATERIAL AND METHODS

The study involved 49 patients (observed group) who had TRUS prostate biopsy, based on previous PHI (Prostatic Health Index) and multiparameter MR spectroscopy studies. In patients, an analysis of PathoHistological Postbioptic finding (PHP) from TRUS biopsy (TransRectal UltraSonographic water biopsy of the prostate) was performed and they were statistically processed and shown through: percentage representation, middle value, table and graphic view of parameters. In the second group of 45 patients (control group) TRUS biopsy was performed only on the basis of PSA findings, physical-digitorectal examination (DRP) and ultrasound examination.

The study was conducted for a period of 2 years in patients followed by the Urological department at the City General Hospital 8th of September-Skopje.

GOAL

-Determining the degree of specificity of PHI and multiparameter MR spectroscopy in early CAP diagnostics in the observed group,

-Analysis of postbioptic pathohistological finding according to the Glison classification in the observed group (6),

-Determination of the correlation of PHI and multiparameter MR spectroscopy with PathoHistological Postbioptic results,

-Determining the criteria for the use of PHI and multiparameter MR spectroscopy when setting an indication of TRUS biopsy according to the study analysis.

RESULTS

Of the 49 patients in the observed group with PSA values between 3.11 ngr/ml to 10.99 ngr/ml, in 63% pf the patients the PHI was with value 55+, the multiparameter MR spectroscopy was valued PIRADS 4 and 5 in 38% of patients, and TRUS biopsy had value for BPH in 61% of patients and CAP in 39% of biopsies.

In the control group of a total of 45 patients with PSA values between 3.5 ngr/ml to 11.02 ngr/ml and a positive digitorectal examination, in 62% of patients the findings of TRUS prostate biopsy were as follows: BPH in 64% of patients and CAP in 36% of biopsies.

DISCUSSION

ProstateHealthIndex

PSA can be found in the serum as different isoforms. Total PSA immune analyses reveal PSA bound to Alpha 1-antichymotrypsin, as well as the free form of PSA. Within the free fractions of PSA (fPSA), there are several isoforms, including PSA's predecessor.

-7 proPSA represents PSA's natural predecessor while -4 and -2 proPSA are abbreviated forms of -7 proPSA.In prostate cancer, there are elevated concentrations of -2 proPSA.

PSA isoforms in prostate cancer

Patients with prostate cancer have a lower %-free PSA (%fPSA) compared to patients with benign conditions. For example, when %fPSA is less than 10%, the probability of cancer is about 56%; while when %fPSA values are greater than 25% the probability of cancer is about 8%. %fPSA is used to improve sensitivity and specificity in patients with PSA between 4–10 ng/mL.

As mentioned above, the free isoform of PSA that has been shown to be increased in prostate cancer is p2PSA. P2PSA has been shown to have a higher specificity than the total and the free PSA in detecting prostate cancer. Even more so, the higher the p2PSA level, the higher the likelihood of finding high-level prostate cancer, as defined by the Gleason score equal to or higher then 7.

- The Prostate Health Index (PHI) is a blood test that includes the free PSA, total PSA and [-2] proPSA isoform of free PSA. The formula combines these test results mathematically to give the PHI result. This PHI result appears to be superior to PSA, free and total PSA and PCA3 in predicting the presence of prostate cancer.

- The Prostate Health Index (PHI) has 75% diagnostic accuracy.

- PHI is determined by a mathematical formula that uses 3 forms of PSA: totalPSA, freePSA and the isoform p2PSA. The result is expressed as a percentage:

(p2PSA / free PSA) x

In clinical practice, PHI can be used to fill the diagnostic gap between PSA screening and prostate biopsy. Combined with the patient's personal and family history, PHI can be used to create an individualized patient treatment plan. If the urologistconcludes- based on PHI and other risk factors-that there is a low likelihood of finding prostate cancer with a biopsy, the patient can be closely monitored instead od undergoing an biopsy. On the other hand, if the urologist finds that the probability for cancer is higher, then the patient is likely to undergo a prostate biopsy.

Multiparameter MR spectroscopy

Lately the Prostate MRI is becoming a standard tool in diagnosing prostate cancer. It can identify and evaluate the stage and localization of suspicious prostate nodes,it can check for extracapsular extension, it can assess seed vesicles and determine an increase in regional lymph nodes that may indicate early metastatic disease.

The combined application of morphological pre-contrast and post-contrast MR imaging and MR spectroscopy is shown as a very applicable method in the initial detection of prostate cancer, allowing preliminary acquisition of useful information in order to optimize and individualize therapeutic protocol in patients with prostate cancer.

While Magnetic Resonance Imaging (MRI) monitors anatomy,Multiparameter MR spectroscopy (MRSI) allows the evaluation of the metabolism of the tumor by determining the value of various metabolites within the tested frame of prostate tissue in vivo, primarily Citrate (Ci), Choline (Cho) and Creatine (Cr).

More specifically, Proton MRSI shows the metabolic profile of tissues. In the case of prostate cancer, three metabolites are of the utmost interest: Citrate, Choline and Creatine. Citrate is found in abundance in normal prostate tissue, but decreases in Ca of the prostate. Choline is a component of the phospholipid membrane of prostate cells and increases in Ca due to rapid multiplication of cells associated with neoplastic proliferation. Creatine is also normally present, but it remains unchanged in the presence of Ca and serves as an internal reference. The relative concentrations of these metabolites are quantified using the ratio of Choline + Creatinine/Citrate and Choline/Citrate.

Results

The tables below are showing patient results based on the following parameters:

Age (year of birth);

Result of PSA;

Result of PHI;

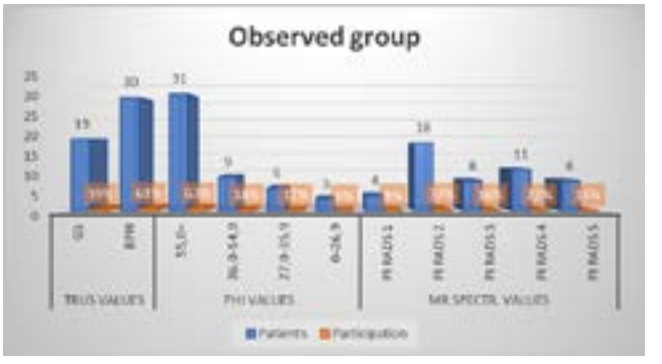
MR spectroscopy result;

Result of TRUS prostate biopsy.

Observed group

No.	Year of birth	PSA	PHI	Mrspectr	TRUS
1	1949	10,82	37,48	Pirads 3	BPH, Pros.chr
2	1950	7.3	44.71	Pirads 3	BPH, Pros.chr
3	1957	6.27	55.0+	Pirads 5	GS 4+4
4	1958	6.06	55.0+	Pirads 2	GS 3+3
5	1939	37.29	55.0+	Pirads 4	GS 4+3
6	1951	6.94	55.0+	Pirads 5	GS 3+3
7	1950	6.65	55.0+	Pirads 5	GS 3+3
8	1957	6.86	55.0+	Pirads 3	BPH, Pros.chr
9	1936	9.21	55.0+	Pirads 5	Gs 4+4
10	1942	10.99	55.0+	Pirads 5	GS 3+3
11	1946	6.16	17.42	Pirads 1	BPH, Pros.chr
12	1947	9.28	55.0+	Pirads 4	GS 3+4
13	1948	8.53	46.55	Pirads 5	GS 3+4
14	1956	7.59	43.60	Pirads 2	BPH, Pros.chr
15	1963	5.21	55.0+	Pirads 5	GS 3+3
16	1947	8.73	32.81	Pirads 1	BPH, Pros.chr
17	1951	6.08	34.85	Pirads 2	BPH, Pros.chr
18	1947	5.80	55.0+	Pirads 2	BPH, Pros.chr
19	1953	4.97	55.0+	Pirads 4	GS 3+4
20	1960	7.01	25.64	Pirads 1	BPH, Pros.chr
21	1946	6.81	55.0+	Pirads 3	BPH
22	1946	9.91	55.0+	Pirads 4	GS 3+4
23	1959	5.91	54.14	Pirads 2	BPH, Pros.chr
24	1949	10,82	37.48	Pirads 3	BPH, Pros.chr
25	1951	9.08	34.79	Pirads 2	BPH, Pros.chr
26	1942	8.33	55.0+	Pirads 4	GS 3+3
27	1949	3.42	22.59	Pirads 2	BPH, Pros.chr
28	1951	3.11	31.09	Pirads 2	BPH, Pros.chr
29	1943	4.7	42.09	Pirads 2	BPH, Pros.chr
30	1956	7.6	34.48	Pirads 2	BPH
31	1958	9.34	55.0+	Pirads 5	GS 4+4
32	1959	8.95	55.0+	Pirads 2	BPH, Pros.chr
33	1969	10,00	55.0+	Pirads 2	BPH, Pros.chr
34	1947	5,55	29,86	Pirads 2	BPH, Pros.chr
35	1949	7,84	55+	Pirads 1	BPH
36	1951	9,32	37,39	Pirads 2	BPH
37	1959	7,72	55.0+	Pirads 4	GS 3+3
38	1956	9,61	55.0+	Pirads 3	BPH,prost.chr
39	1955	8.45	55.0+	Pirads 4	GS 3+3
40	1956	9.68	49.25	Pirads 2	BPH, Pros.chr
41	1946	5.26	55.0+	Pirads 4	BPH,prost.chr
42	1950	5.33	55.0+	Pirads 2	BPH
43	1969	8.16	55.0+	Pirads 2	BPH
44	1954	6.20	55.0+	Pirads 2	BPH
45	1965	10.7	55.0+	Pirads 3	GS 3+3
46	1942	7.10	55.0+	Pirads 4	GS 3+4
47	1955	9.00	55.0+	Pirads 4	BPH ASAP
48	1963	8.93	55.0+	Pirads 3	BPH,prost.chr
49	1957	8.54	55.0+	Pirads 4	GS 3+3

PHI values			Mr Spectroscopy values			TRUS Biopsies values		
	Бр.пац	%		Бр.пац	%		Бр.пац	%
55,0+	31	63%	PI RADS 1	4	8%	CaP	19	39%
36,0-54,9	9	18%	PI RADS 2	18	37%	BPH	30	61%
27,0-35,9	6	12%	PI RADS 3	8	16%	total	49	100%
0-26,9	3	6%	PI RADS 4	11	22%			
total	49	100%	PI RADS 5	8	16%			
			total	49	100%			

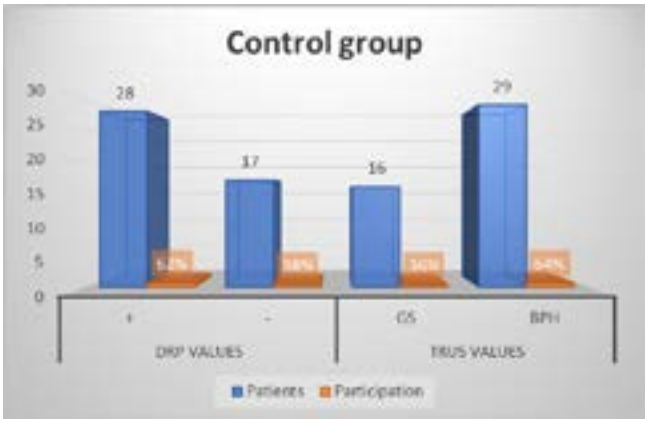


Control group

No	Year of birth	PSA	DRP	TRUS
1	1965	6.65	+	BPH.prost chr
2	1950	9.63	-	GS 3+3
3	1955	7.4	+	GS 3+4
4	1948	8.6	+	BPH
5	1954	9.56	+	GS 3+4
6	1966	6.26	-	BPH.prost chr
7	1956	10.9	+	GS 3+4
8	1951	5.42	+	BPH
9	1964	10.5	+	BPH
10	1964	9.01	+	BPH.prost chr
11	1958	6.6	-	BPH.prost chr
12	1950	9.9	+	GS 3+4
13	1956	8.6	-	BPH.prost chr
14	1948	9.4	+	BPH.ASAP
15	1957	7.2	-	BPH.ASAP
16	1947	9.8	-	GS 3+3
17	1948	8.3	+	BPH.prost chr

18	1952	7.5	+	BPH.prost chr
19	1957	7.2	+	BPH.ASAP
20	1964	9.9	+	BPH.Pros.chr
21	1954	8.9	-	CaP. 3+4
22	1945	10.2	+	CaP. 3+4
23	1956	8.9	+	CaP. 3+4
24	1963	7.6	+	BPH
25	1953	7.03	-	CaP. 3+4
26	1965	6.8	+	BPH.Pros.chr
27	1955	3.83	-	BPH
28	1948	8.7	+	CaP. 3+4
29	1954	10.00	+	BPH.ASAP
30	1949	7	-	BPH.Pros.chr
31	1948	9.32	-	BPH.Pros.chr
32	1947	6.7	+	CaP. 3+4
33	1951	5.47	-	BPH.Pros.chr
34	1957	6.35	-	BPH.Pros.chr
35	1957	9.12	+	CaP. 3+3
36	1951	10.7	+	GS 3+4
37	1954	7.6	-	BPH
38	1951	7.16	+	ASAP.BPH
39	1950	11.02	-	BPH.Pros.chr
40	1960	6.7	-	BPH.Pros.chr
41	1946	3.5	+	BPH
42	1944	10	-	GS 3+3
43	1946	6.4	+	GS 3+4
44	1950	7.34	+	BPH
45	1964	8.2	+	BPH.Pros.chr

DRP values			TRUS values		
	Number of patients	% participation		Number of patients	% participation
+	28	62%	CaP	16	36%
-	17	38%	BPH	29	64%
total	45	100%	total	45	100%



CONCLUSION

- Based on the above mentioned results, we can conclude that prebioptic examination gives better prognostics and refers us to a better treatment of the patients.

- Patients with negative PHI findings and multiparameter MR spectroscopy do not need to be biopsied immediately, but activlymonitored (multiparameter MR spectroscopy once a year) and just in case of a positive finding the next step is to do a prostate biopsy.

- These kind of diagnosed patients have a higher degree of positive diagnosis, meaning a positive PHP prostate cancer result.

- Using PHI and multiparameter MR spectroscopy reduces the percentage of overtreated patients, thereby reducing the cost of hospital days and the cost for TRUS prostate biopsy.

-With reducing the number of unnecessarily biopsyed patients there is also a reducing in the percentage of postbioptic complications in patients.

Keywords: Prostate cancer, TRUS prostate biopsy, BPH, PHI, multiparameter MR spectroscopy, PSA, PHP

LITERATURE

1. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer statistics. CA Cancer J. Clin. 2022, 72, 7–33. [CrossRef] [PubMed]
2. DeSantis, C.E.; Mph, K.D.M.; Sauer, A.G.; Jemal, A.; Siegel, R.L. Cancer statistics for African Americans, 2019. CA Cancer J. Clin. 2019, 69, 211–233. [CrossRef] [PubMed]
3. Andriole, G.L.; Crawford, E.D.; Grubb, R.L., 3rd; Buys, S.S.; Chia, D.; Church, T.R.; Fouad, M.N.; Gelmann, E.P.; Kvale, P.A.; Reding, D.J.; et al. Mortality Results from a Randomized Prostate-Cancer Screening Trial. N. Engl. J. Med. 2009, 360, 1310– 1319. [CrossRef] [PubMed]
4. Schröder, F.H.; Hugosson, J.; Roobol,M.J.; Tammela, T.L.J.; Ciatto, S.; Nelen, V.; Kwiatkowski,M.; Lujan,M.; Lilja, H.; Zappa,M.; et al. Prostate-Cancer Mortality at 11 Years of Follow-up. N. Engl. J. Med. 2012, 366, 981–990. [CrossRef] [PubMed]
5. Negoita, S.; Feuer, E.J.; Mariotto, A.; Cronin, K.A.; Petkov, V.I.; Ms, S.K.H.; Benard, V.; Henley, S.J.; Anderson, R.N.; Fedewa, et al. Annual Report to the Nation on the Status of Cancer, part II: Recent changes in prostate cancer trends and diseasecharacteristics. Cancer 2018, 124, 2801–2814. [CrossRef]

6. Gordetsky J, Epstein J. Grading of prostatic adenocarcinoma: current state and prognostic implications. Diagn Pathol. 2016 Mar 09;11:25. [PMC free article] [PubMed]
7. Stacy Loeb and William J. Catalona The Prostate Health Index: a new test for the detection of prostate cancer. https://doi.org/10.1177/1756287213513488
8. Sangeet Ghai and Masoom A. Haider1Multiparametric-MRI in diagnosis of prostate cancer. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4495493/
9. Ferro, M.; Crocetto, F.;Bruzzese, D.; Imbriaco, M.; Fusco, F.;Longo, N.; Napolitano, L.; La Civita,E.; Cennamo, M.; Liotti, A.; et al.Prostate Health Index and Multiparametric MRI: Partners in Crime Fighting Overdiagnosis and Overtreatment in Prostate Cancer. Cancers 2021, 13, 4723. https://doi.org/10.3390/cancers13184723
10. Po-Fan Hsieh Tzung-Ruei Li,Wei-Ching Lin, Han Chang, Chi-Ping Huang, Chao-Hsiang Chang, Chi-Rei Yang, Chin-Chung Yeh, Wen-Chin Huang and Hsi-Chin Wu-corresponding author Combining prostate health index and multiparametric magnetic resonance imaging in estimating the histological diameter of prostate cancer. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8606059/
11. Yuanchong Chen , Dong Xu , Mingjian Ruan , Haixia Li , Guiting Lin , Gang Song A prospective study of the prostate health index density and multiparametric magnetic resonance imaging in diagnosing clinically significant prostate cancer. https://pubmed.ncbi.nlm.nih.gov/37417561/

Original scientific paper

INVESTIGATING THE RELATIONSHIP BETWEEN ASPIRIN RESISTANCE AND CLINICAL SEVERITY IN ACUTE ISCHEMIC STROKE PATIENTS

Elena Lichkova[1,2], Valentina Velkoska Nakova[1,2], Anita Arsovska[3], Meri Shorova[2,4]

[1]Clinical Hospital, Stip, R.N.Macedonia

[2]Faculty of Medical Sciences, Goce Delcev University, Stip, R.N.Macedonia

[3]University Clinic of Neurology, University "Ss. Cyril and Methodius"-Faculty of Medicine, Skopje, R.N.Macedonia

[4]Institue for transfusion medicine Skopje- Center for transfusione medicine-Shtip

Corresponding Author: Elena Lichkova, Clinical Hospital Shtip, Department of Neurology, University Goce Delchev Shtip, Faculty of Medical Sciences.
adress: Ljuben Ivanov, Shtip
e-mail: eedrovska@yahoo.com
mob: 078394260

Medicus 2024, Vol. 29 (2): 123-127

ABSTRACT

Objective: Ischemic stroke outcomes are influenced by initial severity. We aimed to explore the relationship between aspirin resistance (AR) and stroke severity. Introduction: Stroke severity significantly affects clinical outcomes. Established tools like NIHSS and MRS assess severity, yet the link between aspirin resistance and these measures remains uncertain.

Material and Methods: We enrolled 100 acute ischemic stroke patients, assessing severity with NIHSS and MRS and aspirin resistance using the Innovance PFA 200 system. Statistical analyses employed SPSS 20.0.

Results: Of 100 patients (mean age 61 years, 55% male), 32% showed aspirin resistance. While NIHSS and MRS correlated with certain clinical parameters, no significant correlation was found between aspirin resistance and stroke severity.

Discussion: Despite expectations, no significant link emerged between aspirin resistance and stroke severity measured by NIHSS/MRS. Other factors may outweigh aspirin responsiveness in influencing stroke severity. The positive correlation between age and aspirin resistance merits further exploration for treatment implications in older stroke patients. Conclusion: Aspirin resistance was prevalent among acute stroke patients but didn't impact stroke severity as measured by NIHSS and MRS. This underscores the need for personalized stroke management approaches.

Keywords: Aspirin resistance, Stroke, NIHSS Scale, MRS scale,

Introduction

Ischemic stroke ranks as a major global cause of morbidity and mortality, and the initial severity of the stroke significantly impacts clinical outcomes. Although aspirin is a cornerstone in the prevention and management of stroke, the impact of aspirin resistance on the severity of strokes is still unclear. This study aims to investigate this gap in understanding, as the severity of the initial presentation of ischemic stroke significantly impacts patients' outcomes. The National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS)

are essential instruments for assessing stroke severity, offering a standardized method for clinical evaluation. Despite their significance, the connection between aspirin resistance and these clinical metrics remains ambiguous. By closely examining data from one hundred consecutive acute ischemic stroke patients, this study aims to show the complex interplay between aspirin resistance and stroke severity. By using strong methodologies, including the assessment of aspirin resistance via the Innovance PFA 200 system and statistical analyses using SPSS 20.0, this research aims to show the various determinants of stroke outcomes. Additionally, we're underlining the importance of customizing treatment to fit each patient's unique requirements, especially when it comes to choosing the right type and dose of antiplatelet medication.

MATERIAL AND METHODS

One hundred consecutive patients presenting with acute ischemic stroke were enrolled in the study. Inclusion criteria included at least 30 days of prior aspirin therapy, (acetylsalicylic acid, 100 mg daily) before stroke onset, evidence of ischemic infarct on computed tomography (CT) or magnetic resonance imaging (MRI), and age over 18 years. Exclusion criteria comprised evidence of haemorrhage on imaging or platelet function disorders, and concurrent use of additional antiplatelet, anticoagulant, or nonsteroidal anti-inflammatory medications. Clinical stroke severity was assessed upon admission using NIHSS and MRS scales, while aspirin resistance was determined via the Innovance PFA 200 system. One hundred consecutive patients presenting with acute ischemic stroke were enrolled in the study, visiting the neurology department. Upon admission, clinical stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS) by trained personnel blinded to the diagnosis of aspirin resistance. Additionally, all patients underwent clinical examination, blood sampling, and CT or MRI within the first 48 hours. Subsequently, aspirin resistance was determined using the Innovance PFA 200 system.

The Innovance PFA 200 system enabled a rapid assessment of ASA-induced platelet dysfunction. Blood samples were collected immediately before regular daily ASA intake, and platelet clot formation was measured in 800 microliters of citrated whole venous blood using disposable cartridges. Collagen/epinephrine cassettes, employed in the evaluation, are capable of detecting qualitative platelet defects, including ASA-induced platelet dysfunction. Closure time, the time required for platelet plug formation, was utilized as a parameter to assess platelet function. Normal closure time values in our laboratory ranged from 80 to 150 seconds, with ASA resistance defined as closure time <150 seconds despite regular ASA intake.

Statistical analyses, including Pearson correlation and ANOVA tests, were performed using SPSS 20.0 to explore the relationship between aspirin resistance and stroke severity, as well as the impact of various clinical and demographic factors on stroke severity categories. Results are presented as mean ± SD and percentages. By using the Kruskal–Wallis test, the normal distribution of the variables was proven. T-test for quantitative, x2 test for qualitative variables, and Pearson correlation. $P<0.005$ was considered statistically significant.

Description of Assessment Scales: The National Institutes of Health Stroke Scale (NIHSS) is an essential standardized tool for gauging the severity of stroke symptoms. It evaluates various neurological functions, including consciousness, language, and motor skills, and assigns scores from 0 to 42 to reflect the level of impairment. Primarily utilized during the acute phase of stroke, the NIHSS helps guide decisions regarding treatments such as eligibility for thrombolytic therapy. On the other hand, the Modified Rankin Scale (MRS) focuses on measuring functional disability and overall outcomes after a stroke, assessing the patient's independence in daily activities. This scale ranges from 0 to 6, where higher scores indicate more severe disability. MRS assessments are crucial for understanding long-term outcomes and for planning rehabilitation efforts. Both the NIHSS and MRS are critical in stroke management, serving different urposes at various stages of care and highlighting the need for a thorough understanding of their strengths and limitations in providing effective treatment.

RESULTS

Of the 100 patients analysed, 55 were male, with a mean age of 61±9 years and a mean BMI of 27.71±4.21kg/m2. Aspirin resistance was observed in 32% of patients. The median NIHSS score and MRS were 3 and 1, respectively. NHISS and MRS statistically significantly positively correlated with haemoglobin value ($r=0.198$ and $r=0.216$, $p<0.05$ (0.048 and 0.031)), hematocrit ($r=0.251$ and $r=0.283$, $p<0.05$ and $p< 0.01$ (0.012 and 0.004) and

triglycerides (r=0.202 r=0.219, p<0.05 (0.044 and 0.028)). Only NHISS was statistically significantly positively correlated with patients' age (r=0.193, p=0.044). There was no statistically significant correlation between the severity of the clinical presentation, assessed by NHISS and MRS, and ASA resistance. The age of the patients was statistically significantly positively correlated with ASA resistance (r=0.210, p<0.05). We categorized stroke severity as assessed by the NIHSS score into 5 categories: no symptoms (score 0), minor (score 1-4), moderate (score 5-15), moderate to severe (score 16-20) and severe (score of 21-42) stroke. NIHSS and MRS scores demonstrated statistically significant positive correlations with hemoglobin, hematocrit, and triglyceride levels (p<0.05). NIHSS also correlates significantly with patient age (p<0.05). However, no significant correlation was found between aspirin resistance and stroke severity assessed by NIHSS/MRS. Age showed a positive correlation with aspirin resistance (p<0.05). Using ANOVA haemoglobin, hematocrit, age, fasting glycemia, and presence of diabetes mellitus had a statistically significant effect on stroke severity category (p<0.05) (Table 1).

Table 1. Influence of analyzed parameters on stroke severity

ANOVA						
		Sum of Squares	df	Mean Square	F	Sig.
HGB	Between Groups	3007,181	4	751,795	3,187	,017
	Within Groups	22409,569	95	235,890		
	Total	25416,750	99			
HbA1c	Between Groups	13,110	4	3,278	1,027	,398
	Within Groups	303,212	95	3,192		
	Total	316,322	99			
Glucose	Between Groups	87,593	4	21,898	2,696	,035
	Within Groups	771,607	95	8,122		
	Total	859,200	99			
TRG	Between Groups	8,541	4	2,135	1,630	,173
	Within Groups	124,449	95	1,310		
	Total	132,990	99			
HOL	Between Groups	1,508	4	,377	,236	,917
	Within Groups	151,631	95	1,596		
	Total	153,139	99			
urea	Between Groups	3,949	4	,987	,247	,911
	Within Groups	379,600	95	3,996		
	Total	383,548	99			
creatinin	Between Groups	981,901	4	245,475	,387	,817
	Within Groups	60230,216	95	634,002		
	Total	61212,117	99			
ASA	Between Groups	22367,928	4	5591,982	1,200	,316
	Within Groups	442783,312	95	4660,877		
	Total	465151,240	99			
ACA resistant	Between Groups	,526	4	,131	,588	,672
	Within Groups	21,234	95	,224		
	Total	21,760	99			
gender	Between Groups	1,211	4	,303	1,222	,307
	Within Groups	23,539	95	,248		
	Total	24,750	99			
age	Between Groups	901,484	4	225,371	2,734	,033
	Within Groups	7832,476	95	82,447		
	Total	8733,960	99			
BMI	Between Groups	147,122	4	36,780	2,170	,078
	Within Groups	1610,112	95	16,949		
	Total	1757,234	99			
alcohol	Between Groups	,295	4	,074	,637	,638
	Within Groups	11,015	95	,116		
	Total	11,310	99			
smoking	Between Groups	1,050	4	,263	1,057	,382
	Within Groups	23,590	95	,248		
	Total	24,640	99			
PLT	Between Groups	4484,744	4	1121,186	,275	,893
	Within Groups	387073,046	95	4074,453		
	Total	391557,790	99			
HCT	Between Groups	203,443	4	50,861	3,604	,009
	Within Groups	1340,842	95	14,114		
	Total	1544,285	99			

HTA	Between Groups	,081	4	,020	,301	,877
	Within Groups	6,429	95	,068		
	Total	6,510	99			
DM	Between Groups	10,637	4	2,659	2,832	,029
	Within Groups	89,203	95	,939		
	Total	99,840	99			
KVB	Between Groups	,834	4	,209	,931	,449
	Within Groups	21,276	95	,224		
	Total	22,110	99			
HBI	Between Groups	,051	4	,013	,216	,929
	Within Groups	5,589	95	,059		
	Total	5,640	99			
CLO	Between Groups	1330,938	2	665,469	,068	,934
	Within Groups	234560,914	24	9773,371		
	Total	235891,852	26			

DISCUSSION

The study aimed to explore the potential relationship between aspirin resistance (AR) and the clinical severity of ischemic stroke, assessed by the National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS). Contrary to initial expectations, our findings revealed no statistically significant correlation between aspirin resistance and stroke severity measured by both scales. This indicates that factors beyond aspirin responsiveness may play a more substantial role in determining stroke severity. Our study's methodology involved analyzing data from one hundred consecutive patients with acute ischemic stroke, enhancing the reliability of our findings. Notably, approximately one-third of the patients exhibited aspirin resistance, highlighting a sizable proportion at risk of suboptimal response to aspirin therapy. Despite this, the lack of association between aspirin resistance and clinical severity suggests the involvement of other contributing factors.

While NIHSS and MRS demonstrated significant positive correlations with certain clinical parameters such as hemoglobin, hematocrit, triglycerides, and age, no such correlation was observed between aspirin resistance and NIHSS/MRS scores. This implies that clinical stroke severity may not be directly influenced by aspirin responsiveness alone, indicating the complexity of stroke outcomes. Despite the identification of various potential mechanisms the underlying reasons for aspirin resistance and therapeutic failure are not fully understood [1] . These mechanisms range from patient non-compliance and inadequate dosing to poor absorption and enhanced metabolism of aspirin. Additionally, the biosynthesis of TXA2 through pathways not blocked by aspirin, alternative platelet activation routes not affected by aspirin, smoking habits, and hypercholesterolemia contribute to this phenomenon.

In a study involving 310 patients [2] diagnosed with acute ischemic stroke, high residual platelet reactivity (HRPR), indicative of aspirin resistance, was detected in 27.7% of cases. Those with HRPR displayed elevated initial stroke severity, with a median NIH Stroke Scale score of 6 compared to 3 in non-HRPR patients. Additionally, HRPR patients exhibited larger infarct volumes on diffusion-weighted imaging (DWI). Through multivariable analysis, HRPR was identified as significantly correlated with a 2.1-point increase in NIH Stroke Scale score and a 2.3 cm(3) rise in DWI infarct volume, indicating its predictive role in severe strokes and larger infarct sizes among aspirin-using individuals. A study from Colombia[3] investigating the prevalence of AR in ischemic stroke patients and healthy controls has illuminated key aspects of antiplatelet therapy. The research suggests a substantial link between AR and a history of prior ischemic strokes, which may indicate a connection to recurring strokes[4] [5]. This finding is consistent with earlier studies that associate AR with an increased risk of severe vascular events. Additionally, the detection of AR in healthy controls raises questions about the effectiveness of aspirin as a primary preventive measure, suggesting that AR testing might be warranted before starting aspirin therapy. Although the study did not reveal a statistically significant difference in AR prevalence between patients and controls, it points to the potential for developing secondary AR through prolonged use of aspirin[3]. Furthermore, the complexity of AR stems from various factors, including patient adherence, dosing, absorption, metabolism of aspirin, and alternative platelet activation pathways. Notably, inadequate medication adherence emerges as a significant contributor to AR, potentially being one of the primary causes [6]. Additionally, elevated platelet turnover associated with underlying inflammatory conditions like atherosclerosis and its complications can accelerate platelet regeneration, including COX-1, thereby diminishing the efficacy of

once-daily dosing [7]. Recent advancements include the identification of platelet glycoprotein IIIa as a potential biomarker and underlying mechanism for aspirin resistance, as well as the discovery of an anion efflux pump responsible for expelling intracellular aspirin from platelets [8]. Moreover, the genetic underpinnings of AR are suggested by its occurrence in healthy individuals, and ongoing research is investigating polymorphisms of COX enzymes and platelet surface receptors[9] (Goodman T., 2007).

In a study of 50 patients [10] with recurrent stroke, comorbidities like hypertension, diabetes, and hyperlipidemia were prevalent. Most recurrent stroke patients were elderly (>60 years), hypertensive, and non-compliant with aspirin. Aspirin resistance correlated with antiplatelet on-compliance. Elevated inflammatory biomarkers (hsCRP, PLA2, TNF-α) were observed compared to controls, suggesting a link between inflammation, atherosclerosis, and ischemic stroke [11]. While previous studies examined inflammatory biomarkers in stroke, their role in predicting recurrence remains unclear.The positive correlation between age and aspirin resistance raises intriguing questions about the interplay between age-related factors, aspirin response, and stroke severity. As age is a known risk factor for stroke, understanding its relationship with aspirin resistance could have implications for planning treatment strategies and risk assessment in older stroke patients.

CONCLUSION

In conclusion, while aspirin resistance was prevalent among acute stroke patients, it did not significantly impact clinical severity as assessed by NIHSS and MRS. This underscores the necessity for further exploration of additional factors influencing stroke outcomes and the development of personalized treatment approaches in stroke management. Further research is needed to clarify the complex interplay between aspirin resistance, age, and stroke severity, offering valuable insights for optimizing stroke management strategies.

BIBLIOGRAPHY

1. Roth GJ, Roth CD. Aspirin, platelets, and thrombosis: theory and practice. Blood. 1994;83(4):885–898.
2. Oh MS, Hong HC. Aspirin resistance is associated with increased stroke severity and infarct volume. Neurology. 2016. DOI: 10.1212.
3. Roman-Gonzalez A, Naranjo CA, Cardona-Maya WD, Vallejo D, Garcia F, Franco C, Alvarez L, Tobón LI, López MI, Rua C, Bedoya G, Cadavid Á, Torres JD. Frequency of Aspirin Resistance in Ischemic Stroke Patients and Healthy Controls from Colombia. Stroke Res Treat. 2021;2021:9924710.
4. Helgason CM, Bolin KM. Development of aspirin resistance in persons with previous ischemic stroke. Stroke. 1994;25(12):2331–2336.
5. Englyst NA, Husted SE. Aspirin resistance is more common in lacunar strokes than embolic strokes and is related to stroke severity. J Cereb Blood Flow Metab. 2008;28(6):1196–1203.
6. Maree AO, Curtin RJ. Cyclooxygenase-1 haplotype modulates platelet response to aspirin. J Thromb Haemost. 2005;3(10):2340–2345.
7. Pedersen AK, FitzGerald GA. Dose-related kinetics of aspirin: presystemic acetylation of platelet cyclooxygenase. N Engl J Med. 1984;311(19):1206–1211.
8. Floyd CN, Ferro A. Mechanisms of aspirin resistance. Pharmacol Ther. 2014;141(1):69–78.
9. Goodman T, Prabhakaran S. The genetics of aspirin resistance. Int J Clin Pract. 2007;61(5):826–834.
10. Dash PS. Aspirin resistance and blood biomarkers in predicting ischemic stroke recurrence: An exploratory study. Brain Circ. 2022;8(1):31–37.
11. Kocaman GD. Recurrent Ischemic Stroke Characteristics and Assessment of Sufficiency of Secondary Stroke Prevention. Noro psikiyatri arsivi. 2015;52(2):139–144.

Original scientific paper

CYSTATIN C AS A BIOMARKER OF CHRONIC KIDNEY DISEASE- PEDIATRIC PERSPECTIVES AND CLINICAL IMPLICATIONS

Olivera Jordanova[1], Velibor Tasikj[1], Aspazija Sofijanova[1], Sonja Bojadzieva[1], Albina Bektashi[2]

[1]PHI University Clinic for Children's Diseases-Skopje
[2]PHI Health Centre- Skopje

*Corresponding Author: Olivera Jordanova, MD University Children Hospital-Skopje
adress: Mother Theresa 17-Skopje
e-mail: olivera.jordanova@yahoo.com
mob: 078 346 238

Medicus 2024, Vol. 29 (2): 128-133

ABSTRACT

Introduction: Chronic kidney disease (CKD) in pediatric patients is the progressive and irreversible loss of kidney function over time. Unlike chronic kidney disease, which occurs suddenly and is usually reversible, CKD develops slowly and can cause long-term problems if not treated appropriately.

Objective: The purpose of this study is to evaluate the value of serum cystatin C in early prediction of chronic kidney disease with emphasis on diagnostic and prognostic value, practical considerations, and future directions and as a biomarker for estimating glomerular filtration rate.

Materials and methods: The study was conducted at PHI University Clinic for Children's Diseases-Skopje. It is a retrospective-prospective study, in which 130 patients were evaluated between January 2019y and December 2023y with clinical signs, symptoms, laboratory analyses, and imaging studies for CKD.

Results: The average values of serum Cystatin C (ng /ml) showed that there is a significant difference in relation to this parameter in pediatric patients with congenital anomalies of the kidneys and urinary tract 1,24 ±1.12 in relation to pediatric patients with tubulopathies and metabolic diseases with renal affection 1.13±1.09, pediatric patients with glomerulopathies 1.09 ±1.07, and pediatric patients with other nephrological-urological diseases 1.29±1.1 at the first examination $p<0.05$. The average values of serum Cystatin C (ng /ml) showed that there is a significant difference in relation to this parameter in pediatric patients with renal stages CKD, at the first examination $p<0.05$.

Conclusions: Serum cystatin C is well established as an early and accurate biomarker of CKD, which is particularly useful in patients where creatinine is an inadequate marker or where more cumbersome methods of measuring glomerular filtration rate (GFR) are impractical. Serum Cystatin C has shown promise in detecting subtle changes in renal function earlier than traditional markers, enabling timely intervention and personalized management strategies.

Keywords: Chronic kidney disease (CKD), Cystatin C, pediatric patients, biomarkers, renal stages CKD

INTRODUCTION

Chronic kidney disease (CKD) in pediatric patients is the progressive and irreversible loss of kidney function over time. [1] Unlike chronic kidney disease, which occurs suddenly and is usually reversible, CKD develops slowly and can cause long-term problems if not treated appropriately. Chronic kidney disease (CKD) in children is a chronic disease caused by the weakening of kidney

function. [2]This gradual deterioration impairs the kidney's ability to filter waste and maintain fluid and electrolyte balance. Kidney disease is less common in children than in adults, but it causes health problems that require early intervention to prevent serious problems and improve quality of life. Chronic kidney disease (CKD) is defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min per 1.73 square meters, persisting for 3 months or more. It is a state of progressive loss of kidney function, ultimately resulting in the need for renal replacement therapy (dialysis or transplantation). [3] It can result from various underlying conditions and leads to the progressive loss of kidney function. It is a rare condition in children, affects a small percentage of children, and is a significant problem in treating children. Early diagnosis and management are critical to improving outcomes. CKD disrupts these activities, leading to wasting and energy shortages. or end-stage renal disease (ESRD), in which kidney function is poor or absent. [4-6].

Biomarkers play an important role in the diagnosis, monitoring, and treatment of chronic kidney disease (CKD). It helps evaluate kidney function, determine the underlying cause of kidney damage, and monitor disease progression. Until now, the diagnosis of kidney damage was based on determining the values of serum creatinine, which is the most commonly used parameter for monitoring glomerular filtration. [7].

A biological indicator measured in blood, urine, or other body fluids that reflects a physiological or pathological process. [8]. In CKD, biomarkers help evaluate kidney function, determine the cause of kidney damage, monitor disease progression, and predict patient outcomes. Biomarkers help diagnose CKD by indicating kidney function and damage, sometimes before traditional tests detect significant changes. Regular measurement of biomarkers allows you to monitor the progression of CKD, adjust treatment plans, and evaluate treatment effectiveness. Biomarkers can provide insight into the expected course of CKD, helping to predict outcome and guide clinical decisions. Early detection of kidney damage, more accurate assessment of kidney function, and personalized treatment strategies. Biomarker variability due to factors such as inflammation, medications, and comorbidities. Some biomarkers may be more expensive or less available. Ongoing research aims to identify new biomarkers and improve existing biomarkers to improve management and treatment outcomes in CKD. Integrating existing and new biomarkers with clinical data to improve overall CKD assessment and patient care. Biomarkers are an essential part of modern CKD management, providing valuable information for diagnosis, monitoring.

Cystatin C is a small non-glycosylated protein produced by all nucleated cells and filtered by the kidneys. [9]. It belongs to the cystatin family of cysteine protease inhibitors. Cystatin C is an indicator of kidney function and is considered a potentially more accurate indicator of glomerular filtration rate (GFR) than serum creatinine, especially in patients with variable muscle mass or early stages of CKD. When determining glomerular filtration with serum creatinine, the gender and age of the patients are taken into account. [10-12]. This is not the case with cystatin C, which has been shown to be independent of age and sex, muscle mass and inflammatory conditions. Cystatin C is produced at a constant rate by all nucleated cells and is freely filtered by the glomeruli. Serum levels depend primarily on renal function. [13]. Serum cystatin C levels can be measured using a relatively simple, widely available enzyme-linked immunosorbent assay in clinical laboratories. Serum cystatin C levels are less dependent on muscle mass, age, sex, and diet than serum creatinine. This may provide a more accurate reflection of renal function in patients whose creatinine levels may fluctuate due to these factors. Cystatin C levels may rise earlier than serum creatinine in cases of renal impairment, allowing for the early detection of renal dysfunction. Cystatin C is used to estimate GFR, and equations that include cystatin C (eg, the CKD-EPI cystatin C equation) may provide a more accurate assessment of kidney function than equations based on creatinine. [14,15]. Elevated serum levels of cystatin C may indicate kidney dysfunction and are useful for diagnosing and monitoring CKD, especially in the early stages when creatinine levels may still be normal. Serial cystatin C measurements can be used to monitor the progression of CKD and response to treatment. [16]. The purpose of this review is to evaluate the value of serum cystatin C in early prediction of chronic kidney disease with emphasis on diagnostic and prognostic value, practical considerations, and future directions and future directions and as a biomarker for estimating glomerular filtration rate.

MATHERIAL AND METHODS

The study was conducted at PHI University Clinic for Children's Diseases-Skopje. It is a retrospective-prospective study, in which 130 patients were evaluated

between January 2019 and December 2023 with clinical signs, symptoms, laboratory analyses, and imaging studies for CKD. Inclusion criteria for inclusion in the study are: confirmed chronic kidney disease according to the above parameters, appropriate medical documentation, results of laboratory analyses .Exclusion criteria: incomplete medical documentation, incomplete laboratory analyses. In each child, investigations were carried out which are necessary to define the etiology according to the indication of a competent nephrologist.

The examined group is divided into four groups:

Group I includes patients with congenital anomalies of the kidneys and urinary tract

Group II includes patients with tubulopathies and metabolic diseases with renal affection

Group III includes patients with glomerulopathies

IV group includes patients with other nephrological-urological diseases

Renal function, ie glomerular function, will be determined through serum creatinine values and calculation of glomerular filtration rate according to Schwartz's formula.

eGFR=TV x 0.413 /serum creatinine (mg/dL)

eGFR – estimated glomerular filtration rate

TV – body height

The laboratory analyzes were performed at the Department of Clinical Laboratory at the PHI University Clinic for Children's Diseases-Skopje.Blood samples for serum cystatin C , serum creatinine were taken from all patients at the time of first examination and on the control. Cystatin C (mg/L), and creatinine in serum(umol/L) levels were measured at the biochemistry analyzer Architect c 4000 Abbott.

Statistical analysis

The obtained results were statistically processed with descriptive statistics, and to determine the significance of the differences in the level of the analyzed parameters between the groups, tests for independent samples (t-test for independent samples, Chi-square Pearson test) were used. Pearson correlation coefficient was used to determine correlation between renal markers.

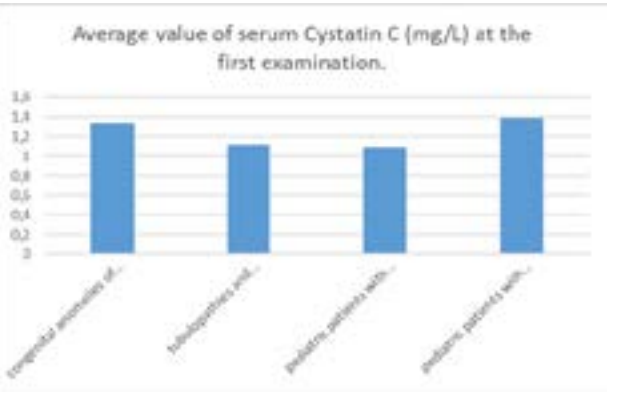
RESULTS

The study was conducted at PHI University Clinic for Children's Diseases-Skopje. It is a retrospective-prospective study, in which 130 patients were evaluated between January 2019 and December 2023 with clinical signs, symptoms, laboratory analyses, and imaging studies for CKD.

The study group is divided into three groups, study group 1, which includes 49/130 pediatric patients (37.69%) with congenital anomalies of the kidneys and urinary tract, study group 2, which includes 40/130 pediatric patients (30.77%) with tubulopathies and metabolic disorders with renal affection, study group three which includes 18/130 pediatric patients (13.85%) with glomerulopathies and IV group which includes 23/130 pediatric patients (17.69%) with other nephrological-urological diseases.

According to gender, the male gender dominated in pediatric patients with congenital anomalies of kidneys and urinary tract 30/49 (61.22%), in pediatric patients with tubulopathies and metabolic diseases with renal affection 26/40 (65%) in pediatric patients with glomerulopathies 11/28 (61,11 %) and in pediatric patients with other nephrological-urological diseases 12/23 (72.22%).There is a statistically significant difference between gender in terms of CKD in the studied groups $p < 0.05$. According to age, there is no significant difference regarding this parameter in the three studied groups $p<0,01$

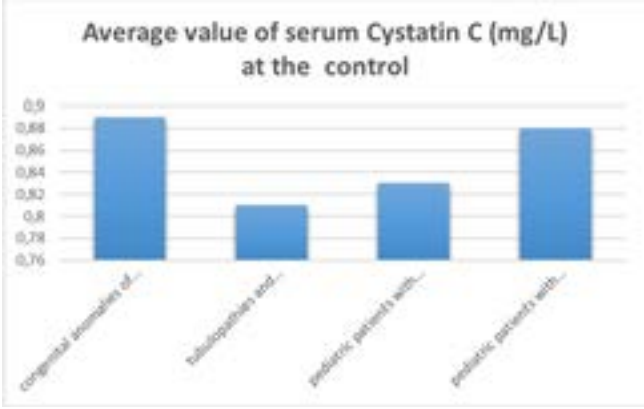
Chart number 1. Distribution of pediatric patients with congenital anomalies of the kidneys and urinary tract, tubulopathies and metabolic diseases with renal affection, pediatric patients with glomerulopathies and pediatric patients with other nephrological-urological diseases according to the average value of serum Cystatin C (ng /ml) at the first examination.



The average values of serum Cystatin C (ng /ml) showed that there is a significant difference in relation to this

parameter in pediatric patients with congenital anomalies of the kidneys and urinary tract 1,24 ±1.12 in relation to pediatric patients with tubulopathies and metabolic diseases with renal affection 1.13±1.09, pediatric patients with glomerulopathies 1.09 ±1.07, and pediatric patients with other nephrological-urological diseases 1.29±1.1 at the first examination p<0.05.

Chart number 2. Distribution of pediatric patients with congenital anomalies of the kidneys and urinary tract, tubulopathies and metabolic diseases with renal affection, pediatric patients with glomerulopathies and pediatric patients with other nephrological-urological diseases according to the average value of serum Cystatin C (ng /ml) at the control



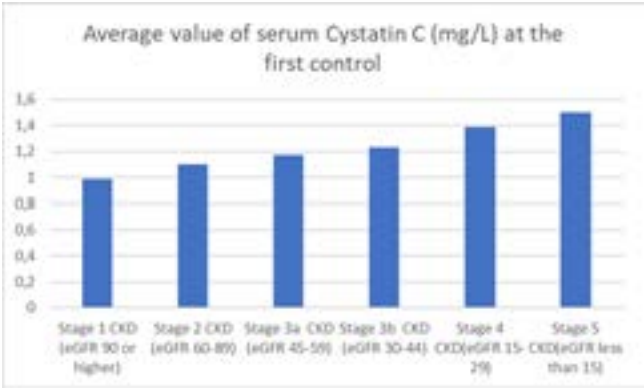
The average values of serum Cystatin C (ng /ml) showed that there is no significant difference

regarding this parameter in pediatric patients with congenital anomalies of kidneys and urinary tract 0,89±1.07 in relation to pediatric patients with tubulopathies, metabolic diseases with renal affection 0,81±1.15, pediatric patients with glomerulopathies 0,83±1.12, and pediatric patients with other nephrological-urological diseases 0,88±1.15 at control examination p<0.01.

The average values of serum Creatinin (umol /L) showed that there is no significant difference

regarding this parameter in pediatric patients with congenital anomalies of kidneys and urinary tract 80±1.15 in relation to pediatric patients with tubulopathies, metabolic diseases with renal affection 75±1.21, pediatric patients with glomerulopathies 75±1.16, and pediatric patients with other nephrological-urological diseases 82±1.12 at the first examination. p<0.01.

Chart number 3. Distribution of pediatric patients with renal stages according to the average value of serum Cystatin C (ng /ml) at first examination.



The average values of serum Cystatin C (ng /ml) showed that there is a significant difference in relation to this parameter in pediatric patients with renal stages CKD. Stage 1 CKD (eGFR 90 or higher) 0,99 ±1.1, Stage 2 CKD (eGFR 60-89) 1,1 ±1.23, Stage 3a CKD (eGFR 45-59) 1,17 ±1.09, Stage 3b CKD (eGFR 30-44) 1,23 ±1.05, Stage 4 CKD(eGFR 15-29) 1,39 ±1.13, Stage 5 CKD(eGFR less than 15) 1,5 ±1.23, at the first examination p<0.05.

The average values of serum Cystatin C (ng /ml) showed that there is a significant difference in relation to this parameter in pediatric patients with renal stages CKD. Stage 1 CKD (eGFR 90 or higher) 0,92 ±1.12, Stage 2 CKD (eGFR 60-89) 1,03 ±1.27, Stage 3a CKD (eGFR 45-59) 1,12 ±1.03, Stage 3b CKD (eGFR 30-44) 1,19 ±1.02, Stage 4 CKD(eGFR 15-29) 1,27 ±1.11, Stage 5 CKD(eGFR less than 15) 1,4 ±1.27, at the control p<0.05.

DISSCUSION

Cystatin C is a non-glycosylated protein that is one of the biomarkers of glomerular filtration. Cystatin C is a small molecule of 13 kDa [17], filtered and catabolized from glomerular blood but not secreted by proximal tubular cells [18,19]. In our study the average values of serum Cystatin C (ng /ml) showed that there is a significant difference in relation to this parameter in pediatric patients with congenital anomalies of the kidneys and urinary tract 1,24 ±1.12 in relation to pediatric patients with tubulopathies and metabolic diseases with renal affection 1.13±1.09, pediatric patients with glomerulopathies 1.09 ±1.07, and pediatric patients with other nephrological-urological diseases 1.29±1.1 at the first examination p<0.05.

Cystatin C has been shown to be produced by all human nucleated cells and is a housekeeping gene, and serum cystatin C levels have been shown to be associated with GFR [12] and diseases. A decrease in estimated GFR

(eGFR) is associated with a decrease in serum cystatin C levels [19]. Serum cystatin C concentrations have also been shown to be unchanged in some diseases or other metabolic disorders [21]. It has also been suggested that cystatin C balance may be useful in the diagnosis of kidney disease in children because cystatin C is independent of many factors that affect serum creatinine, such as age, sex, race, and muscle mass. Patients with muscle involvement. [22-24] Based on many of these findings, it was determined that cystatin C could be used as a new biomarker, in conjunction with serum creatinine, or as a proxy for serum creatinine to better define kidney disease in the general population. There are positive implications for the use of cystatin C as a predictive biomarker in the eGFR prediction equation. Using serum creatinine, eGFR has been shown to be limited in individuals with reduced muscle mass. In contrast, cystatin C was found to have no correlation with body fat, whereas serum creatinine appeared to correlate with body fat. In our study the average values of serum Cystatin C (ng /ml) showed that there is a significant difference in relation to this parameter in pediatric patients with renal stages CKD . Stage 1 CKD (eGFR 90 or higher) 0,99 ±1.1, Stage 2 CKD (eGFR 60-89) 1,1 ±1.23, Stage 3a CKD (eGFR 45-59) 1,17 ±1.09, Stage 3b CKD (eGFR 30-44) 1,23 ±1.05, Stage 4 CKD(eGFR 15-29) 1,39 ±1.13, Stage 5 CKD(eGFR less than 15) 1,5 ±1.23, at the first examination $p<0.05$.This suggested that the use of cystatin C may improve kidney function in individuals with different levels of lean body work analysis. It has also been shown that serum cystatin C is less affected by age and race [21]. Cystatin C may also be useful in determining eGFR for individuals with only reduced GFR (60 to 90 ml/min/1.73 m2), but no change in serum creatinine level has been observed and therefore the GFR prediction equation is less reliable. [25,26]

CONCLUSION

Serum cystatin C is well established as an early and accurate biomarker of CKD, which is particularly useful in patients where creatinine is an inadequate marker or where more cumbersome methods of measuring glomerular filtration rate (GFR) are impractical. The current research question is no longer whether cystatin C should be used in the evaluation of patients with CKD, but rather when and how often it should be used. Early diagnosis and treatment are important to improve outcomes. Cystatin C has several advantages over serum creatinine in estimating GFR. It may be useful to use cystatin C as a confirmatory biomarker in drug dosing decisions or as a confirmatory test in patients with uncertain diagnosis of chronic kidney disease. Cystatin C has shown promise in detecting subtle changes in renal function earlier than traditional markers, enabling timely intervention and personalized management strategies.

REFERENCES

1. Baum M: Overview of chronic kidney disease in children. Curr Opin Pediatr 2010;22:158-160.
2. Wong CJ, et al: CKiD (CKD in children) prospective cohort study: a review of current findings. Am J Kidney Dis 2012;60:1002-1011.
3. Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013; 3: 1–150.
4. Warady B.A. Chadha V.Chronic kidney disease in children: the global perspective.Pediatr Nephrol. 2007; 22: 1999-2009.
5. Harambat J, et al: Epidemiology of chronic kidney disease in children. Pediatr Nephrol 2012;27:363-373.
6. Atkinson MA, Martz K, Warady BA, et al. Risk for anemia in pediatric chronic kidney disease patients: a report of NAPRTCS. Pediatr Nephrol 2010; 25: 1699-706.
7. Davies, R. (2018). The Metabolomic Quest for a Biomarker in Chronic Kidney Disease. Clin. Kidney J. 11 (5), 694–703. doi:10.1093/ckj/sfy037
8. Common sense approaches to urinary biomarker study design.J Am Soc Nephrol. 2009; 20: 1175-1178
9. Coresh J, Laterza OF, Price CP, Scott MG. Cystatin C: An improved estimator of glomerular filtration rate? Clin Chem. 2002;48:699–707.
10. Finney H, Newman DJ, Thakkar H, Fell JM, Price CP. Reference ranges for plasma cystatin C and creatinine measurements in premature infants, neonates, and older children. Arch Dis Child. 2000;82:71–75
11. Uemura O, Ushijima K, Nagai T, et al. Reference serum cystatin C levels in Japanese children. Clin Exp Nephrol. 2010;14:453–456
12. Christensson A, Ekberg J, Grubb A, Ekberg H, Lindstrom V, Lilja H. Serum cystatin C is a more sensitive and more accurate marker of glomerular filtration rate than enzymatic measurements of creatinine in renal transplantation. Nephron Physiol. 2003;94:19–27.
13. Finney H, Newman DJ, Thakkar H, Fell JM, Price CP.

Reference ranges for plasma cystatin C and creatinine measurements in premature infants, neonates, and older children. Arch Dis Child 2000;82:71-75.

14. Dworkin LD. Serum cystatin C as a marker of glomerular filtration rate. Curr Opin Nephrol Hypertens. 2001;10:551–553
15. Zati Iwani AK , Ruziana Mona WZ, Nor Idayu R, Wan Nazaimoon WM. The Usefulness of Cystatin C as a Marker for Chronic Kidney Disease. Universal Journal of Clinical Medicine 1(2): 28-33, 2013
16. Min Zhang , Xueying Cao , Guangyan Cai , DiWu , RibaoWei , Xueli Yuan , Xueyuan Bai , Shuwen Liu and Xiangmei Chen. Clinical evaluation of serum cystatin C and creatinine in patients with chronic kidney disease: A meta-analysis. Journal of International Medical Research 41(4) 944–955
17. Inker LA, Okparavero A. Cystatin C as a marker of glomerular filtration rate: prospects and limitations. Curr Opin Nephrol Hypertens 2011; 20:631–639.
18. Coll E, Botey A, Alvarez L, et al. Serum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker for early renal impairment. Am J Kidney Dis 2000; 36:29–34.
19. 11. Ferguson MA, Waikar SS. Established and emerging markers of kidney function. Clin Chem 2012; 58:680–689.
20. Filler G, Bokenkamp A, Hofmann W, et al. Cystatin C as a marker of GFR – history, indications, and future research. Clin Biochem 2005; 38:1–8.
21. Newman DJ, Thakkar H, Edwards RG, et al. Serum cystatin C measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine. Kidney Int 1995; 47:312–318.
22. Finney H, Newman DJ, Gruber W, et al. Initial evaluation of cystatin C measurement by particle-enhanced immunonephelometry on the Behring nephelometer systems (BNA, BN II). Clin Chem 1997; 43:1016–1022.
23. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis 2002; 40:221–226.
24. 16. Madero M, Sarnak MJ, Stevens LA. Serum cystatin C as a marker of glomerular filtration rate. Curr Opin Nephrol Hypertens 2006; 15:610–616.
25. Mussap M, Plebani M. Biochemistry and clinical role of human cystatin C. Crit Rev Clin Lab Sci 2004; 41:467–550.
26. Chew JS, Saleem M, Florkowski CM, George PM. Cystatin C – a paradigm of evidence based laboratory medicine. Clin Biochem Rev 2008; 29:47–62.

Profesional paper

РАЗВОЈ НА ЛАБОРАТОРИЈА ЗА МОЛЕКУЛАРНА ДИЈАГНОСТИКА ВО ЦЕНТАР ЗА ЈАВНО ЗДРАВЈЕ ТЕТОВО ЗА ВРЕМЕ НА КОВИД-19 ПАНДЕМИЈАТА

Оливера Атанасовска[1,2], Голубинка Бошевска[2,3], Фатиме Даути[1], Мумин Селмани[1], Катерина Бошкоска[1]

[1]Центар за Јавно здравје, Тетово, Република С. Македонија
[2]Факултет за медицински науки, Универзитет Гоце Делчев – Штип, Република С. Македонија,
[3]Институт за Јавно здравје, Скопје, Северна Македонија

oatanasovska19@gmail.com

Medicus 2024, Vol. 29 (2): 134-138

РЕЗИМЕ

Потребата од SARS-CoV-2 тестирање за време на COVID-19 пандемијата беше многу голема. За да се подобри следењето, јавно здравствените авторитети на Македонија донесоа одлука за проширување на SARS-CoV-2 тестирање во центрите за јавно здравје надвор од Институтот за Јавно Здравје Скопје. Целта на овој труд е да се прикажат чекорите за развој на нова лабораторија за молекуларна дијагностика на SARS CoV-2 како дел од одделението за микробиологија при Центарот за Јавно Здравје Тетово, од 15 Мај 2021. Многу активности се превземени за обезбедување на добро организиран тек на работата и добивање на точни резултати покривајќи ги сите фази од пред аналитичка, аналитичка и постаналитичка фаза.

Клучни зборови: молекуларна детекција на SARS-CoV-2, организација на молекуларна лабораторија

ВОВЕД

Појавата на КОВИД-19 пандемијата резултираше со голем број на барања за лабораториско тестирање со цел да се потврди или исклучи инфекција со SARS CoV-2 за соодветен одговор во однос на згрижување на индивидуалните позитивни лица така и кон превземање на соодветни јавно здравствени мерки за контрола на инфекцијата. За да се подобри системот на следење на КОВИД-19, јавно здравствените авторитети на Македонија донесоа одлука за проширување на SARS-CoV-2 тестирањето во центрите за јавно здравје надвор од Институтот за Јавно Здравје Скопје. Одтука и одлуката за воспоставување на лабораторија за молекуларна дијагностика во рамки на одделението за микробиологија при Центар за Јавно Здравје (ЦЈЗ) –Тетово. На 15 Мај 2021 се направени првите тестови за детекција на SARS CoV-2 со примена на Реверзна Транскриптаза – Полимеразно верижна реакција (РТ-ПВР) во реално време за потребите од ваков вид тестирање на територијата која ја покрива ЦЈЗ Тетово т.е. за згрижување на населението во градовите Тетово и Гостивар и прикрепените населени места.

ЦЕЛ НА ТРУДОТ

Цел на трудот е да се прикажат чекорите превземни за развој на лабораторија за молекуларна дијагностика на SARS CoV-2 во Центар за Јавно Здравје Тетово.

МАТЕРИЈАЛИ И МЕТОДИ

Податоци за организацијата на лабораторијата за молекуларна дијагностика како резултатите од спроведените анализи во процесот на следење на КОVID-19 се од Центар за Јавно Здравје (ЦЈЗ) Тетово. Во процесот на организација на лабораторијата се следени препораките на Светската здравствена организација (СЗО) (1) и одредување на методологијата за лабораториска дијагностика на SARS-CoV-2. (2) Примероците за детекција на SARS-CoV-2 се земаат од горен респираторен тракт (назофарингеален брис и орофарингеален брис), според: Протокол за земање на биолошки материјал (брис) од пунктовите за скрининг на лица во ризик од КОВИД-19 (3) и Работно упатство за земање и чување на примероци од лица суспектни за КОВИД-19. (4) Транспорт на примероците од место на земање до место на прва обработка се спроведува согласно: Постапка за транспорт на примероци за лабораториска анализа за КОВИД-19 од болници, Центри за Јавно Здравје и собирни пунктови (5), по препорака на Институт за Јавно Здравје (ИЈЗ) (6), како и според упатството на СЗО за транспорт на биолошки супстанци категорија Б(UN3373, "Biological Substance, Category B"), (7) со примена на правилото на «Тројно пакување«. (8)

Тестирањето се одвива согласно инструкциите на производителот Seegene Allplex™ SARS-CoV-2 Assay (version 2.3; December 13th , 2022) (Cat no. RP10250X / RP10252W). (9)

Со цел да се провери точноста на резултатите добиени од лабораторијата: 1. Се користат контролни материјали за секоја реакција (позитивни и негативни контроли); 2. првите 5 SARS-CoV-2 позитивни и 5 SARS-CoV-2 негативни примероци се испратени на ретестирање во лабораторијата за вирусологија на ИЈЗ; 3. Лабораторијата учествуваше и во тестови на компетентност - ТК (External Quality Assessment EQA) организирани од страна на СЗО за молекуларна детекција на SARS-CoV-2 во јуни и јули 2021, како и август и септември 2022 година.

РЕЗУЛТАТИ

Просторот за земање на примероци и прием на примероци земени од пунктовите е одвоен од самиот лабораториски простор. Лабораторијата за молекуларна дијагностика е организирана во следните простории со соодветна опрема за намената:

- Екстракција на нуклеинска киселина, каде процесот на работа се одвива во Кабинет за микробиолошка безбедност класа 2 и е сместен Апарат екстратор SEEPREP32™;

- Подготовка на мастер микс и чисти раствори обезбедена со ПВР кабинет;

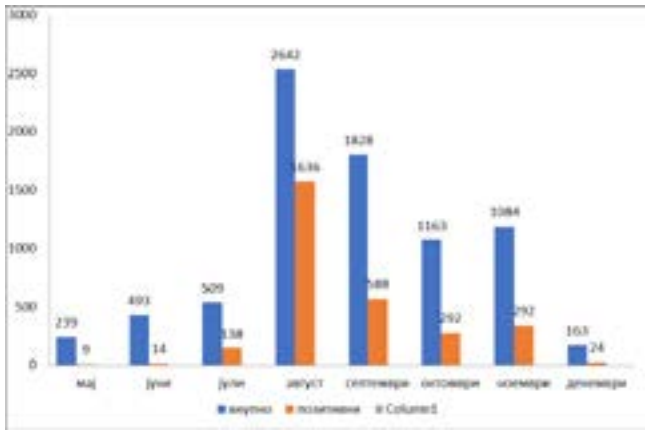
- Спојување на мастер микс со нуклеинската киселина обезбедена со ПВР кабинет;

- Амплификација каде што е сместен ПВР апаратот (Seegene RT-PCR-CFX96-Real Time System);

Процесот на работа е документиран со процедури за работа и записи.

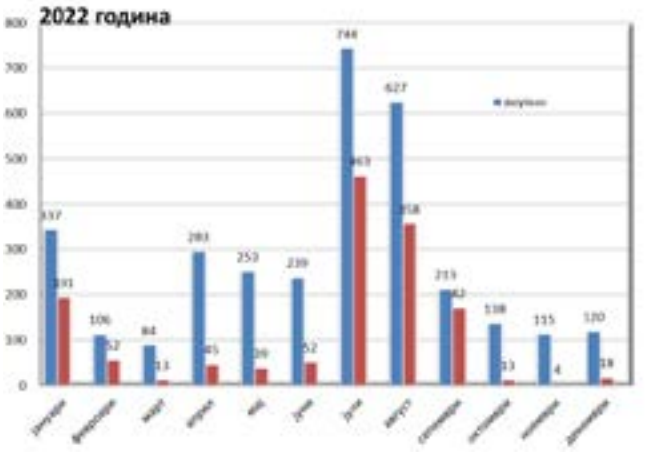
Персоналот кој е вклучен во работата е со предходно искуство за лабораториска работа и дополнителна едукација за извршување на РТ-ПВР тест. Тој ги применува препорачаните мерки за биолошка безбедност и биолошка сигурност препорачани од ИЈЗ согласно СЗО водич за Лабораториска биолошка безбедност поврзана со КОВИД-19. (10)

Во периодот од 15.05.2021–31.12.2021година во молекуларната лабораторија во ЦЈЗ Тетово се тестирани вкупно 8121 пациенти. Од нив 2993 пациенти биле позитивни, а 5128 негативни (графикон 1). Во периодот од 01.01.2022 до 31.12.2022 година се тестирани вкупно 3259 пациенти. Од нив 1290 пациенти биле позитивни,а 1969 негативни (графикон 2).



Графикон бр.1.Вкупно тестирани и позитивни пациенти по месеци од 15.05.2021 до 31.12.2021година.

Gaf No.1.Total tested and positive patients from 15.05.2021 to 31.12.2021 by month



Графикон бр.2.Вкупно тестирани и позитивни пациенти по месеци од 01.01.2022 до 31.12.2022година.

Gaf No.2.Total tested and positive patients from 01.01.2022 to 31.12.2022 by month

Резултатите се интерпретирани после отчитување на интерните контроли и нивна валидација. Одделението за вирусологија при ИЈЗ, како референтна лабораторија во државата за детекција на SARS-CoV-2 ги потврди првите тестирани примероци кои се испратени на ретестирање. Тестовите на компетентност во 2021 и 2022 покажаа 100% точна детереминација на непознатите примероци за тестирање.

ДИСКУСИЈА

Пандемијата со КОВИД-19 и големиот број на суспектни лица, за кои беше потребно да се направи тест за детекција на SARS-CoV-2 ја истакна потребата за воспоставување на лабораторија за молекуларна детекција на патогени агенси, во рамките на одделението за микробиологија при ЈЗУ Тетово. За таа цел беше потребно да се обезбеди соодветен простор, опрема и квалификуван персонал. (11) При дизајнирање на лабораторија за молекуларна детекција мора да се обрати особено внимание на спречување на контаминација. ПВР методите се особено подложни на контаминација бидејќи со нив се добиваат голем број копии од многу мала количина на целната секвенца што од една страна има голема дијагностичка предност, но од друга страна токму оваа способност може да доведе до лажни резултати во случај на контаминација. Лажно позитивни резултати може да се појават поради контаминација од примерок на примерок, транспорт на ампликони од претходна амплификација / иста реакција, вкрстена контаминација на различни реакции подготвени истовремено и контаминација на реагенсите со на матрикс ДНКта. (12) При изведување на РТ-ПВР реакција во реално време епруветките со ампликони не се отвараат и овој критичен момент е избегнат, освен ако има проблем со пластиката и истата се отвори за време на амплификацијата. Во лабораторијата за молекуларна дијагностика на ЈЗУ Тетово не се детектирани лажнопозитивни резултати во анализираниот период. Основните чекори кои се изведуваат во лабораторија за молекуларна дијагностика се поделени на:

1. пред ПВР постапки: подготовка на примерокот, подготовка на мастер микс за ПВР, подготовка на ПВР; и

2. пост-ПВР процедури: ПВР амплификација и пост-ПВР анализа.

Од клучно значење е овие операции да се вршат во физички одделени простории. Персоналот треба постојано да води грижа сите реагенси, материјали и опрема што се користат во поедините простории да се чуваат одвоени и никогаш да не ги префрлуваат од една во друга просторија и секогаш правецот на движење на вработените и материјалите да биде еднонасочен – од чисто кон валкано. На пример лицето кое работело на амплификација не треба да се враќа во просторијата за подготовка на мастер микс. Во просторијата за екстракција на нуклеински кислеини се користи кабинет за биолошка безбедност класа 2 А кој има за цел да ги заштити операторот, надворешната средина и производот од патогени агенси. Просторијата за подготовка на мастер микс е просторијата каде што се манипулира со чисти реагенси, потоа се делат на одреден број мали употребливи делови (аликвоти) и се подготвуваат реакционите смеси (мастер миксови). Оваа просторија треба да биде ослободена од какви било биолошки материјали како што се екстракти од ДНК/РНК, ПЦР производи итн. Подготовката на мастер миксот и ПВР реакциите во ПВР кабинет со ламинарен тек осигурува областа да остане чиста. (13) Опремата и регаенсите кои се применуваат се соодветни да дадат резултати кои одговараат на вистинската состојба на лицето кое се испитува.

Персоналот кој работи е едуциран соодветно за ваков тип на тест. Со редовното практикување на методата за работа во текот на 2021 - 2022 година што се гледа по големиот број на спроведени тестови се одржува

компетентноста на персоналот не само за самиот метод на работа, туку и на практикување на мерките за биолошка безбедност. Издавањето на точни и навремени резултати, кои влеваат доверба и сигурност кај пациентите и јавно здравствените авторитети е од витално значење во секој период, особено за време на пандемија.За:

А) пациентите тоа значи навремено и правилно поставување на дијагнозата, а со тоа нивно навремено лекување, што пак директно ќе влијае на исходот на болеста;

Б) јавно здравствените авторитети тоа значи навремено информирање и превземање на јавно здравствени мерки за контрола и превенција на соодветното заболување.

Затоа во секоја реакција се вклучени внатрешните контроли. Дополнително е важно редовното учество во тестови на компетентност и меѓулабораториска споредба за да се проверува, потврдува и дополнително унапреди квалитетот на тестирањето.

ЗАКЛУЧОК

КОВИД-19 пандемијата беше тригер за развој на молекуларна лабораторија за детекција на SARS-CoV-2 во рамките на одделението за микробиологија при ЦЈЗ Тетово. Истата е организирана според меѓународни стандарди за ваков вид на лабораторија и докажа висока компетентност и издавање на точни резултати. Со ова се создадоа услови за воспоставување на молекуларни методи за детекција на други причинители на инфективни заболувања каде овие ПВР/РТ-ПВР би биле тестови од прва линија или би дале побрза детекција на одреден патоген. На тој начин ќе се овозможи побрзо добивање на резултат за пациентите, а со тоа и соодветен третман и нега на пациентите, како и навремено детектирање на патогени со јавно здравствено значење и брзо превземање на контролни и превентивни јавно здравствени мерки. Крајната цел обезбедување адекватна грижа за здравјето на населението на теритроријата на ЦЈЗ Тетово и пошироко.

ЛИТЕРАТУРА

1. WHO Laboratory biosafety manual, 4th edition: Laboratory design and maintenance. Достапно на https://www.who.int/publications/i/item/9789240011397)
2. WHO Interim guidance, Diagnostic testing for SARS-CoV-2, 11 September 2020, достапно на https://iris.who.int/bitstream/handle/10665/334254/WHO-2019-nCoV-laboratory-2020.6-eng.pdf?sequence=1
3. Доц др Голубинка Бошевска М-р сци Елизабета Јанческа М-р сци Маја Кузмановска Протокол за земање на биолошки материјал(брис)од пунктовите за скрининг на лица во ризик од КОВИД-19. Upatstvo-za-kovid-punktovi-za-skrining-22.03.2020-MKD.pdf. достапно на https://zdravstvo.gov.mk/wp-content/uploads/2020/04/Upatstvo-za-kovid-punktovi-za-skrining-22.03.2020-MKD.pdf
4. Доц др Голубинка Бошевска М-р сци Елизабета Јанческа. Работно упатство за земање и чување на примероци од лица суспектни за КОВИД-19. Достапно на https://zdravstvo.gov.mk/wp-content/uploads/2020/04/Laboratorisko-testirane-na-suspektni-sluchai-za-Covid-19.pdf
5. Постапка за транспорт на примероци за лабораториска анализа за КОВИД-19 од болници, Центри за Јавно Здравје и собирни пунктови. Достапно на https://zdravstvo.gov.mk/wp-content/uploads/2020/04/Postapka-za-transport-na-infektiven-materijal-za-KOVID19.pdf
6. Упатсво за транспорт на примероци за SARS-CoV-2 . Институт за јавно здравје. достапно на https://www.iph.mk/
7. Packaging and Labelling Requirements for Category B Infectious Substances Assigned to UN 3373 Достапно на: https://www.ed.ac.uk/files/atoms/files/packaging-labelling-reqs-catb-infectious-substance.pdf
8. World Health Organization. (‎ 2019)‎ . Guidance on regulations for the transport of infectious substances 2019 – 2020: applicable from 1 January 2019. World Health Organization. Достапно на:https://www.who.int/publications/i/item/WHO-WHE-CPI-2019.20
9. AllplexTM 2019-nCoV Assay (version 2.3; December 13th , 2022) (Cat no. RP10250X / RP10252W) Instructions for Use. Достапно на:https://www.fda.gov/media/137178/download
10. Laboratory biosafety guidance related to coronavirus disease (COVID-19): Interim guidance, 28 January 2021 Достапно на: https://www.who.int/publications/i/item/WHO-WPE-GIH-2021.1
11. Aysal A , Pehlivanoğlu B , Ekmekci S, Gündoğdu B. How to Set Up a Molecular Pathology Lab: A Guide for Pathologists. Turk Patoloji Derg. 2020; 36(3): 179–187. doi:

10.5146/tjpath.2020.01488

12. Standards Unit Public Health England. uuuu [Jan 28; 2020];UK Standards for Microbiology Investigations: Good practice when performing molecular amplification assays. Достапно на https://assets.publishing.service.gov.uk/media/5a8c01ab40f0b6230269dc83/Q4i5.pdf
13. WHO Biosafety manual Iv edition; Standards Unit Public Health England. uuuu [Jan 28; 2020];UK Standards for Microbiology Investigations: Good practice when performing molecular amplification assays. Достапно на https://assets.publishing.service.gov.uk/media/5a8c01ab40f0b6230269dc83/Q4i5.pdf

Profesional paper

BRONCHIOLITIS IN CHILDREN AND CHALLENGES FOR TREATMENT IN PEDIATRIC PRIMARY CARE SETTINGS

Valentina Risteska Nejashmikj

Faculty of Medical Sciences, University "Goce Delchev" Shtip

Medicus 2024, Vol. 29 (2): 139-145

ABSTRACT

Acute bronchiolitis is a common cause of hospitalization in children under 2 years old, often presenting as mild or moderate cases. Despite the prevalence of these forms, a considerable number of children with bronchiolitis are hospitalized, and global estimates of hospitalizations vary. Various treatments have been explored, and reducing hospitalization rates would bring significant benefits to families, healthcare systems, and society. This study aims to assess the effectiveness of a short, combined treatment with intramuscular dexamethasone and inhaled beta-2 agonists (Salbutamol) in reducing hospital admissions for acute bronchiolitis in Primary Pediatric care settings.

Aim: Effectiveness of short combined treatment with intramuscular dexamethasone with inhaled beta 2 agonists (Salbutamol) in children with acute bronchiolitis in reduction of hospital admission in Primary Pediatric care settings.

Materials and Methods: Retrospective data were collected from health records at the Primary Health Care Polyclinic - Pediatric Primary Health Care Practice "Vitalino" in Veles, North Macedonia. The study analyzed three groups of children aged 0-2 years who experienced bronchiolitis in 2016, 2019, and 2022. Treatment involved intramuscular Dexamethasone, inhaled Salbutamol, and, as needed, upper airway suctioning. Budesonide inhalation continued until complete recovery.

Results: The obtained results show: In 2016, out of 258 children, 108 had bronchiolitis, with a hospitalization rate of 8.3% (Odds Ratio: 9.1000, p=0.0078). In 2019, 37 out of 260 children were hospitalized 10.8%, (Odds Ratio: 10.8750, p=0.0508). In 2022, 31 out of 241 children had bronchiolitis, with no hospitalizations. Across all years, out of 759 children, 176 had bronchiolitis, with a total hospitalization rate of 7.4% (Odds Ratio: 10.4651, p=0.0006). Over half of the children with bronchiolitis had atopy (86 children).

Conclusion: The study concludes that children aged 1-6 months are most affected by bronchiolitis. The applied treatment, combining intramuscular Dexamethasone and inhaled Salbutamol, significantly reduces hospitalization rates, proving effective and beneficial. However, successful treatment in Primary Pediatric care demands a high level of commitment, predictive ability, and effective communication with parents.

Key Words: Bronchiolitis, outpatient, treatment

INTRODUCTION

Acute bronchiolitis is defined as an inflammation of the bronchioles usually caused by an acute viral illness and is a common lower respiratory tract infection, often affecting infants and young children on the age of 0-2 years.[1] The most common virus detected in children with bronchiolitis is respiratory syncytial virus (RSV) in 84.2%.[2] Clinically, it can be manifested by cough, tachypnoea, apnea, increased respiratory effort, fever, nasal congestion and rhinorrhea. On chest auscultation, the key feature is diffuse bilateral inspiratory crackles. Several efforts have been made to achieve an effective treatment for bronchiolitis, it has remained mainly

supportive.[3] The inflammation partially or completely blocks the airways, which causes wheezing and less oxygen enters the lungs, potentially causing a decrease in the blood level of oxygen.[4] Acute bronchiolitis is a common reason for hospitalization in children up to 2 years of age, although most cases are presented as mild and moderate forms of the disease, and much less often as severe forms. Severe cases might require hospitalization (2-3%).[5] Despite this, a large percentage of children were hospitalized, in Italy (15-17%) and in USA (17-19%) [5][6]. Estimates of hospitalizations vary widely in different countries. In medium-developed countries, even 1/3 of children with bronchiolitis are hospitalized.[7] This wide variation underscores the complexity of bronchiolitis management and the need for nuanced approach to address diverse healthcare context. Treatment challenge lies in balancing the avoidance of unnecessary admissions and prolonged hospital stays for children with bronchiolitis. Primary pediatric care settings offer psychosocial and economic benefits for various stakeholders, including children, parents, the health system, and society at large.[8] The complexities in treating bronchiolitis in Primary Pediatric care settings arise from factors such as the unpredictable viral nature of the condition, its self-limited nature, the young age of the children, limited effective interventions, potential overuse of medications and antibiotics, and the risk of complications. Challenges also include the fear of doctors, apprehensions about sudden worsening of respiratory function, and the doctor's limited experience in managing such cases.[9] Given that most children with bronchiolitis have a self-limiting mild disease, careful home management with attention to feeding and respiratory status is often a safe option. However, criteria for referral and admission vary between hospitals, contributing to confusion and a lack of evidence regarding the optimal treatment approach. [10] The general management approach is supportive, focusing on hydration, supplemental oxygen if necessary, and close monitoring of breathing difficulties. The absence of a unified treatment strategy underscores the dynamic nature of treatment recommendations influenced by evolving research perspectives.[11][12] Striking a balance between avoiding unnecessary hospitalizations and providing effective care in Primary Pediatric settings remains a critical challenge in optimizing outcomes for children with bronchiolitis. The treatment of children with bronchiolitis is influenced by the organization of the health system, and unfortunately, inappropriate treatments are prevalent, with over half of the patients receiving such care. The wide variation in local prescribing habits indicates a substantial opportunity for improvement, emphasizing the need for standardized practices. Discrepancies persist between clinical practices and evidence-based management of bronchiolitis, contributing to the challenges in providing optimal care.[13]Despite numerous clinical studies assessing the efficacy of various medications, conflicting and controversial results prevail, raising concerns about the pharmacological treatment of bronchiolitis.[14][15] The use of drugs like salbutamol, ipratropium bromide, hypertonic saline, epinephrine, steroids, ribavirin, and montelukast for acute bronchiolitis lacks consistent evidence. Notably, there is no indication that drug treatment can alter the natural course of bronchiolitis, highlighting the need for cautious consideration of these interventions.[16] Research efforts, including a multicentric study in Italy, underscore the importance of evaluating presenting features, treatment approaches, and the impact of medical therapy. This study emphasizes the necessity to enhance adherence to existing guidelines for bronchiolitis treatment, signaling a potential avenue for improving the standard of care in pediatric hospitals.[17]The use of systemic corticosteroids shows promise in preventing hospitalization for children with bronchiolitis, as indicated by research.[18] A specific study demonstrates significant improvement in breathing and a reduction in hospitalization over seven days when implementing a treatment regimen involving epinephrine and systemic dexamethasone, compared to a placebo.[19] Another study explores lower doses of epinephrine and dexamethasone, aiming to optimize the risks and benefits of corticosteroids, particularly considering potential developmental delays or viral spread risks.[20]While systemic corticosteroids and inhaled epinephrine show potential in preventing hospitalization, these treatments are not recommended in Primary Pediatric care settings. [19][20] Hypertonic saline's role is contentious, with AAP guidelines recommending it only for hospitalized children, while NICE guidelines discourage its use altogether.[21] The latest Cochrane review suggests that combining a high dose of systemic dexamethasone and adrenaline may reduce outpatient admissions for moderate bronchiolitis, based on a single large trial requiring further investigation.[22][23] These varied recommendations underscore the ongoing complexity and debate surrounding the optimal treatment for bronchiolitis. A possible upcoming treatment for RSV

bronchiolitis could be antiviral therapy. Ideally, a possible future strategy for the treatment of bronchiolitis may also include the use of a nebulized mucolytic drug that should be able to dissolve the debris that occludes the lumen of the terminal and respiratory bronchioles.[24] A bronchodilator-trial (using short-acting beta-2 agonists with metered-dose inhalers and valved holding chambers) has been proposed in children with bronchiolitis aged >6 months. [25] Acute bronchiolitis relates to early onset of asthma or bronchiolitis is an early exacerbation of asthma. [26]

MATERIALS AND METHODS

In this case report study the date were retrospectively collected from the health records at the Primary Health Care Polyclinic - Pediatric Primary Health Care Practice - "Vitalino" in Veles, North Macedonia. The data were analyzed to determine the effectiveness of the treatment in reducing hospitalization for acute bronchiolitis. An analysis was made of the three case study groups of children aged 0-2 years who suffered from bronchiolitis in 2016, 2019 and 2022. The treatment of the most children from the three groups was carried out with intramuscular application of Dexamethasone in a dose of 0.2-0.3 mg per kg/body weight, during1-4 days depend on the severity of disease and nebulized beta 2 agonists (Salbutamol) for 4-5 days. Upper airway suctioning was performed in 18 children only as needed. The treatment was continued with nebulized Budesonide in a dose of 125 mcg until complete recovery and to reduced bronchial hyperreactivity. The treatment duration for children was tailored based on the severity of the clinical presentation. Five distinct groups were formulated, considering chest auscultation findings, overall health condition, and age. Very mild form: treatment: Nebulized Budesonide for 2 weeks and nebulized Salbutamol for 3-4 days. Mild form-treatment: One-day intramuscular Dexamethasone. Mild-Moderate form-treatment: two-day regimen. Moderate form-treatment: three-day plan. Stronger Moderate form - treatment: Four-day course. All children, regardless of severity, received nebulized Salbutamol for 4-5 days to alleviate respiratory distress.

RESULTS

The case study report provides valuable information about the incidence and hospitalization rates of acute bronchiolitis in children aged 0-2 years over the years 2016, 2019, and 2022. Here are some key points and observations based on the data presented:

Table1 Incidence of Acute Bronchiolitis:

Year	Total Children	Children with Bronchiolitis
2016	258	108
2019	260	37
2022	241	31
Total	759	176

Overall, among 759 children over the study period, 176 suffered from bronchiolitis.

Table 2: Hospitalization Rates by Year

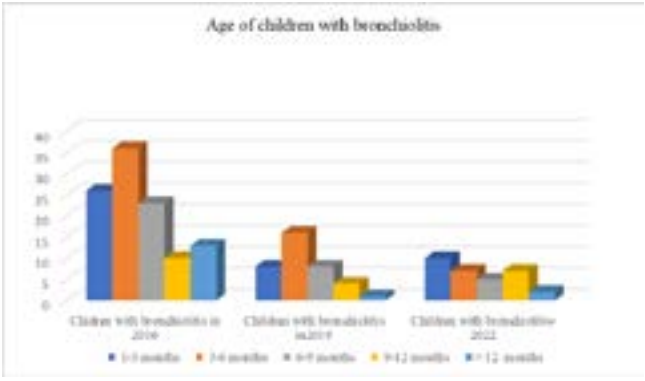
Year	Total Children	Children with Bronchiolitis	Hospitalized	Hospitalization Rate
2016	258	108	9	8.3%
2019	260	37	4	10.8%
2022	241	31	0	0%
Total	759	176	13	7.4%

The overall hospitalization rate for all three years combined was 7.4%.

Gender Differences:

There were no significant gender differences in the presentation of children with bronchiolitis: 90 males (51.1%) and 86 females (48.9%)

Graph1- Age Distribution



In 2016 and 2019, children aged 3-6 months predominated in terms of bronchiolitis presentation.

In 2022, children aged 1-3 months predominated.

The Graph1 shows a significant decrease in the number of children with acute bronchiolitis from 2016 to 2022. Speculation is made about the possible reasons, consider various factors that might have contributed to this trend, such as changes in the virulence of RSV or the impact of protective measures during the COVID-19 pandemic.

Stepwise bronchiolitis treatment with Dexamethasone

2016 - Odds ratio	Odds ratio	95% CI	z statistic	p value
1day treatment	0.0067	0.0004 to 0.1136	3.470	p = 0.0005
2 days treatment	0.056	0.0003 to 0.0973	3.564	P = 0.0004
3 days treatment	0.0121	0.0015 to 0.0951	4.194	p < 0.0001
4 days treatment	0.0049	0.0003 to 0.0948	3.521	p = 0.0004
Without Dexamethasone treatment	0.2500	0.1032 to 0.6053	3.073	p = 0.0021

2019-Odds ratio	Odds ratio	95% CI:	z statistic	p value
1 day treatment	0.0196	0.0010 to 0.3728	2.617	p = 0.0089
2 days treatment	0.0222	0.0012 to 0.3997	2.582	p = 0.0098
3 days treatment	0.0149	0.0007 to 0.3257	2.673	p= 0.0075
Without Dexamethasone treatment	0.3750	0.0903 to 1.5565	1.351	p= 0.1768

2022-Odds ratio	Odds ratio	95% CI	z statistic	p value
1 day treatment	0.0270	0.0015 to 0.4954	2.433	p = 0.0150
2days treatment	0.0244	0.0013 to 0.4532	2.491	p = 0.0127
3 days treatment	0.0256	0.0011 to 0.6130	2.262	p = 0.0237
Without Dexamethasone treatment	0.0909	0.0048 to 1.7278	1.596	p = 0.1105

Calculations of Odds ratio for all groups

2016,2019,2022-Odds ratio	Odds ratio	95% CI	z statistic	p value
1 day treatment	0.0019	0.0001 to 0.0305	4.407	p < 0.0001
2 days treatment	0.0034	0.0002 to 0.0568	3.951	p= 0.0001
3 days treatment	0.0037	0.0002 to 0.0611	3.907	p = 0.0001
4 days treatment	0.0029	0.0002 to 0.0566	3.865	p = 0.0001
Without Dexamethasone treatment	0.2439	0.1174 to 0.5068	3.782	p = 0.0002

The results derived from odds ratio calculations, with a significance level of $p<0.05$ across the three examined groups, underscore the significant impact of treatment interventions on reducing hospitalization rates among children aged 0-2 years with acute bronchiolitis. Specifically, pediatric outpatient clinic treatments involving intramuscular Dexamethasone administered for 1-4 days, coupled with 4-5 days of inhalation with short-acting Salbutamol, demonstrated a substantial reduction in hospitalizations.

Table 3: Atopy in Children with Bronchiolitis

Year	Children with Bronchiolitis	Children with Eczema	% of children with Eczema
2016	108	50	46.3%
2019	37	22	59.5%
2022	31	14	45.2%
Total	176	86	48.9%

These findings emphasize the potential association between eczema and acute bronchiolitis, prompting further investigation into the underlying mechanisms and implications for tailored treatment approaches.

Treatment Implications:

The implications of the combined treatment of Dexamethasone and inhaled Salbutamol are in significant reduction in hospitalization rates (7.4%) which consider the potential benefits for the children, parents, and proper healthcare resource utilization. Tailored Treatment Duration:

The treatment duration for children was intricately tailored based on the severity of the clinical presentation:

1.Very Mild Form (25%)-Treatment: Nebulized Budesonide for 2 weeks and nebulized Salbutamol for 3-4 days.

2.Mild Form (15.9%)-Treatment: One-day intramuscular Dexamethasone

3.Mild-Moderate Form (25%)-Treatment: Two-day regimen.

4.Moderate Form (25%)-Treatment: Three-day plan.

5.Stronger Moderate Form (4.54%)-Treatment: Four-day course.

DISCUSSION

Acute bronchiolitis, primarily caused by viral infections, especially Respiratory Syncytial Virus (RSV), affects infants and young children aged 0-2 years. [1][2][7] The spectrum of clinical manifestations varies from mild to severe, often necessitating hospitalization in rare cases. [12] Despite being mostly mild or moderate, a substantial number of children are admitted to hospitals, influenced not only by disease severity but also by doctor's concerns, parental anxiety, and logistical issues. The lack of a standardized treatment approach complicates the management of bronchiolitis in pediatric care settings.[3]

Treatment approaches vary globally, with contentious findings in research. Some studies suggest preventive effects of systemic corticosteroids on hospitalization

rates, while others explore the efficacy of epinephrine and systemic dexamethasone. Discrepancies in guidelines from entities like the American Academy of Pediatrics (AAP) and the UK National Institute for Health and Care Excellence (NICE) contribute to confusion regarding optimal treatment.[18][19][20][21]

In contrast, the presented research advocates for a combined treatment involving inhaled salbutamol and systemic dexamethasone, demonstrating substantial efficacy in reducing hospitalizations. The personalized regimen, considering the severity of the disease, highlights a notable decrease (7.4%) in hospitalization rates for mild and moderate bronchiolitis cases.

Clinical symptoms, such as cough and tachypnea, vary in severity, with auscultation findings ranging from poor in mild forms to diffuse inspiratory crackles in moderate and severe forms.[10] Hospitalization reasons extend beyond disease severity, encompassing doctor and parental concerns, equipment availability, and fear of worsening.[11] Primary pediatric care settings offer psychosocial and economic benefits, but the lack of standardized referral criteria adds to the confusion in evidence-based management.[13]

The research introduces a compelling approach, emphasizing the importance of tailoring treatment to each child's needs based on disease severity. This personalized strategy, more prevalent in highly developed countries, correlates with reduced hospital admission rates. Notably, the study suggests a potential future avenue with antiviral therapy for RSV bronchiolitis.[12]

Despite global treatment disparities, the research sheds light on a promising direction by proposing a personalized regimen involving reduced doses of systemic dexamethasone and inhaled salbutamol. The need for a unified treatment approach remains crucial, and the study's findings contribute to changing attitudes toward the management of bronchiolitis in primary pediatric care.

In conclusion, the research underscores the complexity of treating acute bronchiolitis, emphasizing the necessity for personalized treatment strategies, effective communication, and continued research to enhance the care of affected children.

CONCLUSION

My study research provides valuable insights into the management of acute bronchiolitis in children aged 0-2 years, emphasizing the effectiveness of a stepped approach treatment in Primary care settings. The summary of key points of my research: My study demonstrates effectiveness of stepped approach treatment for children with mild and moderate form of bronchiolitis. This treatment protocol resulted in a significant reduction in hospitalization rated p=0.0004)

The rate of hospitalization for children aged 0-2 years with acute bronchiolitis is 7.4% based on retrospectively collected data. The treatment of children in Primary Pediatric Care with mild and moderate forms of bronchiolitis, can be treated effectively with a stepped approach and combined therapy. There are mere no harmful consequences for the children's s health, emphasizing the safety of this approach. Daily monitoring and continuous communication with parents are crucial, particularly during the intense period of the fourth and fifth days from the onset of the disease. Emphasis on proactive measures aligns with the understanding that close observation and timely intervention can significantly impact the course of the illness. Personalized treatment approach is also important. Tailoring treatment to each child's needs, considering disease severity, and accounting for health system development is essential. An individualized approach with a focus on commitment, predictive ability, and effective communication with parents is emphasized. My research underscores the substantial burden of bronchiolitis on health care systems. The study supports the need for nuanced, personalized treatment approaches to optimize outcome and reduce hospital admissions. Paradigm shift in Primary Pediatric Care with the stepped approach, individualized treatment plan presented in my research and continuous everyday monitoring for 3-4 days, which can contribute to reducing hospital admissions.

The divergence in global practices highlights the need for tailored treatments aligned with individual needs and the evolution of healthcare systems. My research contributes valuable evidence to the evolving landscape of bronchial management, particularly in primary care settings.

My study lays the groundwork for future research, exploring effective strategies to minimize hospital admissions for bronchiolitis in pediatric care. This research provides a comprehensive overview of the benefits of a stepped approach with the combined therapy of bronchiolitis management, emphasizing personalized treatment in Primary Pediatric Care. The insights gained

from my study have implications for redefining treatment approaches and optimizing outcome for children with this common respiratory condition.

Limitations and Potential Bias: The study is based on retrospective data collected from a single Primary Health Care facility in Veles, North Macedonia. This limits the generalizability of the findings to a broader population, as healthcare practices, patient demographics, and access to care may differ across regions. The analysis is conducted over three specific years (2016, 2019, and 2022). This limited time span might not capture potential variations in bronchiolitis cases and treatment outcomes over an extended period. The sample size, particularly in 2022 with no hospitalizations, is relatively small. This might impact the statistical power of the study and the ability to detect significant differences. Variations in record-keeping practices and missing data could introduce biases. The study does not elaborate on the criteria for selecting the children included in the analysis. The study does not account for external factors that may influence bronchiolitis, such as environmental conditions, circulating viruses, or changes in healthcare policies over the years.

Ethical considerations: The study clarifies the measures taken to ensure patient privacy and confidentiality. This includes the handling and storage of patient data to prevent unauthorized access and potential breaches.

LITERATURE

1. Erickson EN, Bhakta RT, Mendez MD. Pediatric Bronchiolitis. [Updated 2023 Jun 26]. In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519506/
2. Carlone G, Graziano G, Trotta D, Cafagno C, Aricò MO, Campodipietro G, Marabini C, Lizzi M, Fornaro M, Caselli D, Valletta E, Aricò M. Bronchiolitis 2021-2022 epidemic: multicentric analysis of the characteristics and treatment approach in 214 children from different areas in Italy. Eur J Pediatr. 2023 Apr;182(4):1921-1927. doi: 10.1007/s00431-023-04853-0. Epub 2023 Feb 20. PMID: 36807514; PMCID: PMC9943040.
3. Manti S, Staiano A, Orfeo L, Midulla F, Marseglia GL, Ghizzi C, Zampogna S, Carnielli VP, Favilli S, Ruggieri M, Perri D, Di Mauro G, Gattinara GC, D'Avino A, Becherucci P, Prete A, Zampino G, Lanari M, Biban P, Manzoni P, Esposito S, Corsello G, Baraldi E. UPDATE - 2022 Italian guidelines on the management of bronchiolitis in infants. Ital J Pediatr. 2023 Feb 10;49(1):19. doi: 10.1186/s13052-022-01392-6. PMID: 36765418; PMCID: PMC9912214.
4. Pedro A Piedra, MD, Ann R Stark, MD Section Editor: Morven S Edwards, MD Deputy Editor: Mary M Torchia, MD: Patient education: Bronchiolitis (and RSV) in infants and children (Beyond the Basics)
5. Baldassarre ME, Loconsole D, Centrone F, Caselli D, Martire B, Quartulli L, Acquafredda A, D'Amato G, Maffei G, Latorre G, Riganti A, Di Noia M, Chironna M, Laforgia N. Hospitalization for bronchiolitis in children aged ≤ 1year, Southern Italy, year 2021: need for new preventive strategies? Ital J Pediatr. 2023 Jun 6;49(1):66. doi: 10.1186/s13052-023-01455-2. PMID: 37280662; PMCID: PMC10243233.
6. Fujiogi M, Goto T, Yasunaga H, et al. Trends in Bronchiolitis Hospitalizations in the United States: 2000-2016. Pediatrics. 2019 Dec;144(6):e20192614. DOI: 10.1542/peds.2019-2614. PMID: 31699829; PMCID: PMC6889950
7. Biggs HM, Simões EAF, Abu Khader I, Thompson MG, Gordon A, Hunt DR, DeGroote NP, Porter RM, Bino S, Marar BI, Gresh L, de Jesus-Cornejo J, Langley G, Thornburg NJ, Peret TCT, Whitaker B, Zhang Y, Wang L, Patel MC, McMorrow M, Campbell W, Hasibra I, Duka E, Al-Gazo M, Kubale J, Sanchez F, Lucero MG, Tallo VL, Azziz-Baumgartner E, Simaku A, Gerber SI; IRIS Network. Respiratory Syncytial Virus Infection Among Hospitalized Infants in Four Middle-Income Countries. J Pediatric Infect Dis Soc. 2023 Jul 31;12(7):394-405. doi: 10.1093/jpids/piad042. PMID: 37313727.
8. Young, M., Smitherman, L. Socioeconomic Impact of RSV Hospitalization. Infect Dis Ther 10 (Suppl 1), 35–45 (2021). https://doi.org/10.1007/s40121-020-00390-7
9. Eber E. Treatment of acute viral bronchiolitis. Open Microbiol J. 2011;5:159-64. doi: 10.2174/1874285801105010159. Epub 2011 Dec 30. PMID: 22262989; PMCID: PMC3258671
10. Havdal LB, Nakstad B, Fjærli HO, Ness C, Inchley C. Viral lower respiratory tract infections-strict admission guidelines for young children can safely reduce admissions. Eur J Pediatr. 2021 Aug;180(8):2473-2483. doi: 10.1007/s00431-021-04057-4. Epub 2021 Apr 8. Erratum in: Eur J Pediatr. 2023 Mar;182(3):1435. PMID: 33834273; PMCID: PMC8285352.
11. A Systematic Review of Clinical Practice Guidelines for the Diagnosis and Management of Bronchiolitis Amir Kirolos, 1, Sara Manti, 6 Rachel Blacow, 1 Gabriel

Tse, 1 Thomas Wilson, 1 Martin Lister, 4 Steve Cunningham, 2,3 Alasdair Campbell, 5 Harish Nair, 1, Rachel M Reeves, 1 Ricardo M Fernandes, 7 and Harry Campbell, 1, for the RESCEU Investigatorsa 1 Usher Institute of Population Health Sciences and Informatics, 2 Department of Child Life and Health, and 3 Centre for Inflammation Research, University of Edinburgh, and 4 Royal Hospital for Sick Children, Edinburgh, and 5 Alder Hey Children's Hospital, Liverpool, United Kingdom; 6 Department of Pediatrics, University of Messina, Sicily, Italy; and 7 Clinical Pharmacology and Therapeutics, Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon

12. Petrarca L, Jacinto T, Nenna R. The treatment of acute bronchiolitis: past, present and future. Breathe (Sheff). 2017 Mar;13(1):e24-e26. doi: 10.1183/20734735.000717. PMID: 29158779; PMCID: PMC5685214
13. Carlos Ochoa Sangrador, Javier González de Dios & Research Group of the aBREVIADo Project (Bronchiolitis–Study of Variability, Adequacy, and Adherence) European Journal of Pediatrics volume 171, pages1109–1119 (2012) Management of acute bronchiolitis in emergency wards in Spain: variability and appropriateness analysis (aBREVIADo Project)
14. Nordal EB, Granslo HN, Esaiassen E, Leknessund CBB, Forsdahl BA. Bronchiolitis should not be treated with glucocorticoids or antibiotics. Tidsskr Nor Laegeforen. 2021 Dec 30;141(2). English, Norwegian. doi: 10.4045/tidsskr.21.0862. PMID: 35107946.
15. Elliott SA, Gaudet LA, Fernandes RM, et al. Comparative Efficacy of Bronchiolitis Interventions in Acute Care: A Network Meta-analysis. Pediatrics. 2021 May;147(5):e2020040816. DOI: 10.1542/peds.2020-040816. PMID: 33893229.
16. Management of acute bronchiolitis: can evidence based guidelines alter clinical practice? J Barben,1 C E Kuehni,2 D Trachsel,3 J Hammer,3 on behalf of the Swiss Paediatric Respiratory Research Group
17. Carlone G, Graziano G, Trotta D, Cafagno C, Aricò MO, Campodipietro G, Marabini C, Lizzi M, Fornaro M, Caselli D, Valletta E, Aricò M. Bronchiolitis 2021-2022 epidemic: multicentric analysis of the characteristics and treatment approach in 214 children from different areas in Italy. Eur J Pediatr. 2023 Apr;182(4):1921-1927. doi: 10.1007/s00431-023-04853-0. Epub 2023 Feb 20. PMID: 36807514; PMCID: PMC9943040.
18. BMJ Open 2021;11:e043956. doi: 10.1136/bmjopen-2020-043956 Garrison MM, Christakis DA, Harvey E, Cummings P, Davis RL. Systemic corticosteroids in infant bronchiolitis: A meta-analysis. Pediatrics. 2000 Apr;105(4):E44. doi: 10.1542/peds.105.4.e44. PMID: 10742365.
19. Kua KP, Lee SWH. Systematic Review and Meta-Analysis of the Efficacy and Safety of Combined Epinephrine and Corticosteroid Therapy for Acute Bronchiolitis in Infants. Front Pharmacol. 2017 Jun 22;8:396. doi: 10.3389/fphar.2017.00396. PMID: 28690542; PMCID: PMC5479924.
20. Bronchiolitis in children: diagnosis and management. London: National Institute for Health and Care Excellence (NICE); 2021 Aug 9. (NICE Guideline, No. 9.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK573086/
21. Walsh P, Rothenberg SJ. American Academy of Pediatrics 2014 bronchiolitis guidelines: bonfire of the evidence. West J Emerg Med. 2015 Jan;16(1):85-8. doi: 10.5811/westjem.2015.1.24930. Epub 2015 Jan 12. PMID: 25671015; PMCID: PMC4307733.
22. Fernandes RM, Bialy LM, Vandermeer B, Tjosvold L, Plint AC, Patel H, Johnson DW, Klassen TP, Hartling L. Glucocorticoids for acute viral bronchiolitis in infants and young children. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD004878. DOI: 10.1002/14651858.CD004878.pub4
23. Hartling L, Fernandes R M, Bialy L, Milne A, Johnson D, Plint A et al. Steroids and bronchodilators for acute bronchiolitis in the first two years of life: systematic review and meta-analysis BMJ 2011; 342:d1714 doi:10.1136/bmj.d1714
24. Schuh, S; Babl, FE; Dalziel, SR; Freedman, SB; Macias, CG; Stephens, D; et al. (2017). Practice Variation in Acute Bronchiolitis: A Pediatric Emergency Research Networks Study.. University of Leicester. Journal contribution. https://hdl.handle.net/2381/43850
25. Porcaro F, Cutrera R, Vittucci AC, Villani A. Bronchiolitis guidelines: what about the Italian situation in a primary care setting? Ital J Pediatr. 2023 Sep 19;49(1):123. doi: 10.1186/s13052-023-01527-3. PMID: 37726761; PMCID: PMC10510229.
26. Wang G, Han D, Jiang Z, et al Association between early bronchiolitis and the development of childhood asthma:a meta-analysis BMJ Open 2021;11:e043956. doi : 10.1136/bmjopen-2020-043956

Profesional paper

OBESITY AS A HEALTH-THREATENING DISEASE - RESULTS FROM THE CENTER FOR OBESITY MANAGEMENT

I. Ahmeti[1,2], K. Koleci[3], L. Nuredini[4], M. Konstantinovska[5], M. Petrushevska[6]

[1]University St Cyril and Methodius, Medical Faculty Skopje.
[2]University Clinic of Endocrinology, Skopje
[3]Medical Center Debar
[4]Medical Center Gostivar
[5]Medical Center Ohrid
[6]Resident at the University clinic of Endocrinology, Skopje

Medicus 2024, Vol. 29 (2): 146-148

ABSTRACT

Obesity is a chronic metabolic disease associated with many comorbidities. Material and methods. All obese patients at the Center for obesity management (COM) and the diabetes center were analyzed. Diagnosis is made through measurement with the InBody 270, body composition machine, while body mass index (BMI) values are classified into 3 classes of obesity according the WHO obesity classification. Results. Out of 151 obese patients, 113 (74.8%) were women, while 48 (23.2%) were men. The average age was 43.6 years. The average weight was 119kg (min 78kg, max 177kg), while the average BMI was 42.7kg/m2. The obese were classified according to classes, also there: class 1, 16 (10.6%), class 2, 48 (31.8). %) and class 3, 87 (57.6%) patients. Initial therapy in 77 patients (51%) has lifestyle changes. The average weight reduction for 6 months was 2.5 kg. In the group of obese patients treated with plus metformin, which were 41 (27.15%), the reduction in body weight was 5.6 kg, while in the group of obese patients where GLP-1 RA was included in the therapy (liraglutide 3 mg, semaglutide 1 mg injection or tbl. semaglutide 7 or 14 mg) that were 31 patients (20.53%) the average weight loss was 9.4 kg. Conclusion. Systematic approach of obesity at the COM, appropriate management and current treatment are successful in the reduction of body weight.

Key words; obesity, COM, treatment

INTRODUCTION

Obesity is a chronic metabolic disease that is characterized by excesive adiposity in the body and organs and is associated with many disorders in the body that pose a health risk (1). The accumulation of fat in the body and the increase in body weight is a consequence of the imbalance between the excessive consumption of food substances (anabolism), the lack of energy expenditure (catabolism) and associated factors (genetic, biological, psycho-social, drugs, trauma and the factors of environment). Overweight as defined by a BMI ≥ 25 kg/m² - 30 kg/m² [2] is present in more than 50% of the European and American adult population; The prevalence of obesity (BMI ≥ 30 kg/m²) is around 20-30% in most (post) industrial countries and is increasing especially in recent years for a significant part of the population of developing countries (3). The diagnosis of overweight and obesity is usually made through the body mass index (BMI), and according to the values, overweight or "pre-obesity" is classified when the BMI is 25.0 - 30 kg/m², while obesity is classified into three classes: Class 1: BMI of 30.00 kg/m2 - 34.99 kg/m2, Class 2: BMI of 35.00 kg/m2 - 39.99 kg/m2, Class 3: BMI of 40.00 kg/m2 and above (4). Excess adiposity increases the risk of cardiovascular disease, type 2 diabetes, some types of cancer, and early mortality (5). Obesity management often involves a multidisciplinary approach by well-

educated people and not always the same approach applies to every patient. An obesity management center composed of a multidisciplinary team enables an easier approach and gives better results compared to working in day clinics. This approach implies several interventions: switching to healthier ways of eating reduced calorie diet, increased physical activity, behavioral treatment, pharmacologic treatment and bariatric surgery. The Center for Obesity Management (COM) offers complex lifestyle intervention tailored to each patient, including individualized nutrition counseling, cognitive-behavioral training, physical therapy, supervised exercise training, psychological assessment and counseling, pharmacotherapy and bariatric surgery within an established obesity management framework and collaborative network as needed.

PATIENTS AND METHODS

It is a one-year retrospective study conducted at the Center for Obesity Management (COM) at the endocrinology clinic in Skopje. The data recorded in the "Moj Termin" system and in the device for measuring fat tissue and body weight - " InBody 270 ". The data from the patients were statistically processed and obesity was classified into three classes according the WHO obesity classification, After the group classification obesity patients were advised for lifestyle intervention and appropriate treatment. The results were compared with the second visit made after 6 months. Obese patients who were treated with GLP-1RA therapy were not processed unless they had lost at least 5 kg in 15 weeks.

RESULTS

A total of 151 obese patients with and without comorbidities were analyzed. By gender, there were 113 (74.8%) female and 48 (23.2%) male. 132 (79.8%) patients were controlled in the COM and 29 (19.2%) in the diabetes center. The average age was 43.6 years. The average weight was 119kg (min 78kg, max 177kg), while the average BMI was 42.7kg/m2. The obese were classified according to classes, as following: class 1, 16 (10.6%), class 2, 48 (31.8 %) and class 3, 87 (57.6%) patients. The initial therapy in 77 patients (51%) was lifestyle change. The average weight reduction for 6 months was 2.5 kg. In the group of obese patients treated with plus metformin, which were 41 (27.15%), the drop in body weight was 5.6 kg, while in the group of obese patients where GLP-1 RA was included in the therapy (liraglutide 3 mg, semaglutide 1 mg injection) or tbl semaglutide 7 or 14 mg) that were 31 patients (20.53%) the average weight loss was 9.4 kg. In the group treated with GLP-1 RA, the average BMI was 47 kg/m2 at the beginning and 43.1 kg/m2 after 6 months (table 1).

Table 1. Parameters of obesity classified into three classes

Visit 1	class 1	class 2	class 3
No (%)	16 (10.6)	48 (31.8)	87 (57.6)
Age	37.3	41.5	46
sex f/m	11/5	35/9	64/23
Body weight avg	111.2	118.6	128.8
BMI	40.8	42.8	47
Visit V2	class 1	class 2	class 3
No (%)	23 (15.2)	51 (33.8)	77 (51)
Body weight avg	108.68	113.04	119.4
BMI	39.83	41.6	43.1

Patients who were treated at the center for diabetes and who were obese had an average weight of 126.4 kg, while after 6 months it was 120.2 kg ($p<0.05$). The average BMI at the beginning was 46.9 kg/m2, while after 6 months it was 44.6 kg/m2 (figure 1).

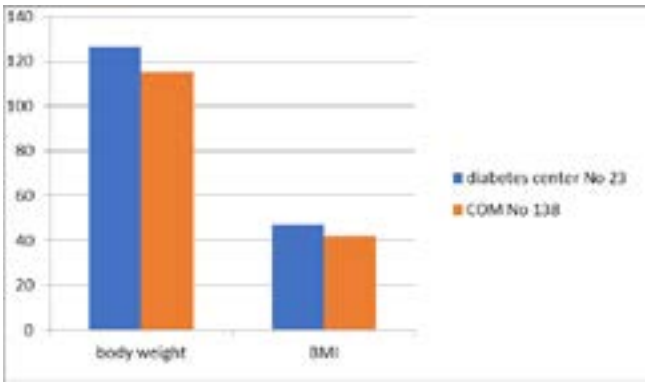


Figure 1. Obesity in the center for diabetes

Patients treated at the center for obesity management (COM) at the beginning had 115.4 kg and after 6 months 110.8 kg (p, 0.05). BMI at the beginning was 42 kg/m2 and after 6 months 40.4 kg/m2 (figure 2).

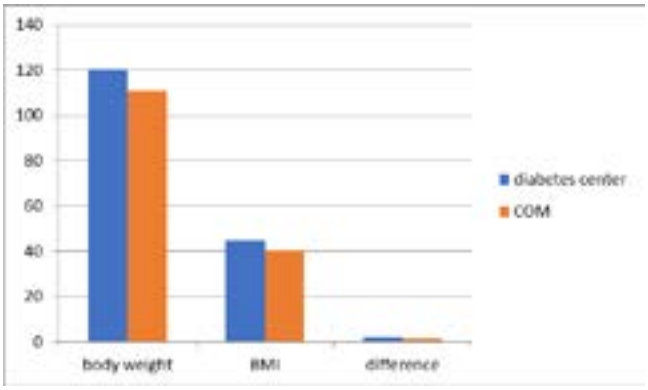


Figure 2. Obesity in COM

Obese patients treated at the COM with liraglutide 3 mg and obese patients with diabetes treated at the diabetes center (semaglutide 1 mg) were divided into groups according to obesity class (fig 3).

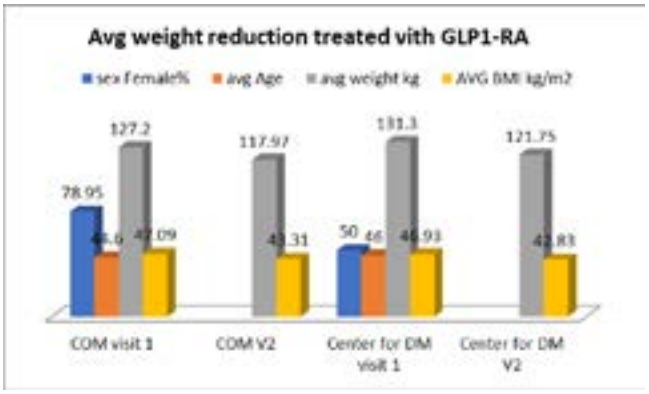


Fig 3. Treatment of obesity with GLP 1 RA.

DISCUSSION

Although obesity in the contemporary world is treated as a chronic disease that is associated with many comorbidities, in developing countries this disease is still neglected both by the population and by medical personnel. The opening of centers for obesity management (COM) aims not only to raise collective awareness, but also with a structured and multidisciplinary approach to promote the need for control for obese patients. In our study, it is observed that the patients who visited the COM and the center for obesity were extremely obese (average BMI 42 kg/m2 – class 3 obesity). If we compare the obese patients who visited the COM with those who visited the diabetes center (patients with T2DM and obesity) and were checked by the same professional team, no statistical difference is observed in both groups (figure 3).

Higher average weight loss is observed in patients with class 3 obesity due to the early initiation of drug therapy compared to class 1 obesity without comorbidities where treatment is initiated with lifestyle changes. ($p<0.05$). Treatment of class 2 and 3 obesity with GLP1-RA (liraglutide 3mg) in COM and obesity associated with DM type 2 in the diabetes center (semaglutide) did not have a statistical impact on the decrease in body weight regardless of the center where the treatment was done. The difference in gender means that the female gender has more easily sought consultation in COM for obesity treatment. The structured obesity approach is effective especially in younger and motivated people (6). The long-term effects of changing the lifestyle and not returning the reduced weight, the involvement of the nutritionist, the psychologist, are a guarantee of the effective reduction of the body weight (7).

REFERENCES

1. Frühbeck G, Busetto L, Dicker D, Yumuk V, Goossens GH, Hebebrand J, Halford JGC, Farpour-Lambert NJ, Blaak EE, Woodward E, Toplak H. The ABCD of Obesity: An EASO Position Statement on a Diagnostic Term with Clinical and Scientific Implications. Obes Facts. 2019;12(2):131-136. doi: 10.1159/000497124. Epub 2019 Mar 7. PMID: 30844811; PMCID: PMC6547280.
2. Sharma A, Campell-Sherer DL. Redefining obesity: beyond the numbers. Obesity (Silver Spring) 2017;25:660–661. [PubMed] [Google Scholar]
3. Nuttall FQ. Body mass index. Obesity, BMI, and health: a critical review. Nutr Today. 2015;50:117–128.
4. Hebebrand J, Holm JC, Woodward E, Baker JL, Blaak E, Durrer Schutz D, Farpour-Lambert NJ, Frühbeck G, Halford JGC, Lissner L, Micic D, Mullerova D, Roman G, Schindler K, Toplak H, Visscher TLS, Yumuk V. A Proposal of the European Association for the Study of Obesity to Improve the ICD-11 Diagnostic Criteria for Obesity Based on the Three Dimensions Etiology, Degree of Adiposity and Health Risk. Obes Facts. 2017;10(4):284-307. doi: 10.1159/000479208. Epub 2017 Jul 22. PMID: 28738325; PMCID: PMC5644953.
5. Srikanthan P., Horwich T.B., Tseng C.H. Relation of muscle mass and fat mass to cardiovascular disease mortality. Am. J. Cardiol. 2016;117:1355–1360 doi: 10.1016/j. amjcard.2016.01.033.
6. Erica Bessell MND, Tania P. Markovic PhD, Nicholas R. Fuller PhD. How to provide a structured clinical assessment of a patient with overweight or obesity. https://doi.org/10.1111/dom.14230
7. Elmaleh-Sachs A, Schwartz JL, Bramante CT, Nicklas JM, Gudzune KA, Jay M. Obesity Management in Adults: A Review. JAMA. 2023;330(20):2000–2015. doi:10.1001/jama.2023.19897

Profesional paper

HOMOCYSTEINE LEVEL AND DURATION OF DIABETES

Mimoza Bafqari-Bakiji[1,2], Luzana Shabani[2], Vjollca Skenderi[1], Sandra Kosteska[3]

[1]Clinical Hospital of Tetovo
[2]Universitety of Tetovo
[3]Institute for Accreditation of the Republic of North Macedonia

*E-mail of corresponding author: mimoza.bafqari@unite.edu.mk

Medicus 2024, Vol. 29 (2): 149-152

ABSTRACT

Homocysteine is a sulfur-containing amino acid derived from methionine after demethylation via two intermediates, S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH). The deleterious effects of homocysteine on endothelial function are well known, and these effects are caused by the elevated plasma homocysteine levels that develop through a mechanism involving oxidative stress. It was found that the longer the duration of type 2 diabetes mellitus, the higher the plasma Hcy levels. Many authors have reported a significant association of plasma homocysteine levels, duration and complications of type 2 diabetes mellitus. Based on these data, the aim of the study is to analyze the influence of the duration of diabetes on serum homocysteine levels in diabetic patients. A total of 100 patients were included in the study, 50 diabetic patients treated with oral hypoglycemics from the age of 38-77 and 50 diabetic patients treated with insulin from the age of 39-79. Serum's homocysteine concentration was measured using the competitive immunological method in the Immulite 2000 apparatus. Our results show that as the duration of diabetes increases, the level of serum Hcy concentration increases in diabetic patients treated with oral hypoglycemics and those with insulin. Hyperhomocysteinemia causes vascular damage and the fact that hyperhomocysteinemia can be treated with folic acid, it is preferable for diabetic patients to monitor their Hcy level and take folic acid as a supplement.

Key words: diabetes, homocysteine, oral hypoglycemics, insulin.

INTRODUCTION

Homocysteine is a sulfur-containing amino acid derived from methionine after demethylation via two intermediates, S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH). Hcy is metabolized via two pathways: remethylation or transsulfuration. In the remethylation pathway, Hcy is first transformed to methionine by adding a methyl group from 5-methyltetrahydrofolate or betaine, while through the transsulfuration pathway, Hcy is transformed to cystathion by cystathion β-synthase (CBS) and finally to cysteine, which as cofactor is vitamin B6 (Zhou et al., 2014).

Regarding homocysteine reference values, the literature suggests a reference range of 5-15 μmol/L for adult men and women. Men tend to have higher levels than women and postmenopausal women also tend to have higher levels than premenopausal women (Ueland et al., 1993).

The deleterious effects of homocysteine on endothelial function are well known, and these effects are caused by elevated plasma homocysteine levels that develop through a mechanism involving oxidative stress (Starkebaum & Harlan, 1986). Homocysteine is involved in redox reactions and causes oxidative stress, it is

also involved in vascular diseases through endotoxic and pro-proliferative effects, which can interfere with glutathione synthesis and methylation reactions. Homocysteine levels in plasma are increased in patients with diabetes, especially in those with diabetes mellitus type 2 as well as in prediabetic individuals with insulin resistance, which is a risk factor for diabetic retinopathy and cardiovascular diseases for these patients (Lei et al., 2018). Folic acid and vitamin B12 play an important role in the metabolism of homocysteine, which was first isolated from bladder stones in 1931. Subsequent studies found that elevated serum Hcy was an independent risk factor for cardiovascular and cerebrovascular disease. In recent years, it has been reported that the serum Hcy level is associated with increased renal function impairment, and with the development of renal impairment serum homocysteine also increases (Ye et al., 2020).

Certain genotypic forms of methyltetrahydrofolate reductase (MTHFR) contribute to the susceptibility of type 2 diabetes mellitus and support the hypothesis that high homocysteine levels are responsible for the increased risk of type 2 diabetes mellitus. Hyperhomocysteinemia may be due to the presence of a heat-labile isoform of this key enzyme. A single base pair substitution (677C>T) in the human MTHFR gene predicts the phenotypic expression of a heat-sensitive variant with reduced enzymatic activity (Huang et al., 2013). It was found that the longer the duration of type 2 diabetes mellitus, the higher the plasma Hcy levels. Many authors have reported a significant association of plasma homocysteine levels, duration and complications of diabetes mellitus type 2 (Noor et al., 2021). Based on these data, the aim of the study is to analyze the influence of the duration of diabetes on serum homocysteine levels in diabetic patients.

MATERIAL AND METHODS

A total of 100 patients were included in this study, 50 diabetic patients treated with oral hypoglycemics (18 men and 32 women), from the age of 38-77 years and 50 diabetic patients treated with insulin (25 men and 25 women), from the age 39-79 years old. The patients included in the study are outpatients who were presented for a routine check-up at the Clinical Hospital of Tetova. Blood sample was taken in the morning, in a sitting position, after 15 minutes of rest. The concentration of homocysteine in the serum was measured using the competitive immunological method in the Immulite 2000 apparatus, which is an automated analyzer that uses chemiluminescence technology, in the biochemical diagnostic laboratory of the Clinical Hospital of Tetovo. The Imulite 2000 device can measure homocysteine level from 2 to 50 µmol/L.

The statistical processing of the data was carried out using the statistical program SPSS version 26. The numerical series were analyzed using measures of central tendency such as average, minimum, and maximum values, as well as distribution measures, and standard deviation. The value of p>0,05 was taken as statistically reliable.

RESULTS

In this study the total number of female patients is 57 (57%), while 43 (43%) male patients. The female gender constitutes the majority of patients diagnosed with diabetes included in this study.

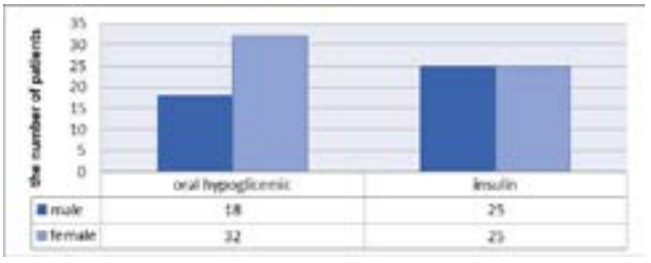


Figure 1. Schematic representation of the patients included in the study

The distribution of the patients included in the study is shown in Figure 1. From this figure, we note that from the total number of patients, 50% of them were treated with oral hypoglycemics, and 50% were treated with insulin.

The comparison of the duration of diabetes and the level of homocysteine in diabetic patients treated with oral hypoglycemic is presented in Table 1, where patients were divided into three groups based on the duration of diabetes, Group I - 0 to 5 years, Group II - 5 to 10 years and Group III - > 10 years.

Table 1. Duration of diabetes and homocysteine level in diabetic patients treated with oral hypoglycemic

	Oral hypoglycemic						
	Homocysteine level (µmol/L)			Duration of diabet (years)			
	Min	Max	xβ±SD	Min	Max	xβ±SD	N
Gr.I	10.20	40.0	18.933±5.619	1	5	3.285±1.487	28
Gr.II	10.27	38.20	20.688±6.993	6	10	7.611±1.577	18
Gr.III	17.83	34.10	25.157±6.841	11	18	13.750±3.403	4

Table 1 shows that the level of homocysteine in patients

treated with oral hypoglycemic agents is higher in group III (duration of diabetes >10 years), with an average homocysteine value of 25.157±6.841, compared to group II (20.688±6.993) and group I (20.688±6.993).

The average duration of diabetes in the first group is 3.285±1.487, with a total number of 28 patients, the average duration in the second group is 7.611±1.577 with N=18, while in the third group, it is 13.750±3.403 with N =4.

Table 2. Duration of diabetes and homocysteine level in diabetic patients treated with insulin

	Homocysteine level (µmol/L)			Duration of diabet (years)			N
	Min	Max	xβ±SD	Min	Max	xβ±SD	
Gr.I	9.80	25.30	16.584±3.807	1	5	2.85±1.460	20
Gr.II	13.00	30.40	20.144±4.800	6	9	7.06±1.099	15
Gr.III	10.80	32.10	20.886±6.159	11	30	17.133±4.940	15

The results presented in Table 2 show that the level of homocysteine in patients treated with insulin is higher in patients of the II and III groups (20.144±4.800 and 20.886±6.159) compared to the first group (16.584±3.807). A large number of patients was tested in the first group (N=20) with an average duration of diabetes of 2.85±1.460. The average duration of diabetes in group II (5-10 years) is 7.06±1.099, while in group III (>10 years) it is 17.133±4.940.

Table 3. Comparison of homocysteine level in patients treated with oral hypoglycemics and those with insulin

	Homocysteine level(µmol/L)		P
	Oral hypoglycemic ($\bar{x}$±SD)	Insulin ($\bar{x}$±SD)	
Gr.I	18.933±5.619	16.584±3.807	0.112
Gr.II	20.688±6.993	20.144±4.800	0.800
Gr.III	25.157±6.841	20.886±6.159	0.243

After the statistical processing of the data, where for each group of diabetic patients such as those treated with oral hypoglycemics, as well as those treated with insulin, the level of homocysteine is above the reference values (table 3). This table also shows that there are no significant differences in the level of homocysteine in any of the groups treated with oral hypoglycemic vs. insulin and the value of p>0,05.

Table 4 Intergroup comparison of the level of homocysteine in patients treated with oral hypoglycemic vs. insulin

	Homocysteine level (µmol/L) xβ±SD (oral hypoglicemic)	P	Homocysteine level (µmol/L) xβ±SD (insulin)	P
Gr.I vs. Gr.II	18.933±5.619vs. 20.688±6.993	0.352	16.584±3.807 vs. 20.144±4.800	0.019
Gr.I vs. Gr.III	18.933±5.619vs. 25.157±6.841	0.052	16.584±3.807 vs. 20.886±6.159	0.015
Gr.II vs. Gr.III	20.688±6.993vs. 25.157±6.841	0.259	20.144±4.800 vs.20.886±6.159	0.715

Table 4 shows that the level of Hcy between groups I and III in patients treated with oral hypoglicemic has a difference in average values but is not statistically significant (p=0.052). Statistically significant differences were not observed in the comparisons of Gr. I vs. Gr.II and Gr. II vs. Gr. III. Unlike the groups treated with oral hypoglicemic, in the patients treated with insulin, in the intergroup comparison, a statistically significant difference was observed between Gr. I vs. Gr.II with p=0.019 and between Gr. I vs. Gr.III with a value of p=0.015.

DISCUSSION

Many studies have reported that medication treatment in diabetic patients can have a negative effect on homocysteine levels. Certain medications are believed to alter Hcy concentration by affecting folate or vit levels. B12 and B6 or affecting kidney function (Muzurovic et al. 2020). Studies conducted by Shaikh et al. (2012) show that Hcy levels increase in diabetic patients treated with both insulin and oral hypoglycemics, data which coincide with the findings of the current study (Shaikh et al., 2012). Hcy and diabetes have been reported to have a synergistic vascular deleterious effect involving atherothrombotic changes throughout the arterial vascular system and microvascular changes such as nephropathy, retinopathy, and neuropathy (Becker et al., 2003).

In our study the Hcy level is affected by the duration of diabetes. Homocysteine was found to be higher in patients with diabetes duration over 10 years, with an average value of 25.157±6.841 in group I treated with oral hypoglycemic and 20.886±6.159 in group I treated with insulin. The Hcy level between the three groups does not result in a statistically significant difference in group I treated with oral hypoglycemic, while a significant difference was found between the three groups in patients treated with insulin (GI vs. G II; p= 0.019; GI vs. G III ; p=0.015).

The study conducted by Zulfania et al (2018), showed a

significant positive correlation between the duration of diabetes and Hcy levels (Zulfania et al., 2018). Similar results were also obtained in a study carried out by Sonkar et al, in which a positive correlation was found between the Hcy level and the duration and complications of type 2 diabetes (Sonkar et al., 2014). Mundu et al report that the association between the duration of diabetes and serum homocysteine levels is statistically significant (p = 0.028) (Mundu et al., 2017).

CONCLUSION

From this study, we can conclude that the level of Hcy in patients treated with oral hypoglycemic and with duration of diabetes over 10 years is higher. Based on the extensive data showing that hyperhomocysteinemia causes vascular damage and the fact that hyperhomocysteinemia can be treated with folic acid, diabetic patients should monitor their Hcy level and take folic acid as a supplement.

REFERENCES

1. Becker, A., Smulders, Y. M., Van Guldener, C., & Stehouwer, C. D. A. (2003). Epidemiology of homocysteine as a risk factor in diabetes. Metabolic syndrome and related disorders, 1(2), 105-120.
2. Huang, T., Ren, J., Huang, J., & Li, D. (2013). Association of homocysteine with type 2 diabetes: a meta-analysis implementing Mendelian randomization approach. BMC Genomics, 14(1). https://doi.org/10.1186/1471-2164-14-867.
3. Lei, X., Zeng, G., Zhang, Y., Li, Q., Zhang, J., Bai, Z., & Yang, K. (2018). Association between homocysteine level and the risk of diabetic retinopathy: a systematic review and meta-analysis. Diabetology & Metabolic Syndrome, 10(1). https://doi.org/10.1186/s13098-018-0362-1.
4. Mundu, P. A., Kumar, B., Mitra, J. K., Kumar, M., & Sinha, R. (2017). Study of assessment of plasma homocysteine level in microvascular complications of type 2 diabetes mellitus. Int J Contemporary Med Res, 4(4), 879-883.
5. Muzurović, E., Kraljević, I., Solak, M., Dragnić, S., & Mikhailidis, D. P. (2021). Homocysteine and diabetes: Role in macrovascular and microvascular complications. Journal of diabetes and its complications, 35(3), 107834. https://doi.org/10.1016/j.jdiacomp.2020.107834
6. Noor, A., Rahman, M. U., Faraz, N., Samin, K., Ullah, H., & Ali, A. (2021). Relationship ofhomocysteine with gender, blood pressure, body mass index, hemoglobin a1c, and the duration of diabetes mellitus type 2. Cureus. https://doi.org/10.7759/cureus.19211.
7. Shaikh, M. K., Devrajani, B. R., Shaikh, A., Shah, S. Z. A., Shaikh, S., & Singh, D. (2012). Plasma homocysteine level in patients with diabetes mellitus. World Applied Sciences Journal, 16(9), 1269-1273.
8. Sonkar, S. K., Sonkar, G. K., Soni, D., Soni, D., & Usman, K. (2014). Plasma Homocysteine level and its clinical correlation with type 2 diabetes mellitus and its complications. International Journal of Diabetes in Developing Countries, 34, 3-6.
9. Starkebaum, G., & Harlan, J. M. (1986). Endothelial cell injury due to copper-catalyzed hydrogen peroxide generation from homocysteine. Journal of Clinical Investigation, 77(4), 1370–1376. https://doi.org/10.1172/jci112442.
10. Ueland, P. M., Refsum, H., Stabler, S. P., Malinow, M. R., Andersson, A., & Allen, R. H. (1993). Total homocysteine in plasma or serum: methods and clinical applications. Clinical Chemistry, 39(9), 1764–1779. https://doi.org/10.1093/clinchem/39.9.1764.
11. Ye, B., Zhu, X., Zeng, Z., Ji, X. & Ji, M. (2021). Clinical significance of serum homocysteine as a biomarker for early diagnosis of diabetic nephropathy in type 2 diabetes mellitus patients. Pteridines, 32(1), 11-16. https://doi.org/10.1515/pteridines-2020-0025.
12. Zhou, S., Zhang, Z., & Xu, G. (2014). Notable epigenetic role of hyperhomocysteinemia in atherogenesis. Lipids in health and disease, 13, 134. https://doi.org/10.1186/1476-511X-13-134.
13. Zulfania, Khan, A., Rehman, S., & Ghaffar, T. (2018). Association of homocysteine with body mass index, blood pressure, HbA1c and duration of diabetes in type 2 diabetics. Pakistan journal of medical sciences, 34(6), 1483–1487. https://doi.org/10.12669/pjms.346.16032

Review

ХИПЕРТЕНЗИВНИ УВЕИТИ: ПРЕГЛЕД НА ЛИТЕРАТУРА

Андријана Петрушевска[1,2], Весна Челева Марковска[1,2], Ева Марковска[1], Елена Тевдовска[1], Александра Михајлова[1]

[1]Универзитетска Клиника за очни болести, Скопје

[2]Медицински факултет, Универзитет „Св. Кирил и Методиј" Скопје РС Македонија

Medicus 2024, Vol. 29 (2): 153-158

АПСТРАКТ

Увеити се воспаленија на увеалниот тракт со хроничен, рецидивирачки тек, најчесто со билатерално зафаќање. Покачувањето на интраокуларниот притисок кај увеитите се смета дека е трета најчеста компликција, после цистоиден едем на макула и катаракта. Два најчести механизми кои доведуваат до покачување на ИОП кај увеитите се воспаление на трабекулумот (трабекулитис) или опструкција на дренажниот систем со ексудат. Предни увеити предизвикан од одредени вируси, увеитичните ентитети како што се Posner-Schlossman-ов синдром и Fuchs-ов хетерохромен циклитис, потоа Vogt–Koyanagi–Harada синдормот, Mb.Behcet, саркоидоза и јувенилен идиопатски артритис се особено повразни со покачување на интраокуларниот притисок.

ВОВЕД

Увеити се воспаленија на увеалниот тракт (ирис, цилијарно тело и хороидеа) со хроничен, рецидивирачки тек, најчесто со билатерално зафаќање. Тие се одговорни за 10-35% од слепилото кај пациенти под 65 години. (1)

Покачувањето на интраокуларниот притисок (ИОП) кај увеитите се смета дека е трета најчеста компликција, после цистоиден едем на макула и катаракта. Преваленцата на покачен ИОП кај увеитични пациенти и оние кои треба да се лекуваат за покачувањето на ИОП е 41,8 и 29,8%, соодветно, според една ретроспективна анализа на 216 пациенти по просечен период на следење од 7,5 години. (1,2)

Интраокуларниот притисок во тек на увеитите може значајно да варира. Во почетокот на воспалението често постои намалување на ИОП поради намалена продукција на очна водичка – хипосекреција. Хиперсекреција може да доведе до покачување на ИОП. (3)

ПАТОФИЗИОЛОГИЈА

Два најчести механизми кои доведуваат до покачување на ИОП кај увеитите се воспаление на трабекулумот (трабекулитис) или опструкција на дренажниот систем со ексудат. (4)

Кај трабекулитис од зарадивоспалениеиедемнастанува намалување на дијаметарот на интертрабекуларниот простор, со што е отежнато истекувањето на очната водичка. Исто така, и употребата на кортикостероиди може да доведе до промени во трабекуларниот систем кај особи кои имаат предиспозиција.(5)

Опструкација на дренажниот систем со ексудат, претставува релативно чест механизам кој доведува

до покачување на ИОП кај увеитите. Самиот факт дека очната водичка кај увеитите е богата со белковини, укажува дека истекувањето на очната водичка е отежнато. (5,6,7)

Организација на ексудатите во иридокорнеалниот агол и во трабекулумот предизвикува трајно зголемување на ИОП. Така доаѓа до формирање или на фиброваскуларна мембрана во аголот или гонио-синехии.

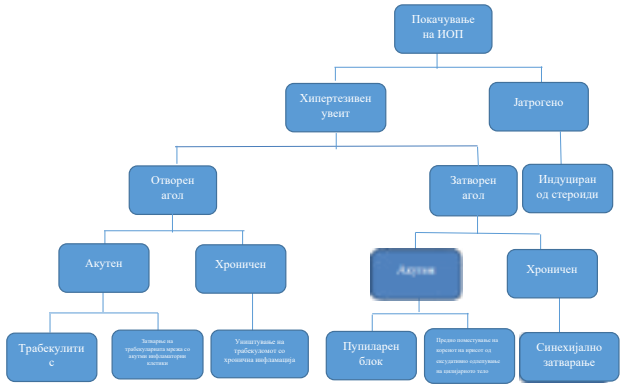
Seclusio et occlusio pupillae е исто така резултат на организација на ексудатите, заради што е оневозможено поминување на очната водичка од задната во предната комора. (7)

ЕТИОЛОГИЈА

Етиологијата, односно механизмот на покачување на ИОП кај увеитите може широко да се подели на две категории. (Слика 1) Прво, покачувањето на ИОП како резултат на болеста (попозната како хипертензивен увеит) и второ, јатрогено покачување на ИОП. (4,5)

Првата група понатаму може да биде поделена на покачување на ИОП со отворен или затворен агол. Акутна и минлива ИОП елевација со отворен агол се верува дека се должи на затнувањето на трабекуларна мрежа со воспалителни клетки и трабекулитис, предизвикувајќи намалено истекување на очната водичка. Може да придонесе и хроничното воспаление што доведува до оштетување на трабекуларната мрежа и до покачување на ИОП со отворен агол. ИОП со затворен агол, од друга страна може да се подели на пупиларен блок (најчесто акутен) и синехијално затворање (најчесто хронично).

Во втората категорија, покачување на ИОП предизвикано од кортикостероиди, кои се важен фактор во справувањето со интраокуларното воспаление. Кортикостероидите ја зголемуваат отпорноста на истекување на очна водичка, што влијае и на екстрацелуларниот матрикс во трабекуларната мрежа и цитоскелетот на трабекулоцитите. Во повеќето случаи, ИОП се намалува спонтано до основните нивоа по прекинот на терапијата со стероиди. (7)



Слика 1. Алгоритам на механизмот за покачен ИОП кај увеити

Предни увеити предизвикан од одредени вируси, како што се цитомегаловирус (CMV), херпес симплекс вирус (HSV) односно херпетичен кератоувеит, варичела зостер вирус (VZV) и вирусот на рубеола (RV) се особено поврзани со покачување на ИОП. (8)

Освен кај вирусните увеити, ИОП може да биде покачен и кај Vogt–Koyanagi–Harada синдромот, Mb.Behcet и кај саркоидоза. (9)

Кај педијатриската популација, преваленцата на покачен ИОП е околу 19%; а речиси половина од нив се деца со увеитис асоциран со јувенилен идиопатски артритис (ЈИА). (10)

Покачување на ИОП почесто се забележува кај хронични увеити, повозрсни пациенти и кај пациенти со подолго траење на увеитот. (11)

Вирусни увеити

Вирусните увеити се карактеризираат со преден увеит со покачен ИОП, дифузни преципитати на корнеа, присуство на пигментација во активните корнеални прецепитати и атрофични промени на ирисот. Најчести вируси кои предизвикуваат увеитис се: херпес симплекс (HSV), варичела-зостер (VZV), цитомегаловирус (CMV) и рубеола (RV). Херпетичниот увеитис е далеку најчест од вирусните увеитиси, на кој отпаѓа 5-10% од сите случаи на увеитис во Западниот свет и 0.9-8.3% од сите инфективни увеити. (11)

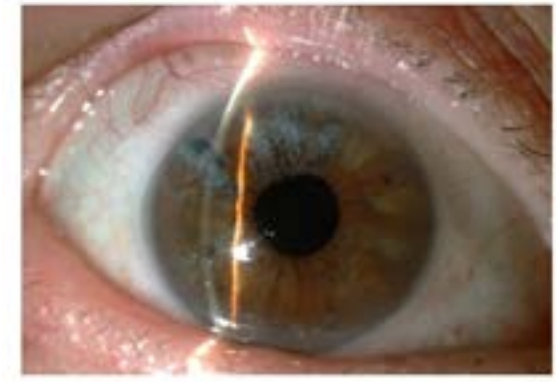
Херпес симплекс вирус

Херпетичниот увеит вообичаено е предизвикан од HSV-тип 1. Може да има историја на рекурентна треска, групирани везикули околу очните капаци со дифузен едем. Обично е унилатерален, но може да биде

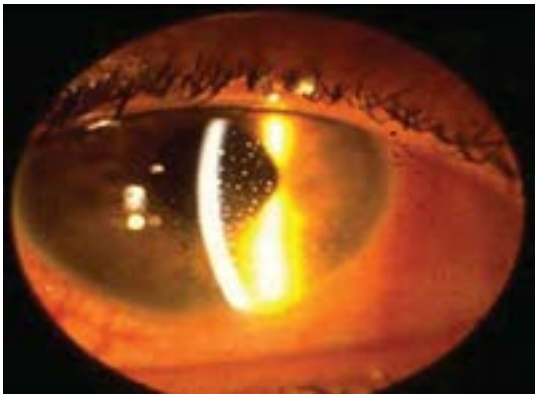
билатерален во 18% случаи. Симптомите вклучуваат акутна силна болка во очите, црвенило, солзење, фотофобија, заматување на видот.

Херпетичниот преден увеит се карактеризира со мали до средни корнеални преципитати, некои од овие кои се свежи, може да бидат пигментирани. Зголемен интраокуларен притисок се јавува поради трабекулитис и тоа може да биде епизодно. Исто така, се јавува деформација на пупилата и атрофија на ирисот. Присуството на секторска атрофија на ирисот е забележано кај рекурентна или хронична болест и може да отсуствува во многу рана фаза на болеста. Катаракта може да се јави подоцна во текот на болеста. Задниот увеит е фокален, пратен со васкулитис на ретината. (9,11)

a.



b.

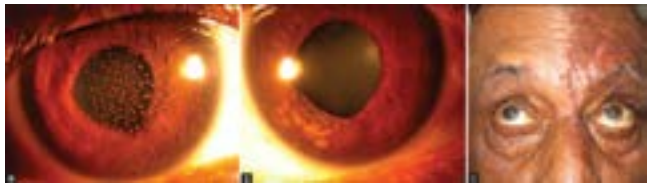


Слика бр.2 Приказ на биомикроскоп кај херпетичен увеит со секторна атрофија на ирис (a) и преципитати на корнеа (b)

Херпес зостер вирус

Херпес зостер вирус (HZV) е во мирување во нервните сензорни ганглии по примарна инфекција обично во детството и се реактивира кога специфичниот имунитет опаѓа, типично во текот на 6-та или 7-мата деценија од животот. Алтернативно, може да се појави кај млади имунокомпетентни лица, состојби кои предизвикуваат имуносупресија како синдром на стекната имунодефициенција или примена на имуносупресивни лекови.

Типично, херпес зостер увеititот се манифестира во форма на акутен хипертензивен преден увеит, серофибринозен, со преципитати кои рано пигментираат, деформирана пупила и секторна атрофија на ирисот. Задниот увеит е најчесто фокален хориоретинит со васкулит, со можност за зафаќање и на очниот нерв. (11)



Слика бр.3 Приказ на биомикроскоп кај варичела зостер увеит со пигментни преципитати на корнеа (a) и секторна атрофија на ирис (b), фотографија на која се прикажани лузни на лицето од лузни од херпес зостер офталмикус на левата страна на челото и носот

Цитомегаловирус

Цитомегаловирус (CMV) е важна причина за хипертензивен преден увеит кај имунокомпетентни индивидуи. Окуларните ткива, како ирисот и цилијарното тело може да бидат место на латентност на овој вирус.

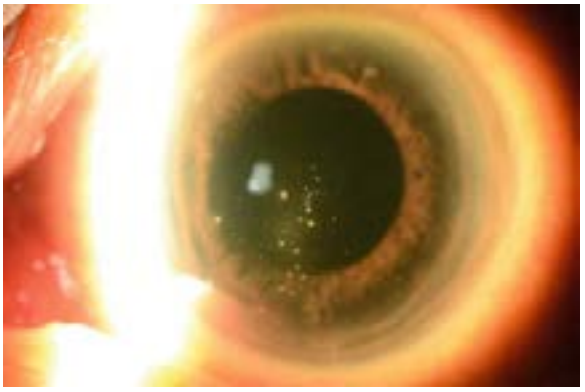
Цитомегаловирусот се смета дека е причина за акутен хипертензивен преден увеит со релапс (Posner-Schlossman-ов синдром). Типична презентација е пациент во 3-5-та деценија со акутен почеток на појава на халоа, едностранo благо заматување на видот поврзан со ипсилатерална главоболка и со историја на слични епизоди. ИОП често надминува 50 mmHg за време на нападот во присуство на суптилен субепителен едем. Силно покачениот ИОП често е непропорционален со наодите за благо воспаление на предниот сегмент. Корнеалните преципитати се средни до големи, бели или сиви обоени.

Хроничниот цитомегаловирусен увеит почесто ги погодува постарите пациенти во 5-7-та деценија, на просечна возраст од 65 години, кои може да се манифестираат со окуларна непријатност и заматување на видот. CMV е главна причина за Fuchs во

Источна Азија, особено во Сингапур, Тајван и Јапонија. Ирисот може да изгледа како изеден од молец поради стромална атрофија, која е почесто дифузна.

Корнеален ендотелитис е воспаление на корнеалниот ендотел што се карактеризира со локализиран стромален едем на рожницата и корнеални преципитати. ИОП може да биде покачен. (11,12)

a.



b.

Слика бр.4 Биомикроскоп на цитомегаловирусен преден увеит (a) и приказ на ендотелитис предизвикан од CMV (b)

Увеитични ентитети

Глаукомо – циклични кризи или Posner-Schlossman-ов синдром

Posner и Schlossman првпат објавија серија од девет пациенти со карактеристична презентација на унилатерално акутно покачувања на ИОП во 1948 година. Оваа болест подоцна станала позната како Posner-Schlossman-ов синдром (PSS). Тоа е едностранa окуларна болест која се карактеризира со рекурентни епизоди на акутен негрануломатозен преден увеит и зголемен ИОП. (13)

PSS обично ги погодува возрасните од 20-50 години, иако е пријавен случај на заболено 13-годишно момче. Мажите имаат поголем ризик од жените. (14,15)

Голем број на теории се предложени како предизвикувачки и/или фактори кои придонесуваат за PSS, но вистинското потекло на овој синдром сеуште не е објаснето. (16)

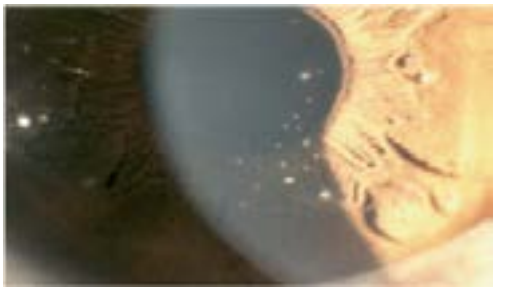
Posner и Schlossman први објавиле дека глаукомоцикличната криза е резултат на автономна дисрегулација. Тие забележале дека 4 пациенти во нивната оригинална серија случаи од 1948 година, исто така, имале историја на мигрена.

Во раните серии на случаи на пациенти со PSS, забележани се асоцијации со алергиски состојби. Во оригиналната серија случаи на Posner и Schlossman, 2 пациенти имале поленска треска, 2 имале астма и 2 имале истовремена уртикарија на истата страна од лицето како и покачениот ИОП.

Една студија на јапонска група од 22 пациенти со PSS покажа дека 41% имале хаплотип HLA-Bw54 наспроти 8% од контролите. HLA-Bw54, исто така, е чест наод во синдромот Vogt–Koyanagi–Harada.

Од инфективните причинители се споменуваат: H. pylori, HSV/VZV и CMV како можни причинители. (17,18)

Пациентите обично се јавуваат со едностранo заматен вид и благи непријатност или болка во очите. Ретко се пријавени случаи на билатерална презентација. Покачувањето на ИОП е значајно, со вредности од 50-60mmHg. Обично после неколку часови или денови, а ретко после 2-3 недели, доаѓа до спонтана нормализација на ИОП. (19,20,21)



Слика 5. Мали, бели, дискретни корнеални преципитати кај PSS

Fuchs-ов хетерохромен циклитис

Ernst Fuchs во 1906 година опишал 38 случаеви на хроничен циклитис на хипохромното око со комплицирана катаракта. Тоа е хронично воспаление

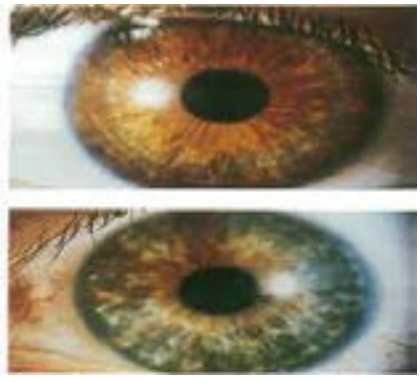
и најчесто е едностранo (90%). Се јавува кај особи од 8-73 години и претставува 3% од сите увеитиси. Може да започне во раното детство, но дијагнозата често покасно се поставува, бидејќи карактеристичните наоди може да не се присутни при почетокот на болеста. (22)

Постојат неколку теории кои тежнеат да ја објаснат патогенезата на оваа заболување.

Инфективното потекло наведува улога на бактерии и вируси. Во времето на Fuchs заболувањето се доведувало во врска со туберкулозата. Покасно, од очната водичка други автори изолирале бактерија, чија поатогена моќ била слаба. Исто така, се застапува и гледиштето за улогата на токсоплазмата во настанување на Fuchs-ов хетерохромен циклитис.Денес се мисли дека во САД и Европа, рубеола вирусот (RV) е главниот етиолошки агенс, додека CMV е доминантна причина во Азија. (23)

Слика 6. Корнеални преципитати кај Fuchs-ов хетерохромен циклитис

Основни клинички карактеристики се: хетерохромија, најчесто хипохромија на заболеното око, преципитати на ендотел на корнеа и задна кортикална, субкапсуларна катаракта.



Слика 7. Очи на пациент со Fuchs-ов хетерохромен циклитис

ТРЕТМАН

Како и во третманот на други видови на покачување на ИОП, б-блокатори сèуште се најчести и прва линија на третман при покачување на ИОП кај увеитите. Се користи или како монотерапија или во комбинација со други капки. На приближно 20% од пациентите им треба повеќе од еден лек за намалување на ИОП, кои вклучуваат а-агонисти и инхибитори на јаглена анхидраза. Употребата на аналози на простагландин го поттикнува воспалението кај пациенти со увеит, па нивната употреба е контраиндицирана кај овие паценти.

Хирушки третаман се користи во случаи кога ИОП не може да се контролира со користење на максимална терапија, особено кога се појавуваат знаци на глаукоматозно оштетување на оптичкиот нерв или промени на видното поле. Една серија случаи пријавила 8 пациенти со PSS кои биле подложени на трабекулектомија со митомицин-С поради неконтролирани ИОП и дефекти на видното поле. На крајот од следењето, на сите пациенти не им биле потребни капки за намалување на ИОП, и иако било забележано повторување на иритис кај 2 пациенти, ИОП останал стабилен за време на епизодите. (13,21)

ЗАКЛУЧОК

Зголемувањето на ИОП кај увеитис може да се должи на секундарни механизими на затворање на иридокорнеалниот агол или пак покачување на ИОП со отворен агол. Може да биде индуцирано и од кортикостероиди. Зголемувањето на ИОП кај увеитисите може да доведе до глаукоматозна оптичка невропатија и губење на видното поле. Третманот зависи од етиологијата на увеитисот.

ЛИТЕРАТУРА

1. Stanojevic-Paovic A, Uveitisi, Medicinski fakultet Univeziteta u Beogradu, 2008.
2. Din NM, Isa H, Taylor SR, Barton K, Lightman SL. Intraocular pressure elevation in uveitis. Expert Review of Ophthalmology. 2012;7(1):45–59.
3. Blagojevic M, Latkovic Z., Endogeni uveitisi, Beograd, 1992.
4. Herbert HM, Viswanathan A, Jackson H, Lightman SL. Risk factors for elevated intraocular pressure in uveitis. J. Glaucoma13(2), 96–99 (2004).
5. Sijssens KM, Rothova A, Berendschot TTJM, de Boer JH. Ocular hypertension and secondary glaucoma in

children with uveitis. Ophthalmology113(5), 853–859.e2 (2006).

6. Tawara A, Tou N, Kubota T, Harada Y, Yokota K. Immunohistochemical evaluation of the extracellular matrix in trabecular meshwork in steroid-induced glaucoma. Graefes Arch. Clin. Exp. Ophthalmol.246(7), 1021–1028 (2008).
7. Sallam A, Sheth HG, Habot-Wilner Z, Lightman S. Outcome of raised intraocular pressure in uveitic eyes with and without a corticosteroid-induced hypertensive response. Am. J. Ophthalmol.148(2), 207–213.e1 (2009).
8. Sungur GK, Hazirolan D, Yalvac IS et al. Incidence and prognosis of ocular hypertension secondary to viral uveitis. Int. Ophthalmol.30(2), 191–194 (2010).
9. Wensing B, Relvas LM, Caspers LE et al. Comparison of rubella virus- and herpes virus-associated anterior uveitis clinical manifestations and visual prognosis. Ophthalmology118(10), 1905–1910 (2011).
10. Reddy S, Cubillan LDP, Hovakimyan A, Cunningham ET. Inflammatory ocular hypertension syndrome (IOHS) in patients with syphilitic uveitis. Br. J. Ophthalmol.91(12), 1610–1612 (2007).
11. Babu K, Konana VK, Ganesh SK, Patnaik G, Chan NSW, Chee SP, Sobolewska B, Zierhut M. Viral anterior uveitis. Indian J Ophthalmol. 2020 Sep;68(9):1764-1773.
12. Rodier-Bonifas C, Cornut PL, Billaud G, Lina B, Burillon C, Denis P. «Cytomegalovirus research using polymerase chain reaction in Posner-Schlossman syndrome.» J Fr Ophtalmol. 2011 Jan;34(1):24-9.
13. Hung PT, Chang JM. Treatment of glaucomatocyclitic crises. Am J Ophthalmol. 1974 Feb;77(2):169-72.
14. Su CC, Hu FR, Wang TH, Huang JY, Yeh PT, Lin CP, Wang IJ. Clinical outcomes in cytomegalovirus-positive Posner-Schlossman syndrome patients treated with topical ganciclovir therapy. Am J Ophthalmol. 2014 Nov;158(5):1024-1031.e2.
15. Cao G, Tan C, Zhang Y, Kong X, Sun X, Ma Y, Chen J, Guan M. Digital droplet polymerase chain reaction analysis of common viruses in the aqueous humour of patients with Posner-Schlossman syndrome in Chinese population. Clin Exp Ophthalmol. 2019 May;47(4):513-520.
16. Rodier-Bonifas C, Cornut PL, Billaud G, Lina B, Burillon C, Denis P. [Cytomegalovirus research using polymerase chain reaction in Posner-Schlossman syndrome]. J Fr Ophtalmol. 2011 Jan;34(1):24-9.
17. Rodier-Bonifas C, Cornut PL, Billaud G, Lina B, Burillon C, Denis P. [Cytomegalovirus research using polymerase chain reaction in Posner-Schlossman syndrome]. J Fr Ophtalmol. 2011 Jan;34(1):24-9.
18. Megaw R, Agarwal PK. Posner-Schlossman syndrome. Surv Ophthalmol. 2017 May-Jun;62(3):277-285.
19. Shazly TA, Aljajeh M, Latina MA. Posner-Schlossman glaucomatocyclitic crisis. Semin Ophthalmol. 2011 Jul-Sep;26(4-5):282-4.
20. Takusagawa HL, Liu Y, Wiggs JL. Infectious theories of Posner-Schlossman syndrome. Int Ophthalmol Clin. 2011 Fall;51(4):105-15.
21. Babu K, Konana VK, Ganesh SK, Patnaik G, Chan NSW, Chee SP, Sobolewska B, Zierhut M. Viral anterior uveitis. Indian J Ophthalmol. 2020 Sep;68(9):1764-1773.
22. E La Hey, P T V M de Jong, A Kijlstra. Fuchs› heterochromic cyclitis: review of the literature on the pathogenetic mechanisms. British Journal of Ophthalmology 1994; 78: 307-312.
23. Bonfioli AA, Curi AL, Orefice F. Fuchs› heterochromic cyclitis. Semin Ophthalmol. 2005 Jul-Sep;20(3):143-6. doi: 10.1080/08820530500231995.

Review

PEPTIDET NATRIURETIKE TË TIPIT B SI PARAMETËR DIAGNOSTIKË NË FEMIJET ME SËMUNDJE KARDIOVASKULARE

Blend R. Bejiqi[1], Ragip J. Retkoceri[2], Arlinda H. Maloku[2], Afërdita I. Mustafa[2], Alije Keka[2], Ramush H. Bejiqi[2], Rinor R. Bejiqi[2]

[1]Poliklinika "Echo Scan, Prishtinë, Republika e Kosovës,
[2]Klinika e Pediatrisë, Qendra Klinike Universitare e Kosovës, Prishtinë, Republika e Kosovës,

Autori korrespondent:
Rinor Bejiqi, +383 49 585564
e-mail: rinorbejiqi25@gmail.com

Medicus 2024, Vol. 29 (2): 159-168

ABSTRAKT

Në aspektin klinik, niveli i polipeptideve natriuretike në plazëm është tregues i rëndësishëm diagnostik dhe prognostik te sëmundjet kardiovaskulare te fëmijët. Peptidet natriuretike gjithashtu luajnë rol të rëndësishëm në rritjen dhe përbërjen e trupit. Së bashku me sistemin simpatik nervor dhe sistemin endokrinologjik peptidet luajnë rol kyç në rregullimin e homeostazës të fluideve dhe shtypjes të gjakut. Ndryshimet në këtë ekuilibër çojnë në mosfunksionim të endothelit dhe ventrikulit të majtë, gjë që mund të shkaktojë komplikime të rënda. Te shumë sëmundje kardiovaskulare peptidet natriuretike shërbejnë jo vetëm si tregues në vënien e diagnozës dhe prognozës, por ato kanë edhe rëndësi terapeutike. Aplikimi terapeutik i sistemit të polipeptideve natriuretike mund të ofrojë informata të reja për sëmundjet kardiake, renale, kockore dhe metabolike tek fëmijët.

Peptidet natriuretike (NP) lirohen nga zemra si përgjigje ndaj presionit dhe mbingarkesës me vëllim. Vetitë biologjike të PN përfshijnë kundërrregullimin e rrugës renin-angiotensin - aldosterone dhe ulje të tonusit simpatik, që rezulton me diurezë, natriurezë dhe vazodilatim. Peptidet natriuretike, me mekanizma të ndryshëm dhe tejtet të komplikuar, ndihmojnë në ruajtjen e ekuilibrit të lëngjeve dhe shtypjes së gjakut në organizëm, në kushte fiziologjike.

Për këtë arsye, peptidi natriuretik i tipit B (brain natriuretic peptide - BNP) i njohur edhe si B-type natriuretic peptide, dhe prekursori i tij, N-terminal (N-terminal precursor brain natriuretic peptide - NTpBNP) janë bërë biomarkues të rëndësishëm në diagnostikimin dhe përcjelljen e fëmijëve të prekur me sëmundje të ndryshime kardiovaskulare (SKV). Kjo përmbledhje gjithpërfshirëse përshkruan rëndësinë dhe përfitimet nga përcaktimi i vlerave të BNP dhe NTpBNP te sëmundjet e ndryshme kardiovaskulare, të lindura ose të fituara, në grupmoshat neonatale dhe pediatrike.

Pasi që BNP nuk është një test i pavarur dhe specifik, ai nuk duhet te zëvendesoj metodat tjera diagnostike, duke përfshihrë të dhënat anamnestike, ekzaminimin fizik dhe gjetjet klinike, por ka një vlerë të qartë biokimike dhe klinike në zgjerimin e detajeve në të gjitha periudhat e sëmundjes. Në këtë mënyrë peptidet natriuretike japin një kontribut të rëndësishëm mjekëve të vijës së parë në diagnostikimin dhe përcjelljen e këtyre fëmijëve, veçanërisht në Njësitë e kujdesit intensiv.

Fjalet kyçe Peptidet natiruretike, brain natriuretic peptide, semundjet kardiovaskulare tek femijet, N-terminal precursor brain natriuretic peptide, pamjaftueshmëria e zemrës

HYRJE

Grupi i peptideve natriuretike te gjitarët përbëhet nga tre polipeptide: polipeptidi atrial (atrial natriuretic peptide - ANP), polipeptidi nga truri [tipi B; brain natriuretic peptide - BNP] dhe polipeptidet natriuretike të tipit C (C natriuretic polipetide - CNP) dhe tre receptorë, receptorët natriuretikë-A (NPR-A), -B (NPR-B) dhe -C (NPR-C). Si ANP ashtu edhe BNP janë prezentë në sasi të madhe në zemër dhe sekretohen kryesisht nga atriumet dhe ventrikujt, respektivisht. Në kontrast me këto, CNP është prezente kryesisht në sistemin nervor qendror, në kocka dhe sistemin vaskular. Të sëmundjet kardiovaskulare vjen deri te ngritja e përqendrimit të ANP dhe BNP dhe, pasi që niveli i rritjes së BNP është zakonisht më i madh se rritja e ANP, kjo bën që BNP të jetë një tregues diagnostik më i dobishëm për disa gjendje patologjike, duke përfshirë pamjaftueshmerine e zemrës, rimodelimin ventrikular, hipertensionin pulmonar dhe te keqformimet e lindura të zemrës. Studimet e fundit kanë treguar se përveç BNP-32, në plazmë rritet edhe niveli i proBNP-108 dhe se nivelet e të dy formave janë rritur në këto gjendje patologjike. Për më tepër, proBNP-108 është O-glycociluar dhe qarkullon në plazmë në këtë formë.

Me shumëllojshmërinë e manifestimit patoanatomik dhe klinik sëmundjet kardiovaskulare (SKV) tek të porsalindurit dhe femijët shpesh paraqesin sfida shtesë për mjekët e profileve të ndryshme pediatrike, duke filluar nga anamneza e sëmundjes deri te gama e analizave laboratorike dhe ekzaminimeve diagnostike. Edhepse protokollet në numrin më të madh janë shumë të qarta, pengesat fillojnë nga mungesa e një historie mirë të dokumentuar, e cila zakonisht mungon ose është e pamjaftueshme në të dhëna themelore për etiologji të sëmundjes ose për ecurinë e saj.

Keqformimet e lindura të zemrës dhe sëmundjet e sistemit kardiovaskualr në këtë moshë prezantohen me një spektër të gjërë të simptomave klinike, duke përfshirë dispnen, refuzimin e ushqimit, ngecjën në rritje dhe zhvillim deri te edemat difuze dhe cianoza qendrore e shkallës së ndryshme (1). Vlerësimi i shpejtë i këtyre shenjave klinike në moshat neonatale dhe fëmijërore janë të nevojshme për të lehtësuar klasifikimin e duhur të fëmijës vitalisht të rrezikuar. Përcaktimi i vlerave të peptideve natriuretike në plazmë (brain natriuretic peptide - BNP) dhe prekursorit të tij, N-terminal (N-terminal precursor brain natriuretic peptide - NTpBNP) mund të ndihmojnë si udhërrëfyes në këtë skenar të menaxhimit të shpejtë dhe efektiv të fëmijës (2).

Kohëve të fundit, në shumë publikime të bazuara në studime klinike, është treguar se niveli i peptideve natriuretike në plazmë është një test i besueshëm për diagnozën e sëmundjeve strukturore dhe funksionale të SKV në të gjitha moshat fëmijërore. Megjithatë, edhepse përdorimi i vlerave të BNP dhe NTpBNP rritë saktësinë diagnostike dhe është parashikues i mirë në prognozën e fëmijëve me sëmundje të ndryshme kardiovaskulare, në krahasim me testet tradicionale diagnostike, këto teste ende nuk janë gjerësisht të pranuara në mbarë botën dhe mungon një standardizim dhe rishikim i literaturës (2).

Peptidet BNP dhe NTpBNP

Megjithëse BNP dhe NTpBNP kanë rol të madh në skriningun dhe diagnostifikimin e SKV, por edhe në monitorimin e reagimit ndaj trajtimit terapeutik, në fëmijë dhe të rritur, përzgjedhja e peptidit natriuretik shpeshherë është thjesht më shumë vendim institucional. Në përgjithësi, vlerat e niveleve të BNP dhe të NTpBNP janë të ndërlidhura dhe korelojnë mirë dhe secila nga to mund të përdoret në kujdesin ndaj fëmijës kardiopat. Per shkak se BNP ka një gjysëm-jetë prej mesatarisht 20 min dhe eleminohet shpejt përmes disa mekanizmave mirë të hulumtuar dhe gjerësisht të përshkruar, nivelet në plazmë ndryshojnë në krahasim me NTpBNP (3).

Në kontrast me BNP, NTpBNP ka gjysëm-jetë më të gjatë dhe sillet mesatarisht nga 1 deri në 2 orë. Kjo mundëson që në plazmë të kemi nivele qarkulluese më të larta dhe luhatje më të ngadalta të niveleve të NTpBNP, pavarësisht sekrecionit të barabartë të dy peptideve me raport 1:1 të NTpBNP dhe BNP. Përveç kësaj, BNP është e qëndrueshme në gjakun e plotë në temperaturë të dhomës vetëm 24 orë, përderisa NTpBNP është e qëndrueshme në të njëjtat kushte për të paktën 72 orë. Është e rëndësishme të thekosohet se të dy peptidet natriuretike, BNP dhe NTpBNP janë stabile gjatë shkrirjes dhe ngrirjes.

Cilat janë vlerat normale të peptideve natriuretike?

Deri tani kemi një numër të madh të studimeve dhe publikimeve në të cilat është raportuar për vlerat normale të NP-ve në moshën neonatale dhe moshën e femijerisë. Si një udhëzues i pergjithshëm mund të merret se 90 % e të rriturve dhe të fëmijëve të shëndoshë kanë nivelin e BNP në plazmë më të vogël se 25 pg/ml dhe nivelin e NTpBNP më të vogël ose të barabartë me 70 pg/ml. Nivelet e NP janë specifike për moshë dhe gjini, keshtu qe vlerat "normale" mund të ndryshojnë. Në një publikim të Law et al. sugjerohet se niveli i BNP mbi 170 pg/ml, tek të

porsalindurit dhe 41 pg/ml për grupmoshat më të vjetra, kanë një sensitivitet diagnostik prej 94 % dhe specificitet prej 87 % për SKV me defekte anatomike.

Përdorimi i peptideve natriuretike në diagnostikim

Në disa seksione më poshtë kemi bërë paraqitjen e gjetjeve që kanë të bëjnë me përfitimet e matjeve të NP në diagnostikimin e distresit respirator, pamjaftueshmërisë të zemrës, te hipertensioni persistent pulmonar i të porsalindurit, hipertesnioni pulmonar, te fibroza cistike, hernia diafragmale kongjenitale, te semundjet kongjenitale të zemrës, në periudhen perioperative në zemër, të kardiomiopatitë, të semundja Kaëasaki dhe në fëmijë pas transplantimit të zemrës.

Peptidet natriuretike te distresi respirator

Të dy peptidet natriuretike, BNP dhe NTpBNP, janë bërë tregues të rëndësishëm diagnostik në dallimin e shkakëtarëve të distresit respirator, posaqërisht në diferentimin mes shkaktarëve kardiak dhe mushkëror, tek të porsalindurit dhe fëmijët e moshave të ndryshme (4,5,6). Në një studim ku janë përfshirë të porsalindurit me distres respirator, është përcaktuar vlera e NTpBNP në plazmë, me qëllim identifikimin e shkakëtarit fillestar të distresit, ndërmjet pamjaftueshmërisë së zemrës dhe sëmundjeve të mushkërive. Në të gjithë fëmijët e përfshirë në studim, me patologji iniciale kardiake dhe mushkërore, niveli më i lartë i NTpBNP të fëmijët me sëmundje të mushkërive, ka qenë 1.341 pg/ml, përderisa niveli më i ultë në mesin e fëmijëve me pamjaftueshmëri të zemrës ishte 5.375 pg/ml. Vlera e llogaritur kufitare e NTpBNP që dallon fëmijët me patologji kardiake nga fëmijët e kontrollit dhe me sëmundje të mushkërive ishte sinjfikante në vlera prej 2.940 pg/ml (7).

Në të njëjtin studim, te fëmijët me distres respirator, me etiologji kardiake, është treguar se niveli i NTpBNP në plazmë është tregues i rëndësishëm dhe i besueshëm në vlerësimin e përmirësimit klinik, pasi që vlera e NTpBNP në plazmë korrespondon mirë me një rritje të konsiderueshme të ngopjes së oksigjenit të ajrit të dhomës dhe rënje të konsiderueshme në ritmin e frymëmarrjes, pas trajtimit të suksesshëm të pamjfatueshmërisë së zemrës. Edhe në studimet tjera tek fëmijët me distres respirator është treguar se nivel i BNP më i lartë se 40 pg/ml është në 84 % të fëmijëvë i saktë në dallimin e pamjaftuesmërisë të zemres nga sëmundjet respiratore (4). Në një studim tjetër, në të cilin janë përfshirë 73 fëmijë të porsalindur me distres respirator, për diferencimin e të porsalindurve më sëmundje kardiovaskulare, vlerat më të larta të BNP=se kanë qenë 346 pg/ml brenda 18 orëve të jetës, 421pg/ml në prej18 deri 36 orë të jetës, 570 pg/ml në periudhën 36 - 60 orë të jetës dhe 191 pg/ml pas 60 orësh jete (8,9). Megjithëse niveli i BNP në plazmë nuk është test i vetëm për të konfirmuar apo eliminuar shkakëtarin e distresit respirator tek të porsalindurit, është treguar se vëlerat e peptideve natriuretike në plazmë kanë një senzitivitet të lartë pozitiv diagnostik dhe vlerë të lartë parashikuese negative për ti përjashtuar me shpejtësi problemet serioze kardiovaskulare tek neonatet me distres respirator.

Pamjaftueshmëria e zemrës

Lirimi i BNP nga ventrikujt tek të rriturit dhe fëmijët bëhet përmës një procesi tejet të komplikuar, nëpërmjet reduktimit të vëllimit, vazodilatimit dhe kundërveprimit të kaskadës renin – angiotenzin – aldosteron. Për më tepër, BNP përmirëson funksionin diastolik duke kundërshtuar hipertrofinë kardiake dhe fibrozën. Shumica e publikimeve të fundit, të cilat merren me menaxhimin e pamjaftueshmërisë së zemrës tek të rriturit, rekomandojnë përcaktimin e vlerave të peptideve natriuretike si parametër i besueshëm në diagnostikimin dhe përcjelljen e pamjaftueshmërisë së zemrës në të gjitha fazat, nga pamjaftueshmëria deri te përmirësimi i gjendjës (9,10).

Në anën tjetër, roli i BNP dhe NTpBNP në diagnostikimin dhe menaxhimin e pamjaftueshmërisë së zemrës te fëmijet është i kufizuar. Në një studim të Price et al. i cili ka përfshirë 53 fëmijë, si kriter për disfunksion kronik të ventrikulit të majtë e kanë përcaktuar një zemër biventrikulare, me fraksion të ejektimit më pak se 50 %, së paku 3 muaj pas vënies së diagnozës. Në këtë punim ata kanë ardhur deri te konkludimi se niveli i BNP në plazmë në vlera nga 300 pg/ml ose më të larta kanë vlerë prediktive për një ecuri të padëshiruar si vdekja nga shkakëtarët kardiak, hospitalizimi i lidhur me probleme kardiake deri në futje në regjistra për transplantim të zemrës, nga vlerësimi paraprak së paku 90-të ditor. Vlera prediktive pozitive dhe negative e peptideve natriuretike ka qenë 88% dhe 97% (11). Në një studim tjetër, i cili ka përfshirë 92 mostra të BNP nga 48 fëmijë, niveli i BNP-së më i lartë se 290 pg/ml, tek fëmijët me pamjaftueshmëri të zemrës, ka qenë parashikues i besueshëm i një ecurie të pafavorshme si vdekja, transplantimi i zemrës ose hospitalizimi, i lidhur me probleme kardiake.

Në një studim tjetër ad hoc Pediatric Carvedilol Trial, niveli i BNP më i lartë se 148 pg/ml ka qenë

sinjifikant te fëmijët me rrezik të lartë për zhvillimin e pamjaftueshmërisë kardiake brenda një viti (9). Në anën tjeter, niveli përfundimtar i BNP në plazmë prej 760 pg/ml ose më i lartë, pas trajtimit të deshtimit të zemrës të dekompenzuar, tek fëmijët e shtruar në Njësinë e kujdesit intensiv, është parametër tejet i fuqishëm i një ecurie dhe prognoze negative si rreziku nga vdekja ose rihospitalizimet e shpeshta (1).

Nga të dhënat e disponueshme për fëmijet me pamjaftueshmëri të zemrës, është shumë e arsyeshme të konkludohet se vlerësimet serike të nivelit të BNP janë të dobishme në monitorimin e efekasitetit të terapisë te pamjatueshmëria e zemrës dhe tregues i besueshëm në parashikimin e prognozës definitive te fëmijët me pamjaftueshmëri kardiake (14).

Mirëpo, duhet të pranojmë se deri tani mungojnë studime multicentrike në Qendra të mëdha pediatrike kurse rezultatet e deritanishme nuk janë të mjaftueshme për të filluar me aplikimin e gjerë të matjes të nivelit të peptideve natriuretike si tregues obligativ tek femijet me pamjaftueshmëri të zemrës.

Hipertensioni pulmonar perzistent tek të porsalindurit

Vendosja e diagnozës e hipertensionit pulmonar persistent tek i porsalinduri (Persistent Pulmonary Hypertension in Newborn – PPHN) shpesh herë mund të jetë e veshtirë, veçanërisht në kushte spitalore ku aplikimi i ekokardiografisë nuk mund të kryhet për shkaqe teknike apo mungesë të kuadrit profesional (12).

Në këto kushte, por edhe në Qendra ku mundësite diagnostike janë të përmbushura, përcaktimi i nivelit të BNP ndihmon shumë dhe është parametër i besueshëm në vendosjen e diagnozës së PPHN, por edhe në përcjelljën e efikasitetit të terapsë së aplikuar.

Në një studim të aplikuar në 47 fëmijë të porsalindur në tërmin, Reynolds et al. kanë gjetur se niveli fillestar i BNP më i lartë se 550 pg/ml është parashikues i fuqishëm i PPHN, me një senzitivitet prej 83% dhe një specificitet prej 100%. Në po të njëjtin studim rritja e nivelit të BNP ka qenë tregues i përkeqesimit të gjendjës klinike dhe ka qenë treguesi me i rëndesishëm i ashpërsisë së sëmundjes, në krahasim me gjetjet tjera laboratorike. Njëkohësisht, nivelet e BNP kanë qenë në korelim të mirë me gradientet e presionit të gjakut në nivelin e valvulës triskupidale (r2 = 0.83) (13). Si konkludim nga ky punim, por edhe nga punimet tjera të publikuara, mund të merret se niveli i BNP duket të jetë një biomarker i ndjeshëm që mund të përdoret si ndihmues ndaj treguesve dhe rezultateve tjera klinike dhe laboratorike në vendosjen e diagnozës së PPHN, veçanërisht në institucione shëndetësore ku nuk ka mundësi të aplikohet ekokardiografia pediatrike shpejtë apo në kohë (1,3,9).

Hipertensioni pulmonar, fibroza cistike dhe hernia kongjenitale diafragmale

Nivelet plazmatike të ANP dhe BNP janë të ngritura në pacientët me mbingarkesë të ventrikulit të djathtë, si ajo e shkaktuar nga hipertensioni pulmonar, ose mbingarkesa me vëllim e ventrikulit të djathtë, ashtu edhe te ajo e shkaktuar nga defekti i septit interatrial. Është interesante se ANP është më shumë e ngritur te defektet e septit interatrial, ndërsa BNP është mbizotëruese te hipertensioni pulmonar (9). Mirëpo, në raste kur hipertensioni pulmonar është i shkaktuar nga defekti i septit interatrial, atëherë prap BNP është mbizotëruese. Nivelet e ANP dhe BNP tregojnë një korelim të mirë me nivelin e presionit mesatar arterial pulmonar, presionin në atriumin e djathtë, presionin end-diastolik të ventrikulit të djathte dhe rezistencën totale pulmonare, në pacientët me hipertension pulmonar. Njëkohësisht, nivelet e ANP dhe BNP bien së bashku me reduktimin e rezistencës pulmonare totale, pas terapisë afatgjatë, si me terapi me prostaglandine. Niveli i BNP-së në plazmë është gjithashtu i ngritur në pacientët me emboli akute pulmonare. Në këta pacientë, BNP e ngritur është e lidhur me një prognozë të keqe dhe vdekshëmri të larte. Kështu, rritja e presionit në atriumin dhe ventrikulin e djathtë stimulon sekrecionin ANP dhe BNP, në mënyrë të pavarur nga etiologjia. Nivelet plazmatike të këtyre peptideve janë tregues të mirë të ashpërsisë dhe efekteve të trajtimit në pacientët me mbingarkesë të ventrikulit të djathtë (14). Këto rezultate sugjerojnë se matja e BNP është një metodë e dobishme për të vlerësuar ashpërsinë e sëmundjeve, efektin e trajtimit me medikamente dhe parashikes i ecurisë së sëmundjës te pacientët me sëmundje kardiovaskulare(15).

Në të rriturit me hipertension primar pulmonar vlerat e BNP korelojnë mirë me vlerat e fituara për rezistencën vaskulare pulmonare, presionin në arterien pulmonare dhe presionin në atriumin e djathtë, kurse kanë raport negativ me indeksin kardiak. Në një studim ku janë analizuar 78 fëmijë me hipertension pulmonar, (26 prej tyre me hipertension primar pulmonar) Bernus et al. kanë treguar se fëmijët me vlera të BNP mbi 180 pg/ml kanë shkallë më të ultë të mbijetesës. Megjithëatë, në këtë studim nuk kanë gjetë korelim të mirë ndërmjet gjetjës ekokardiografike dhe hemodinamikes me nivelin e BNP

në plazmë. Në të njëjtin studim Bernus et al. kanë treguar se ndryshimet e vlerave të BNP janë shumë më profitabile dhe ofrojnë më shumë informata në menxhimin e këtyre fëmijëve se një vlerë fillestare, çka tregon se nevojiten vlera sukcesive gjatë trajtimit të fëmijëve më këtë problemattikë (1,3,9).

Diagnostikimi i dështimit të zemrës së djathtë dhe hipertensionit pulmonar, në pacientet me fibrozë cistike dhe me sëmundje pulmonare të avansuar, ndonjëherë është e vështire vetëm me gjetjet klinike. Niveli i ngritur NTpBNP në pacientet me fibrozë cistike, është treguar të jetë parashikues i mirë i hipertensionit pulmonar dhe i dështimit të zemrës. Në një model të hernisë kongjenitale diafragmale te miu, hipertensioni pulmonar ka ngritur presionin end-diastolik (overload) të ventrikulit të djathtë dhe ka quar deri të mbi ekspresioni i kodimit të ARN-mesengjerë për BNP si dhe përbëresit tjerë gjenetik të sistemit renin-angiotensiongjen dhe endotelinë – 1 në pasardhësit e tyre.

Në një studim tjetër të kufizuar, ku janë kyqur 28 fëmijë të porsalindur, të diagnostikuar me herni diafragmale kongjenitale, Baptista et al. kanë treguar se niveli i NTpBNP – së korrespondon mirë me presionin e parashikuar të arteries pulmonare, Tei-indeksin e ventrikulit të djathtë dhe dëmtimin diastolik të ventrikulit të djathtë. Në të njëjtin studim ata treguan se vlera e NTpBNP më e lartë së 11.500 pg/ml, në fëmijet me herni diafragmale kongjenitale, ka një prognozë përfundimtare të keqe (15).

Poashtu, ata treguan se rritja e hershme e nivelit të NTpBNP duket se është një alarm i rëndësishëm të një nëngrup i foshnjave me herni diafragmale kongjenitale me prognozë të keqe.

Peptidet natriuretike dhe sëmundjet e lindura të zemrës

Deri me tani janë bërë shumë studime në analizën e përfitimive të përcaktimit të vlerave te peptideve natriuretike te llojet e ndryshme të keqformimeve të lindura të zemres dhe rroli i tyre në diagnostikimin, vlerësimin e prognozës dhe monitorimin e përparimit të disfunksionit ventrikular. Në një studim sistematik është analizuar vlera diagnostike e BNP në plazmë, në pacientet pediatrik me keqformime të lindura të zemrës, dhe është zbuluar se përqëndrimi i BNP në plazmë rritet ndjeshëm në pacientet me pamjaftueshmëri ventrikulare (7, 14,15).

Te fëmijët me keqformime të lindura të zemrës, me shunt majtë – djathtë, vlerat e BNP plazmatike korelojnë mirë me ashpersinë – sasinë e shunt-it, presionin sistolik në ventrikulin e djathtë, presionin mesatar në arterien pumonare dhe me rritjen e rezistences vaskulare pulmonare. Niveli i BNP plazmatike prej 20 pg/ml ose më i lartë mund të identifikojë fëmijet me presion mesatar në arterien pulmonare prej 20mmHg ose me shumë, me një senstivitet prej 82% deri 97% dhe specificitet prej 89% dhe 84%, respektivisht. Megjithatë, ekziston një raport paradoksal në mes të vlereave të BNP dhe hipertensionit pulmonar në pacientet me defekt të septit interventrikular dhe sindromës Eisenmenger (16). Shpjegimi i mundshëm për uljen e nivelit të BNP te fëmijët me sindromë Eisenmenger qëndron te rritja e stresit të murit të ventrikulit të djathtë (right ventricle - RV) për shkak të rezistencës së lartë vaskulare pulmonare, e cila mund të zvogëloj ngarkesën e vëllumit të ventrikulit të majtë (left ventricle - LV).

Ekziston një korrelim i mire dhe i rëndësishëm ndërmjet parametrave hemodinamike të ventrikulit të djathte (presioni end-diastolik i ventrikulit të djathtë) dhe përqëndrimit të BNP në plazmë tek fëmijët me mbingarkese më vëllim të ventrikulit të djathtë, si pasojë e keqformimeve të ndryshme kongjenitale të zemrës si në tetralogjinë Fallot pas korrigjimit komplet, te regurgjitimi pulmonar, stenoza pulmonare, atrezioni pulmonar, defekti i septit interatrial apo derdhja totale anomale i venave pulmonare (18).

Monitorimi i vlerave të BNP paraqet një biomarker të rëndësishëm për përcjelljen e presionit në ventrikulin e djathtë dhe mbingarkesa me vëllim në këta fëmijë. Në një studim ku janë përfshirë 21 pacientë pediatrik me tetralogji Fallot (mosha 12.06 vjeç ± 2.54 vjet) pas korrigjimit komplet kardiokirurgjik, nivelet e NTpBNP në plazme më të larta se 115 pg/ml paraqesin tregues të mirë në zbulimin e zgjërimit dhe disfunksionin e ventrikulit të djathte (17).

Në një studim ku janë përfshirë 38 fëmijë me fiziologji të zemrës me një barkushë, duke përfshirë fazën e parë të sëmundjës (shunt: 10 pacientë), fazën e dytë të sëmundjes (Glenn: 13 pacientë) dhe fazën e tretë të sëmundjes (Fontan: 15 pacientë), niveli i BNP ishte me i lartë pas intervenimit kardiokirurgjik të parë palliativ, ku kemi mbingarkesë me vëllim të barkushës ekzistuese (shkalla e parë - stage 1), e ngjashme me atë te fëmijet pas intervenimit kardiokirurgjik të formës Glenn ose Fontan. Pas klasifikimit të këtyre fëmijëve në bazë të barkushës ekzistuese funksionale në ata me morfologji të ventrikulit të majtë dhe në ata me morfologji të ventrikulit të djathtë, u tregua se nivelet e BNP janë më të larta në ata fëmijë ku

ekziston morfologjia e ventrikulit të djathtë (19).

Niveli i BNP poashtu ka rëndësi në identifikimin dhe vlerësimin e fëmijëve me disfunksion ventrikular, pas intervenimeve paliative të formës Glenn ose Fontan, te fëmijët me zemër me fiziologji të një barkushe.

Në disa punime të publikuara deri tani është treguar se ekziston variacion i gjërë i vlerave të BNP, të lidhura me duktusin arterial perzistent, i cili është me rëndësi hemodinamike (persistent ductus arteriosus - PDA-se).

Edhepse matja e vlerave të BNP nuk mund të zëvendesojë vlerësimin e keqformimeve të linduar të zemrës e cili bëhët me aplikimin e metodave ekokardiografike, duke përfshirë edhe PDA, ato mund të menjanojnë nevojen e përseritjës së ekokardiografisë për konfirmimin e mbylljes se duktusit arterial, pas trajtimit medikamentoz ose kardiologjik/kardiokirurgjik.

Pasi që NTpBNP ka një qëndrueshmëri dhe gjysëm-jetë më të gjatë në plazmë, ky mund të shërbejë si një parametër më i mirë se BNP. Në një studim ku janë përfshirë 49 fëmijë, të lindur para kohe, me moshë gjestacionale nga 24 deri 33 javë dhe me peshë trupore në lindje nga 550 deri 1950g, janë matur nivelet e NTpBNP në ditën e parë, të tretë, të pestë dhe ditën e dhjetë të jetës, njëkohësisht me aplikimin edhe të ekokardiografisë. Në 18 nga 49 fëmijë vlera kufitare dhe sinjifikante e NTpBNP ishte 11.395 pg/ml te neonatet me PDA me rëndësi hemodinamike (rrjedhje e madhe duktale >1.6mm PDA), me karakteristika klinike të mbingarkesës pulmonare (17,18).

Periudha perioperative kardiokirurgjike

Vlera prognostike e peptideve natriuretike si tregues të sigurtë perioperativ të funksionit ventrikular ose si parashikues i rezultateve postoperative për pacientet pediatrike me sëmundje kongjenitale të zemrës deri tani është dokumentuar në shumë studime klinike (18).

Në një studim të 40 fëmijëve, të cilet iu nenshtruan intervenimit kardiokirurgjik me qëllim trajtimin e keqformimeve të lindura të zemrës, u analizuan disa parametra si parashikues dhe tregues potencial të rezultateve postoperative. U analizua vlera e NTpBNp, vlera e troponinës T, acidit laktik, proteinës C – reaktive dhe numri i leukociteve në gjak. Ky studim konfirmoi se niveli preoperativ i NTpBNP ishte i vetmi parashikues i saktë për kohëzgjatjen dhe rezultatin e mbeshtetjës inotropike postoperative. Nivelet e larta plazmatike preoperative të NTpBNP-se poashtu kanë lidhshmëri të bgushtë me rezultatet e komplikuara postoperative, te fëmijet tek të cilet u krye intervenimi kardiokirurgjik, me risk të ulët (19).

Rritja e nivelit të BNP në periudhën postoperative (12 orë pas intervenimit kardiokirurgjik) është tregues i mirë prediktiv dhe parashikuese i mirë i gjendjës se prodhimit të ultë kardiak brenda 48 orëve nga operimi, me një senzitivitet prej 87 % dhe specifitet prej 90 %. Pra, BNP dhe NTpBNP janë parametra të dobishëm në klasifikimin e rrezikut te fëmijët me keqformime të lindura të zemrës dhe ku është bërë intervenimi kardiokirurgjik. Në një studim tjetër për vlerësimin e implikimit klinik të BNP pas intervenimit kardiokirurgjik, në 15 fëmijë me mbeshtetje mekanike të qarkullimit të gjakut, është treguar se niveli i BNP ishte më i lartë te ata fëmijë qe nuk mbijetuan intervenimin kardiokirugjik, në krahasim me ata që intervenimin e mbijetuan me sukses. Poashtu, sugjerohet që nivelet serike të BNP mund të jenë tregues të mundshëm dhe të dobishëm në monitorimin e fëmijëve që janë me mbështetje mekanike të qarkullimit të gjakut (20,21).

Peptidet natriuretike te kardiomiopatitë

Gjetjet në shumë studime kanë treguar se nivelet e BNP korelojnë mirë me parametrat joinvaziv të ashpërsisë së sëmundjes tek femijet me kardiomiopati hipertrofike, duke përfshirë presionin e ngritur të mbushjes të ventrikulit të majtë, trashësinë maksimale të murit të ventrikulit të majtë, gradientin e pjesës dalëse të ventrikulit të majtë, Ea transmitrale/septale (E/Ea[s]) dhe përqindja e konsumit maksimal të parashikuar të oksigjenit (VO2). Kaski et al. kanë raportuar se tek femijet me kardiomiopati hipertrofike, nivelet e BNP në plazmë variojnë nga 4 në 791 pg/ml (mesatarja, 187 ± 192 pg/ml; mesatare, 135 pg/ml; diapazoni interkuartil [IQR], 26 - 306 pg/ml). Në pacientet me kardiomiopati hipertrofike, 71% kishin nivele të BNP që tejkalonin kufirin e sipërm të normales (abnormal, > 32.7 pg/ml). Nivelet e BNP në serum ishin dukshem më të larta në pacientet qe ishin nënshtruar implantimit të defibrillatorit intrakavitar (intracavitary defibrillator -ICD) (309 pg/ml) sesa në ata qe nuk ishin me ICD (50 pg/ml) (22,23).

Nuk është gjetur asnjë lidhje domethënëse mes BNP në serum dhe z-score të dimensioneve të kavitetit të ventrikulit të majtë dhe shkurtimit fraksional, të fëmijët me kardiomiopati hipertrofike. Një vlerë kufitare prej 50 pg/ml ishte me e sakta në përgjithësi për parashikimin e mosfunksionimit diastolik dhe kjo vlerë mund të merret si parametër shtesë për vlerësimin e ashpërsisë

të sëmundjës dhe demitimit hemodinamik, te fëmijët me kardiomiopati hipertrofike.

Te fëmijët me disfunksion të ventrikulit të majtë, nivelet e BNP u gjeten të ishin më të larta se te fëmijët e shendosh, të kontrollit (mesatare, 78 kundrejt 7 pg/ml; p< 0.0002). Përqëndrimet e BNP ishin gjithasthu të ngritura te fëmijët me disfunksion kronik sistolik të ventrikulit të majtë, duke parashikuar ecurinë e keqe të sëmundjës deri në vdekje, në 90 ditet e ardhshme, hospitalizimet e shpeshta dhe futja në regjistra për trasnplantim kardiak. Për mjekët klinik, këto gjetje nënkuptojnë se një test i thjeshtë nga gjaku dhe relativisht me kosto të vogël, mund të shërbejë si një parametër shtesë dhe i besueshëm për monitorimin e fëmijëve me dështim kronik të zemrës, në kushte ambulantore. Niveli i BNP mund të jetë veçanërisht i dobishëm te fëmijët shumë të vegjël ose te fëmijët ku ende nuk janë manifestuar shenjat klnike (23).

Ka shumë publikime klinike që tregojnë së vlerat e NtpBNP janë gjithasthu një tregues i mirë për disfunksionin e vazhdueshëm të ventirkulit të majtë në fëmijët me miokardit akut ose me kardiomiopati. Nasser et al. kanë treguar se vlerat e NTpBNP korrelojnë mirë me mosfunksionimin e vazhdueshem të ventrikulit të majtë, se sa matjet e fituara nga ekzaminimi ekokardiografik dhe parametrat e fituar me ekzaminim ekokardiografik si: fraksioni i shkurtimit, fraksioni i ejektimit si dhe rezultatet klinike. Në këtë grup të pacientëve nivelet e NTpBNP-se ishin në vlera normale për ata fëmijë që u sheruan në aspektin ekokardiografik, duke sugjeruar se nuk ka çrregullime hemodinamike. Përkeqësimi klinik nga sëmundjet virale ose shkaqet tjera, në pacientet me pamjfatueshmëri kardiake për shkak të kardiomiopatisë dilatative, mund të prezantohen si mosfunksionim akut i ventrikulit të majtë.

Megjithatë, Fried et al. në publikimet e fundit, kanë raportuar se vlera e NTpBNP e ngritur (>20.000 pg/ml) ka më shumë gjasa të jetë shoqëruese me mosfunksionim akut të ventrikulit të majtë se sa me përkeqësimin ose deshtimin kronik të zemrës. Njëkohësisht, nivelet e NTpBNP në këto grupe janë të dobishme në monitorimin dhe trajtimin e duhur të pamjaftueshmërisë së zemrës (24).

Në disa studime gjetjet kanë treguar se si BNP ashtu edhe NTpBNP janë biomarker të besueshëm proteomik për monitorimin e funksionit kardiak tek fëmijët që marrin kimioterapi si antraciklina. Niveli i BNP në plazmë është gjithasthu i dobishëm në dallimin e perikarditit konstriktiv idiopatik nga kardiomiopatia restriktive, pasi që u tregua se nivelet e BNP-se ishin të ulëta te perikardit konstrikitv idiopatik, por të larta te kardiomiopatitë restriktive (23,24).

Peptidet natriuretike te Sëmundja Kawasaki

Sëmundja Kawasaki (Kawasaki disease- KD) është një vaskulit i gjeneralizuar i enëve të vogla dhe të mesme të gjakut dhe më së shumti prek fëmijët në moshë nën 5 vjeç, me manifestime të theksuara kardiovaskulare që përfshijnë perikardin, miokardin, endokardin dhe më së shumti arteriet koronare. Duke pasur parasysh shpeshtësinë e sëmundjës dhe pasojat, deri tani janë bërë qindra studime me qëllim identifikimin e shkakëtarit etiologjik dhe parandalimin e pasojave në arteriet koronare. Poashtu, janë bërë studime në gjetjen e biomarkerëve specifik me qëllim, diagnostikimin dhe përcjellën e efikasitetit të terapisë të ordinuar, pasi që terapi specifike ende nuk ekziston. Në shumë studime gjetjet kanë treguar se niveli i BNP në plazmë është një marker biokimik i dobishëm për diagnositikim dhe për përcjellje të ecurisë të miokarditit të KD (25).

Kontraktiliteti abnormal i miokardit, disfunksioni i zemrës dhe stresi oksidativ i shtuar, i vërejtur të fëmijët me KD, mund të kontribuojnë në rritjen e nivelit të BNP plazmatike. Përqëndrimi i BNP në plazmë te pacintet me KD, në fazën akute, është dukshëm më i lartë (niveli mestar i BNP, 55.0 ± 39.5 pg/ml) sesa në pacientet me infeksion tjetër viral (niveli mesatar i BNP, 6.8 ± 7.3 pg/ml) (p<0.0001), por edhe me rënie të niveleve të BNP pas trajtimit, në të njëjtin grup, gjatë fazës rekonvaleshente. Kur niveli i BNP në plazmë është më i lartë se 16.8 pg/ml, me një ndjeshmëri të madhe prej 96.6% dhe nje specficitet prej 86.2% sugjerohet për Kawasaki disease. Njëkohësisht, u tregua se niveli i BNP në fëmijët me KD dhe efuzion perikardial është dukshëm më i lartë se në fëmijë me KD por pa efusion perikardial. Në një studim të ngjashëm, niveli i BNP në plazmë ishte dukshem më i lartë te fëmijët me KD në fazën akute të sëmundjës (65 ± 9 pg/ml) sesa tek fëmijët e kontrollit (13 ± 2 pg/ml). Pacientet me titër të BNP më të lartë se 50 pg/ml kishin më shpesh ndryshime abnormale në elektrokardiogramë dhe kishin më shumë gjasa të zhvillojnë miokardit, se ata me vlera të BNP më të vogla se 50 pg/ml (26).

Në një studim tjetër prospektiv, te 25 fëmijë në fazën akute të KD, por me funksion të ruajtur sistolik të ventrikulit të majtë, u gjetën nivelet e ngrituara të BNP (mesatarja, 54.0 ± 102.8 pg/ml). Supozimet ishin se funksioni diastolik

i dëmtuar ishte shkaku kryesor i rritjes së nivelit të BNP dhe shpejtësia e mbushjës mitrale (shpejtësia e valës E-mitrale) ishte ngusht e lidhur pozitivisht me nivelin e BNP. Sidoqoftë, nuk u vu re asnjë korrelacion i rëndesishëm midis niveleve të BNP dhe indeksit të vëllimit end-diastolik të ventrikulit të majtë (26).

Ndryshimet në artieriet koronare dhe disfunksioni i miokardit janë zakonisht pjesët vulnerabile në KD. Në një studim prospektiv me 43 fëmijë të prekur të dhe sapo diagonstifikuar me KD dhe 19 fëmijë të kontrollit, me sëmundje febrile por je me Kawasaki disease, Dahdah et al. kanë treguar se nivelet e NTpBNP janë tregues më të mirë të përfshirjës së miokardit në KD sesa nivelet e BNP. Pacientet me kritere jo të plota diagnostikuese për KD kanë më pak gjasa të manifestojnë nivele të ngritura të BNP, por njëkohësisht, kanë nivele të ngritura të NTpBNP-së. Për këtë arsye, nivelet normale të BNP nuk përjashtojnë KD dhe NTpBNP mund të jetë tregues më i mirë i përfshirjes së miokardit në KD (25,26).

Transplantimi i zemrës dhe peptidet natriuretike

Dihet se përqëndirmi i BNP në plazmë është i ngritur pas trasnplantimit ortotropik të zemrës (Orthotropic Heart Transplantation - OHT) tek fëmijët dhe është vërejtur ulja në mënyrë eksponenciale në kohë, në vlera prej 100 pg/ml deri në 14 jave pas OHT. Megjithatë, nëse BNP është ngritur në mënyrë kronike te transplantimi i zemrës, kjo ndoshta pasqyron më mire mosfunksionimin diastolik, vaskulopatinë kardiake të alograftit dhe rezultatet e dobëta më vonë të transplantimit (27).

Në një studim me 59 pacientë pediatrik me transplantim ortotropik të zemrës, nivelet e BNP ishin dukshëm më të ulëta në pacientet me mostër biopsie negative për refuzim sesa në pacientet me biopsi pozitive për refuzim ($p < 0.04$). Nivelet më të larta të BNP plazmatike u vunë re gjithashtu në rastet e përkeqësimit të hipertrofisë të ventrikulit të majtë dhe te disfunksioni i ventrikulit të majtë. Nivelet e BNP u ulen ndjeshëm me trajtimin e suksesshëm per refuzim të zemrës së transplantuar ($p < 0.007$) (28).

Përdorimi i analizës së shepjtë të BNP pranë shtratit të pacientit mund të siguroj një tregues zëvendësues joinvaziv për vlerësimin gjithëpërfshirës të funksionit të alograftit kardiak. Në marrësit klinikisht të qetë te transplantimi i zemrës, përqëndrimet e ngritura të BNP korelojnë në mënyrë sinjifikantë me rritjen e shprehjes së gjeneve për molekulat e lidhura me rimodelimin e vazhdueshëm aktiv të strukturës kardiake, me dëmitimin vaskular, infalamacionin dhe proceset aloimune. Në mënyrë të veçantë, analiza e mikrovargjeve të qeliazve mononukleare perfierike në pacientet me transplantim të zemrës, tregojnë rritje të manifestimit të gjeneve në domenet e gelsolinës (actin cytoskeleton), rritje të matriksit të metalopeptidazave (degradimi i kolagjenit), rritje të funksionit të trombociteve dhe aktivitetit imunitar (përfshirë sistemin e antigjenit të leukociteve humane, proteinat e shokut, mastocitet dhe qelizat B) (28).

Me këto gjetje të korrelimit mes BNP dhe funksionit të alograftit, nivelet e BNP janë jo vetëm një marker i statusit hemodinamik, por edhe një metodë e besueshme për vlerësimin e dëmtimit dhe riparimit të alograftit kardiak. Është raportuar se nivelet e BNP më të larta se 100 pg/ml kanë një senzitivitet 100% dhe një vlerë 100 % parashikuese negative për identifikimin e patologjive të graftit në pacientet marrës pediatrik te transplantimi i zemrës.

Përdorimi terapeutik i BNP rekombinante

Nesiritide është një peptid human natriuretik rekombinante i miratuar nga FDA dhe ka rezultuar të jetë i dobishëm në menaxhimin e dështimit të zemrës të dekompensuar tek të rriturit. Përvoja me Nesiritide në popullatën pediatrike, me pajmaftueshmëri të zemrës, është ende e vogël dhe në studim e sipër (29).

Në një studim pilot prospektiv dhe dyfishtë të kontrolluar, ku janë përfshirë 20 fëmijë (9 të randomizuar me Nesiritide dhe 11 me placebo), janë ordinuar infuzionet vetëm me Nesiritide ose në kombinim me medikamente tjera për trajtimin e pajmaftueshmërisë së zemrës. Në këtë studim u zbulua se Nesiritide ulë presionin e kapilarëve pulmonarë, ul presionin mesatar arterial pulmonar dhe presionin sistolik të gjakut, tek fëmijët me kardiomiopati dilatative. Këto gjetje sugjerojnë se Nesiritide mund të jetë i dobishëm për trajtimin e pamjaftueshmërisë së zemrës të dekompenzuar te fëmijët. Por, bazuar në përvojën e vogël dhe studime të pakta, rekomandohet rritja e vigjilencës në raste kur Nesiritide ordinohet te pacientet pediatrik (29,30).

KONKLUZIONET

Duket paradoksale që nivelet e peptideve natriuretike të ngritura janë "tregues i mirë" për pamjafueshmërinë e zemrës, por, njëkohësisht, përqëndrimet e larta të NP sugjerojnë për sëmundje serioze të zemrës. Për vlerësim të drejtë ka më shumë kuptim të shikojmë BNP dhe

NTpBNP jo vetëm si tregues të sëmundjeve kardiake, por edhe si tregues të ndërveprimeve komplekse molekulare që vijnë nga dëmtimi dhe rikthimi kardiak. Të dy peptidet natriuretike (BNP dhe NTpBNP) mund të përdoren për të monitoruar përgjigjën ndaj trajtimit të fëmijës me disfunksion ventrikular, për të identifikuar dështimin e zemrës në pacientet me dispne ose simptoma tjera që sugjerojnë sëmundje të zëmrës dhe për të parashikuar prognozën. Megjithatë, gjetjet nga hulumtimet mbi përdorimin e niveleve të NP për të përcaktuar diagnozën dhe trajtimin e pacientëve të rritur nuk mund të transferohen drejtpërdrejt në diagnostikimin dhe trajtim tek fëmijët. Ndikimi klinik i matjes se NP në plazmë është një "shtesë" e historisë të sëmundjës dhe gjetjeve tjera klinike dhe diagnostike. Një vlerë normale e NP nuk mund të përjashtojë ndonjë patologji por pasqyron një status kompenzus të zemrës tek fëmijët.

REFERENCAT

1. Daniel LB, Maisel AS (2007) Natriuretic peptides. J Am Coll Cardiol 50:2357–2368
2. Law YM, Hoyer AW, Reller MD, Silberbach M (2009) Accuracy of plasma B-type natriuretic peptide to diagnose significant cardiovascular diseases in children: the Better Not Pout Children! Study. J Am Coll Cardiol 541:1467–1475
3. Daniels LB, Allison MA, Clopton P et al (2008) Use of natriuretic peptides in pre-participation screening of college athletes. Int J Cardiol 124:411–414
4. Berry JG, Askovich B, Shaddy RE, Hawkins JA, Cowley CG (2008) Prognostic value of B-type natriuretic peptide in surgical palliation of children with single-ventricle congenital heart disease. Paediatr Cardiol 29:70–75
5. Khositseth A, Manop J, Khowsathit P, Siripornpitak S, Pornkul R, Lolekha P, Attanawanich S (2007) N-terminal pro-BNP as a marker in follow-up patients with tetralogy of Fallot after total correction. Pediatr Cardiol 28:333–338
6. Koch A, Zink S, Singer H (2006) B-type natriuretic peptide in pediatric patients with congenital heart disease. Eur Heart J 27:861–866
7. Behera SK, Zuccaro JC, Wetzel GT, Alejos JC (2009) Nesiritde improves hemodynamics in children with dilated cardiomyopathy. Pediatr Cardiol 30:26–34
8. Cowley CG, Bradley JD, Shaddy RE (2004) B-type natriuretic peptide levels in congenital heart disease. Pediatr Cardiol 25:336–340
9. Farombi-Oghuvbu I, Matthews T, Mayne PD, Guerin H, Corcoran JD (2008) N-terminal pro-B-type natriuretic peptide: a measure of significant patent ductus arteriosus. Arch Dis Child Fetal Neonatal Ed 93:F257–F260
10. Leuchte HH, Holzapfel M, Baumgartner RA et al (2004) Clinical significance of brain natriuretic peptide in primary pulmonary hypertension. Am Coll Cardiol 43:764–770
11. Lindblade CL, Chun DS, Darragh RK, Caldwell RL, Murphy DJ, Schamberger MS (2005) Value of plasma B-type natriuretic peptide as a marker for rejection in pediatric heart transplant recipients. Am J Cardiol 95:909–911
12. Paul MA, Backer CL, Binns HJ, Mavroudis C, Webb CL, Yogev R, Franklin WH (2009) B-type natriuretic peptide and heart failure in patients with ventricular septal defect: a pilot study. Pediatr Card 30:1094–1097
13. Reynolds EW, Ellington JG, Vranicar M et al (2004) Brain-type natriuretic peptide in the diagnosis and management of persistent pulmonary hypertension of the newborn. Pediatrics 114:1297–1304
14. Sanjeev S, Petersen M, Lua J et al (2005) Role of plasma B-type natriuretic peptide in screening for hemodynamically significant patent ductus arteriosus in preterm neonates. J Perinatol 25:709–713
15. Cohen S, Springer C, Avital A et al (2005) Amino-terminal pro-brain-type natriuretic peptide: heart or lung disease in pediatric respiratory distress. Pediatrics 115:1347–1350
16. Gessler P, Knirsch W, Schmitt B, Rousson V, von Eckardstein A (2006) Prognostic value of plasma n-terminal pro-brain natriuretic peptide in children with congenital heart defects and open-heart surgery. J Pediatr 148:372–376
17. Law YM, Keller BB, Feingold BM, Boyle GJ (2005) Usefulness of plasma B-type natriuretic peptide to identify ventricular dysfunction in pediatric and adult patients with congenital heart disease. Am J Cardiol 95:474–478
18. Ozhan H, Albayrak S, Uzun H, Ordu S, Kaya A, Yazici M (2007) Correlation of plasma B-type natriuretic peptide with shunt severity in patients with atrial or ventricular septal defect. Pedaitr Cardiol 28:272–275
19. Holmgren D, Westerlind A, Berggren H, Lundberg PA, Wahlander H (2008) Increased natriuretic peptide type B level after the second palliative step in children with univentricular hearts with right ventricular morphology but not left ventricular morphology. Pediatr Cardiol

29:786–792

20. Lan YT, Chang RK, Alejos JC, Burch C, Wetzel GT (2004) B-type natriuretic peptide in children after cardiac transplantation. J Heart Lung Transplant 23:558–563
21. Huang SC, Wu ET, Ko WJ et al (2006) Clinical implication of blood levels of B-type natriuretic peptide in pediatric patients on mechanical support. Ann Thorac Surg 81:2267–2272
22. Babuin L, Alegria RJ, Oh JK, Nishimura RA, Jaffe AS (2006) Brain natriuretic peptide levels in constrictive pericarditis and restrictive cardiomyopathy. J Am Coll Cardiol 47:1489–1491
23. Kaski JP, Tomé-Esteban MT, Mead-Regan S, Pantazis A, Marek J, Deanfield JE, McKenna WJ, Elliott PM (2008) B-type natriuretic peptide predicts disease severity in children with hypertrophic cardiomyopathy. Heart 94:1307–1311
24. Fried I, Bar-Oz B, Perles Z, Rein AJ, Zonis Z, Nir A (2006) N-terminal pro-B-type natriuretic peptide levels in acute versus chronic left ventricular dysfunction. J Pediatr 149:28–31
25. Kawamura T, Wago M (2002) Brain natriuretic peptide can be a useful biochemical marker for myocarditis in patients with Kawasaki disease. Cardiol Young 12:153–158
26. Kurotobi S, Kawakami N, Shimizu K et al (2005) Brain natriuretic peptide as a hormonal marker of ventricular diastolic dysfunction in children with Kawasaki disease. Pediatr Cardiol 26:425–430
27. Mehra MR, Uber PA, Walther D et al (2006) Gene expression profiles and B-type natriuretic peptide elevation in heart transplantation: more than a hemodynamic marker. Circulation 114(Suppl I):121–126
28. Shah A, Feraco AM, Harmon C, Tacy T, Fineman JR, Bernstein HS (2009) Usefulness of various plasma biomarkers for diagnosis of heart failure in children with single ventricle physiology. Am J Cardiol 104:1280–1284
29. Feingold B, Law YM (2004) Nesiritde use in pediatric patients with congestive heart failure. J Heart Lung Transplant 23:1455–1459
30. Nasser N, Perles Z, Rein AJJT, Nir A (2006) NT-proBNP as a marker for persistent cardiac disease in children with a history of dilated cardiomyopathy and myocarditis. Pediatr Cardiol 27:87–90

THE SIGNIFICANCE OF ELECTROENCEPHALOGRAPHY IN PATIENTS WITH EPILEPSY WITH EYELID MYOCLONIA OR JEAVON SYNDROME – CASE REPORT

Zelije Ilazi[1], Dritëro Kokale[3], Emilija Cvetkovska[2], Mirajet Tela – Kokale[3]

[1]ISHP Spitali Klinik i Tetovës
[2]University Clinic for Neurology, Department of Epileptic Disease – Skopje
[3]PHI "Banjat e Dibrës Capa" – Debar

Medicus 2024, Vol. 29 (2): 169-171

ABSTRACT

Epilepsy with eyelid myoclonia or Jeavon syndrome is an idiopathic generalized epilepsy characterized by a triad of: eyelid myoclonia with or without absence seizures, EEG paroxysms caused by eyelid closure (epileptiform outbursts bilaterally consisting of spike-wave complexes of 3 Hz) and photosensitivity. The onset occurs in childhood with a peak age of 6-8 years. The overall prognosis of the disease is good, although in this type of epilepsy the treatment is lifelong. Many patients develop medically refractory epilepsy while seizures tend to persist throughout life. Jeavon syndrome is a type of reflex epilepsy. There is a female predominance over the male gender. Intellectual disability and psychiatric disorders are not rare. There are focal EEG abnormalities that are frequently observed and present in two-thirds of cases. A good knowledge of the clinical characteristics allows a quick diagnosis and the start of treatment in these patients. However, this syndrome is often under-reported and under-recognized by medical personnel. Treatment should be aimed at controlling seizures. Antiepileptic choices include Levetiracetam, Sodium Valproate, Lamotrigine, and Ethosuximide, although drug resistance is not uncommon. It has also been shown to respond favorably to the ketogenic diet. Therefore, a good knowledge of the syndrome and a high level of suspicion for it with the help of diagnostic methods (EEG, MRI) are needed to establish an accurate diagnosis. A routine EEG is sufficient to diagnose Jeavon syndrome (multiple spikes and slow waves with a frequency of 3-6 Hz).

Keywords: Epilepsy with eyelid myoclonia, Jeavon syndrome.

INTRODUCTION

Epilepsy with eyelid myoclonia or Jeavon syndrome is an idiopathic generalized epilepsy characterized by a triad of: eyelid myoclonus with or without absence seizures, EEG paroxysms caused by eyelid closure (epileptiform outbursts bilaterally consisting of spike-wave complexes of 3 Hz) and photosensitivity. Eyelid myoclonus is the main clinical feature and may or may not be associated with short (less than 6s) absences. Closing the eyes in the presence of continuous light is the main causative factor (clinically it can appear as eyelid fluttering and simultaneous eye rolling). It has been hypothesized that the occipital cortex may play an important role in the pathophysiology, as well as the occurrence of variations in certain genes including CH2, KCNB1, KIAA2022 and NAA10. The onset occurs in childhood with a peak age of 6-8 years. The overall prognosis of the disease is good, although in Jeavon syndrome the treatment is lifelong. Many patients develop medically refractory epilepsy while seizures tend to persist throughout life.

PURPOSE

The purpose of this case is to improve our understanding and diagnosis of Jeavon syndrome from a well-taken history, neurological examination and findings from other investigations (EEG, brain MRI). In our case, the patient was introduced to antiepileptic therapy with Valproic acid (tbl. Valproate 300mg 2x1).

CASE DESCRIPTION

A 14-year-old patient was examined and admitted to hospital due to an unclear onset of loss of consciousness. At home, he was sitting and playing on the computer when he suddenly turned in his chair and fell. He was shaking with his whole body, lasting several minutes. After that the patient was confused and disoriented. Computed tomography report (soft tissue edema) and biochemical laboratory (to note Leukocytosis and CK=1210..608...437.5 U/L) were realized. Information was taken from the parents that the child had frequent examinations at the Children's Disease Clinic in the past, for high febrile episodes without febrile convulsions, as well as for Cystinuria, Hydronephrosis type 2 and Guillain Barre syndrome. The patient's neurological examination was normal. At the age of eight, the patient had appearances accompanied by blinking of the eyelids for a few seconds, when he was also absent for a few seconds. Then he was put on Valproate therapy, he took it for a short time (3 months) and after that period the family members stopped by themselves. The electroencephalography carried out in our clinic was with characteristic finding (regular brain basic activity. On several occasions, when closing the eyes, epileptiform outbursts were registered bilaterally posteriorly, consisting of spike-wave complexes of 3Hz with a duration of 1 second. On one occasion, a rhythmic slow activity posteriorly for a duration of 8 seconds. During this period no clinical manifestations were recorded by the technical staff. Conclusion: Epileptiform activity bilaterally.) as well as the finding of MRI of the brain performed in 2016 (In standard pulse sequences with asymmetric MR scans, cerebellum and brainstem without MR signals for parieto-occipital lesions. A similar change is observed in the projection of the middle frontal gyrus to the right – regular MRI findings), favor the diagnosis of this syndrome.

DISCUSSION

Jeavon syndrome is a type of reflex epilepsy. There is a female predominance over the male gender. Intellectual disability and psychiatric disorders are not rare. There are focal EEG abnormalities that are frequently observed and present in two-thirds of cases. Generalized or predominantly frontorolandic paroxysmal discharges occur as part of the propagation of the visual response to the occipital cortex through transcortical or thalamocortical interactions. Reciprocal interaction of thalamocortical pathways is essential for the generation of rhythmic spike and wave (and absence) after the initial polyspike and myoclonic bursts. A good knowledge of the clinical characteristics allows a quick diagnosis and the start of treatment in these patients. However, this syndrome is often under-reported and under-recognized by medical personnel. Treatment should be aimed at controlling seizures. Antiepileptic choices include Levetiracetam, Sodium Valproate, Lamotrigine, and Ethosuximide, although drug resistance is not uncommon. It has also been shown to respond favorably to the ketogenic diet.

CONCLUSION

Often, parents take their children for examination when the first generalized tonic-clonic seizure appears, which presents a scary picture to them. In the neurological examination, the signs of blinking of the eyelids that trigger an attack should be noted. Therefore, a good knowledge of the syndrome and a high level of suspicion for it with the help of diagnostic methods (EEG, MRI) are needed to establish an accurate diagnosis. A routine EEG is sufficient to diagnose Jeavon syndrome (multiple spikes and slow waves with a frequency of 3-6 Hz).

REFERENCES

1. Appleton RE, Panayiotopoulos CP, Acomb BA, Beirne M. Eyelid myoclonia with typical absences: an epilepsy syndrome. J Neurol Neurosurg Psychiatry. 1993 Dec;56(12):1312-6. doi: 10.1136/jnnp.56.12.1312. PMID: 8270934; PMCID: PMC1015381.
2. Zawar I, Knight EP. Epilepsy With Eyelid Myoclonia (Jeavons Syndrome). Pediatr Neurol. 2021 Aug;121:75-80. doi: 10.1016/j.pediatrneurol.2020.11.018. Epub 2020 Dec 1. PMID: 34167046.
3. Smith KM, Youssef PE, Wirrell EC, Nickels KC, Payne ET, Britton JW, Shin C, Cascino GD, Patterson MC, Wong-Kisiel LC. Jeavons Syndrome: Clinical Features and Response to Treatment. Pediatr Neurol. 2018 Sep;86:46-51.

doi: 10.1016/j.pediatrneurol.2018.06.001. Epub 2018 Jul 10. PMID: 30082241.

4. Yuan Y, Yang F, Huo L, Fan Y, Liu X, Wu Q, Wang H. Case Report: A Case of Eyelid Myoclonic Status With Tonic-Clonic Seizure and Literature Review. Front Pediatr. 2021 Apr 22;9:671732. doi: 10.3389/fped.2021.671732. PMID: 33968862; PMCID: PMC8100049.

photo nr. 1: Bilateral posterior epileptiform seizures consisting of 3Hz spike-wave complexes

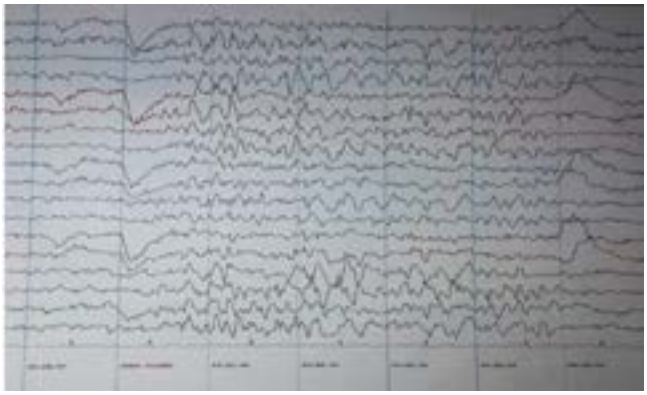
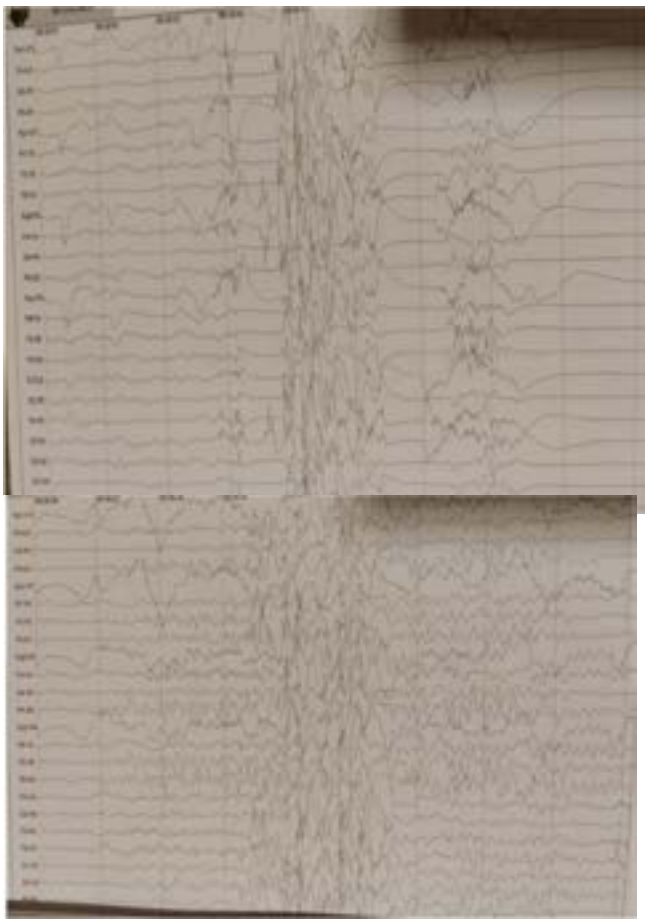


Photo nr. 2 and 3: multiple spikes and slow waves with a frequency of 3-6 Hz



CASE REPORT: FEMALE PATIENT WITH SUSPECTED BALÓ'S CONCENTRIC SCLEROSIS

Maja Petrovska[1], Alexandra Stojanoska Trajcheska[2], Glorija Gashpar[3], Bojan Boshkovski[4], Emilija Cvetkovska[5]

[1]Clinical Hospital – Bitola, North Macedonia,
[2]General Hospital – Prilep, North Macedonia
[3]PHI Specialized Hospital for Geriatric and Palliative Medicine '' 13th November '', Skopje, North Macedonia
[4]University Clinic of Neurology – Department of Epilepsy – Skopje, North Macedonia
[5]University Clinic of Neurology – Department of Epilepsy – Skopje, North Macedonia

Medicus 2024, Vol. 29 (2): 172-175

ABSTRACT

Aim, results and conclusions: The aim of this case report is to improve our understanding of Baló's concentric sclerosis and highlight the importance of thorough evaluation and collaboration in diagnosing rare neurological conditions.Baló's concentric sclerosis (BCS) is a rare, inflammatory demyelinating disease of the central nervous system (CNS). The diagnosis is based on clinical presentation, MRI features, and exclusion of differential diagnoses. The challenge of distinguishing this rare demyelinating condition from more common entities such as multiple sclerosis and ADEM can be overcome with typical MRI findings for BCS. Therefore, the role of MR imaging in patients with BCS can significantly influence the course of the disease, enabling earlier diagnosis and treatment.

Key words: Baló's concentric sclerosis (BCS), the role of MR imaging, differential diagnoses.

INTRODUCTION

Baló's concentric sclerosis (BCS) is a rare inflammatory demyelinating disease characterized by typical radiological (MRI) features, which differentiate it from more common entities such as multiple sclerosis and ADEM.

AIM

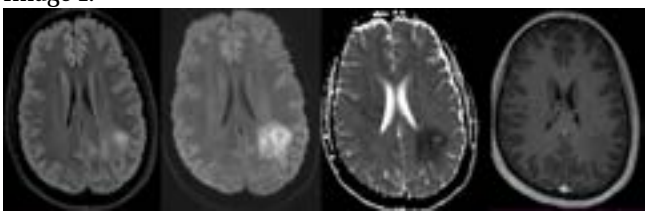
The purpose of this case report is to improve our understanding of Baló's concentric sclerosis, confirm or reject the working diagnosis, and highlight the importance of thorough evaluation and collaboration in diagnosing rare neurological conditions.

CASE DESCRIPTION

A 19-year-old female student presented with initial symptomatology in April 2022, including vertigo, nausea, confusion, drowsiness, and altered speech, occurring three days before admission. First, she was examined by a toxicologist, who performed toxicological analyses ruling out drug intoxication. Subsequently, she was evaluated by an infectologist due to suspicion of encephalitis, and a lumbar puncture was performed, revealing normal findings. In the meantime, conversion disorder was suspected, and she was evaluated by a psychiatrist. Subsequently, the patient was referred to UC for neurology for further investigation and was admitted in April 2022. During the first neurological examination, the following findings were noted: sensory and nominal dysphasia, literal paraphasia, dyscalculia, dysgraphia, and dyslexia. Due to suspicion of non-convulsive status epilepticus, an EEG was performed, revealing continuous slow activity over the left hemisphere, predominantly over the temporoparietal regions. This finding supports left posterior brain dysfunction. Brain MRI was also performed, revealing a large irregular hypersignal

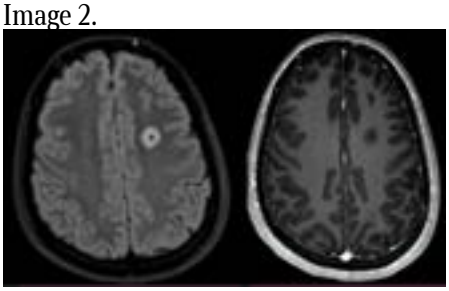
lesion located in the temporoparieto-occipital white matter extending to the subcortical region. The lesion showed concentrically different signals of hyperintensity and hypointensity on FLAIR, as well as peripheral restriction on the DWI sequence with varying values on the ADC map. There was a very discrete mass effect and discrete heterogeneous contrast enhancement – (image 1). Another smaller round lesion was observed in the centrum semiovale, localized frontally, with concentric rings of different signals and a central cystic component – (image 2).

Image 1.



T2 FLAIR DWI ADC T1 C+

Image 2.



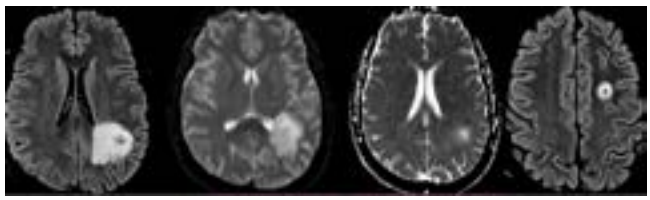
T2 FLAIR T1 C+

During the hospitalization, several diagnostic investigations were performed: serological analyses for infectious agents (EBV IgG positive), cytochemical analysis of cerebrospinal fluid with normal findings, electrophoresis of gamma globulin type, immunological analyses for systemic diseases including rheumatoid factor, ANA, ANCA, and a panel of antinuclear antibodies (ds DNA, nRNP/Sm, Sm, Jo-1, histones, SS-A/Ro, SS-B/La, ribosomal P protein, centromeres, Scl-70), antiphospholipid antibodies, autoantibodies to glutamic acid decarboxylase (GAD 65), and autoantibodies to NMDA receptor, all yielding negative results. Additionally, cardiology examination and Doppler ultrasound of neck blood vessels showed no abnormalities. MR spectroscopy indicated an inflammatory process.

During the hospitalization, the patient was treated with pulse doses of corticosteroid therapy (1 gram of methylprednisolone IV) for five days, followed by oral corticosteroid therapy (60 mg prednisolone tablets).

First follow-up after hospitalization in May 2022 revealed slight improvement in the somato-neurological condition. The patient could answer questions correctly and was able to read and write independently. The patient was still receiving oral corticosteroid therapy, with a gradual reduction of the dose. A follow-up MRI of the brain was performed, revealing enlargement and clearer definition of the initial lesion localized temporoparieto-occipitally, with concentrically different signals of hyperintensity and hypointensity on FLAIR, as well as peripheral restriction on DWI (image 3).

Image 3.



T2 FLAIR DWI ADC T2 FLAIR

Second follow-up in August 2022: The patient's condition has improved compared to the previous follow-up.

Third follow-up in April 2023: Upon comparative review of MRI scans from May 2022, there is noted volumetric reduction of the previously described lesion located temporoparieto-occipitally, accompanied by surrounding gliosis. Additionally, moderate expansion and traction of the occipital horn of the left lateral ventricle were observed. The demyelinating zone in the frontal left area has decreased by approximately 1mm compared to the MRI from May 2022. No new demyelinating plaques were detected.

Fourth follow-up in February 2024: Upon comparative MRI review with scans from April 2023, the previously described demyelinating lesions exhibit identical localization and size.

In the differential diagnosis of our patient, three diseases were considered, which share very similar clinical characteristics but exhibit distinct radiological findings. The differential diagnosis included suspicion of Baló's concentric sclerosis, ADEM (acute disseminated encephalomyelitis), and Marburg variant of multiple sclerosis.

DISCUSSION

Baló's concentric sclerosis typically occurs at an average age of 32 years and presents with symptoms such as headache, aphasia, cognitive and behavioral changes, as

well as multifocal neurological symptoms. The clinical course can vary from monophasic to relapsing-remitting, or even rapidly progressive, potentially leading to a fatal outcome. ADEM (acute disseminated encephalomyelitis) mostly occurs in children, often following infection or vaccination. It typically presents with symptoms of fever, headache, encephalopathy, and multifocal neurological symptoms. ADEM usually follows a monophasic course. The Marburg variant of multiple sclerosis typically occurs between the ages of 20 to 40 years. It is characterized by symptoms such as elevated intracranial pressure (ICP) and often follows a fulminant course. In Baló's concentric sclerosis, it is possible to detect oligoclonal bands (OCB) in the cerebrospinal fluid (CSF), whereas in the other two conditions (ADEM and the Marburg variant of multiple sclerosis), oligoclonal bands are typically not found. In the acute phase of these three diseases corticosteroid therapy is typically initiated. Subsequent treatment strategies depend on the specific clinical course and response to initial therapy.

As previously mentioned, these three diseases overlap clinically but exhibit distinct differences in their radiological characteristics.

Baló's concentric sclerosis on MRI is characterized by concentric rings of iso- and hypointensity on T1-weighted images, hypo- and hypersignal on FLAIR images, retention of contrast in areas of active demyelination, and peripheral restriction on the DWI (Diffusion-Weighted Imaging) sequence. In ADEM on MRI: T1-weighted images typically show hypointense changes without concentric rings, T2-weighted and FLAIR sequences reveal hyperintense changes with surrounding edema, post-contrast series may show an open ring sign, DWI often demonstrates peripheral restriction. The Marburg variant of multiple sclerosis is characterized by expansive confluent tumefactive lesions with a surrounding mass effect. On post-contrast MRI, these lesions typically show incomplete ring enhancement.

Baló's concentric sclerosis (BCS) is a rare inflammatory demyelinating disease of the central nervous system (CNS), characterized by alternating zones of demyelination and preserved myelin. On MRI, these lesions appear as concentric rings with varying signals in the white matter, evident on T1-weighted, T2-weighted, diffusion-weighted imaging, and post-contrast sequences.

Although initially considered a very severe variant of multiple sclerosis mainly diagnosed at autopsy in patients with a catastrophic course, the increased availability of MRI has changed the perception of Baló's concentric sclerosis (BCS).

There are overlapping clinical features as well as distinct pathological and radiological characteristics between multiple sclerosis (MS), tumefactive demyelination, and Baló's concentric sclerosis (BCS). It has been demonstrated that BCS lesions or tumefactive lesions can appear during the clinical course of typical relapsing-remitting multiple sclerosis (RRMS).

Numerous cases of Baló's concentric sclerosis (BCS) have been described in the literature, both as isolated cases with a benign course and as occurring during the evolution of other inflammatory neurological diseases as an initial event (such as MS, NMO, CADASIL, and systemic diseases). It is considered that in patients with BCS who exhibit MS-like lesions on brain MRI and positive oligoclonal bands in the cerebrospinal fluid, there is an increased risk for further development of relapsing-remitting multiple sclerosis (RRMS).

The clinical course of Baló's concentric sclerosis (BCS) is variable and can be categorized into several types, including: a single and self-limited event., relapsing-remitting, primary progressive course. Historically, reports suggested a primary progressive course with a grim prognosis, often leading to death within weeks to months. However, more recent reports have shown extended survival, cases of spontaneous remission, and even instances of asymptomatic presentation.

Larger studies are needed to further confirm these findings, which could lead to the development of better treatment algorithms and improved clinical outcomes for Baló's concentric sclerosis (BCS). Unfortunately, most of the previously published studies have included only a small number of patients due to the rarity of the disease. This limitation hinders the interpretation and generalization of the data.

CONCLUSION

Baló's concentric sclerosis (BCS) is a rare, inflammatory demyelinating disease of the central nervous system (CNS). Historically, BCS was thought to be uniformly fatal and diagnosis was based on postmortem findings. However, with advances in modern neuroimaging, BCS is now defined by the presence of characteristic radiological features on MRI, which distinguish it from Multiple Sclerosis.

Conflict of interest: We declare no conflict of interest.

REFERENCES

1. T.A. Hardy et al. Atypical inflammatory demyelinating syndromes of the CNS Lancet Neurol. (2016)
2. T.A. Hardy et al. Baló's concentric sclerosis Lancet Neurol.(2014)
3. T.A. Hardy et al. Exploring the overlap between multiple sclerosis, tumefactive demyelination and Baló's concentric sclerosis Mult. Scler.(2016)
4. Baló's concentric sclerosis – A rare entity within the spectrum of demyelinating diseases Jim Shenchu Xie , Trishal Jeeva-Patel , Edward Margolin 2021, Journal of the Neurological Sciences
5. W. Chaodong et al. Balo's disease showing benign clinical course and co-existence with multiple sclerosis-like lesions in Chinese Mult. Scler.(2008)
6. A.M. Pietroboni et al. Balò's concentric sclerosis: still to be considered as a variant of multiple sclerosis? Neurol. Sci. (2015)
7. Pathognomonic MR Imaging Findings in Balo Concentric Sclerosis Jamie T. Caracciolo,a Ryan D. Murtagh,a Amyn M. Rojiani,a and F. Reed Murtagha AJNR Am J Neuroradiol. 2001 Feb; 22(2): 292–293.

PURPLE URINE BAG SYNDROME: A CASE REPORT

Shkelqim Muharremi[1], Valon Sadiku[2], Silvana Stefanovska Petrova[3], Irena Gjoneska Pantek[1]

[1]Specialized Hospital of Nephrology-Struga
[2]Health Center Ohrid
[3]Health Center Makedonski Brod

*Correspondence address. Department of Nephrology, Specialized hospital of nephrology-Struga
E-mail: shkelqimmuharremi@hotmail.com

Medicus 2024, Vol. 29 (2): 176-178

ABSTRACT

Purple urine bag syndrome (PUBS) is a rare and striking manifestation, typically seen in elderly ladies with constipation, urinary tract infection and concurrent urinary catheterisation associated with urinary tract infection involving bright purple discoloration of the lining and tubing of a urinary catheter bag. We present the interesting case of a 74-year- old female patient who developed PUBS . Uniquely, in this case, PUBS acts as an important clinical sign in supporting the diagnosis of urinary tract infection in a high-risk patient, as well as its association with increased morbidity and mortality.

INTRODUCTION

Urine discoloration is a very common clinical sign encountered in clinical practice. Red urine discoloration is usually attributable to the differential diagnoses associated with macroscopic haematuria. Brown discoloration may indicate biliary obstruction or hepatocellular disease.

Purple urine discoloration, however, is a rarely reported presentation. It can cause great concern for patients, family members and healthcare workers when encountered. In the vast majority of circumstances it is a benign process, which does not require intervention. Purple urine bag syndrome (PUBS) is, however, an important clinical sign of urinary tract infection.

CASE REPORT

A 74-year-old female was admitted to our hospital due to worsening of kidney function and need of hemodialysis treatment. In admition and during the hospitalization the communication proved to be very difficult due to her history of progressive, advanced vascular dementia. She was disorientated in person, place and time and had significant expressive dysphasia. She also tried to escape from the hospital. Relevant medical history included diabetes mellitus type 2, arterial hypertension and recurrent urinary tract infections.

The hemodialysis process went without any difficulties but with the passing days the patient became more confused and agitated than her baseline but remained haemodynamically stable and apyrexial.

She also developed sarcopenia and required urinary catheterization.

During this period, we noticed that the urinary catheter bag and the urine within it had become a purple colour (Fig. 1).

Figure 1: Image of the urinary catheter bag showing purple colored

Due to the patient's profound expressive dysphasia, the presence of urinary symptoms could not be confirmed. Dipstick urinalysis was performed and a catheter specimen of urine was sent to the laboratory for microscopy, culture and sensitivity analysis.

The urine tested positive for nitrites, protein, haemoglobin and leucocytes and had a pH of 8.0. Treatment for urinary tract infection was commenced with a course of Nitrofurantoin 50 mg orally four times daily for 7 days, as per hospital guidelines. The catheter bag was replaced and oral hydration was encouraged. Urine culture subsequently showed a heavy mixed growth of >50.000 cfu/ml bacteria of Escherichia coli. But this was just the beginning because our patient had two others positive urine culture with Staphyloccocus coagulase negative and the next one with Proteus vulgaris, in all the cases replaced the catheter and treated by antibiogram but her medical condition worsened and she passed away.

DISCUSSION

PUBS was first reported in The Lancet in 1978 [1]. Despite being a very rarely reported and poorly understood clinical presentation, it's prevalence has been seen to be as common as 9.8% [2] and 16.7% [3] in studies of certain cohorts of long-term catheterized patients.

The hypothesis of PUBS, accepted by most authors, involves a sequence of reactions beginning with dietary intake of tryptophan [4]. Tryptophan deamination to indole, hepatic conjugation to indoxyl sulphate, bacterial enzyme action to produce indoxyl and further substrate oxidation in the urinary tract results in the production of indigo and indirubin pigments [4]. These pigments combine, causing striking purple staining of the PVC lining of the urinary catheter bag. Proposed risk factors include constipation [5], female gender [5], high bacterial load in the urinary tract [5], an alkaline urine environment [5] and a diet rich in tryptophan [6]. Bacteria species most commonly implicated include providencia stuartii and klebsiella pneumo- niae [4], although, association of PUBS with many other bac- teria, including proteus species, has also been described [4, 7]. The bacterial enzymes involved have been shown to have indoxyl sulphatase and indoxyl phosphatase activity which is not present in strains unable to produce indigo pigment [4].

Other observations made include increased incidence of PUBS in patients on haemodialysis with chronic kidney disease.[8] and cases of unexplained purple urine in acidic urine environments [9] or without indicanuria [5].

In this case, PUBS acted as a valuable clinical sign to support the diagnosis of urinary tract infection where profound dementia limited the patient's ability to communicate. The clinical importance of this observation is reinforced by the fact that up to 90% of patients who develop PUBS have been shown to have comorbid dementia [6] and an association with infections of increased morbidity and mortality [10] has been demonstrated. We would urge healthcare providers to be cognisant of this association.

This is an interesting case of Purple Urine Bag Syndrome (PUBS) in a patient with advanced vascular dementia and urinary catheterization. PUBS is a rare but clinically important phenomenon that can indicate underlying urinary tract infections.

PUBS is a rare and poorly understood clinical presentation where the urinary catheter bag and urine within it become a purple color. The hypothesis involves a sequence of reactions beginning with the dietary intake of tryptophan, resulting in the production of indigo and indirubin pigments. Proposed risk factors include

constipation, female gender, high bacterial load in the urinary tract, an alkaline urine environment, and a diet rich in tryptophan. The bacterial enzymes involved have indoxyl sulphatase and indoxyl phosphatase activity, which is not present in strains unable to produce indigo pigment. PUBS can act as a valuable clinical sign to support the diagnosis of urinary tract infections in patients who may have limited communication abilities, such as those with dementia. Urinary catheter bag replacement and antibiotic treatment based on culture and sensitivity analysis remain the standard of care for treating urinary tract infections.

CONCLUSION

Purple Urine Bag Syndrome (PUBS) is a rare but important clinical sign that can help in the diagnosis of urinary tract infections, especially in patients with communication difficulties. Our case highlights the importance of recognizing and understanding this rare phenomenon, particularly in patients with comorbidities such as advanced dementia. Identifying PUBS can prompt appropriate investigations and timely treatment for urinary tract infections, ultimately leading to better patient outcomes.

Healthcare providers should be aware of the risk factors and underlying mechanisms of PUBS, as well as its association with increased morbidity and mortality. Further research is needed to better understand this condition and improve its management in clinical settings. By increasing awareness and knowledge of PUBS, healthcare professionals can enhance their ability to provide quality care for patients experiencing this unique and potentially concerning phenomenon.

REFERENCES

1. Barlow GB, Dickson JAS. Purple urine bags. Lancet 1978;311: 220–1.
2. Dealler SF, Belfield PW, Bedford M, Whitley AJ, Mulley GP. Purple urine bags. J Urol 1989;142:769–70.
3. Shiao CC, Weng CY, Chuang JC, Huang MS, Chen ZY. Purple urine bag syndrome: a community-based study and literature review. Nephrology (Carlton) 2008;13:554–9.
4. Dealler SF, Hawkey PM, Millar MR. Enzymatic degradation of urinary indoxyl sulfate by providencia stuartii and Klebsiella pneumonia causes the purple urine bag syndrome. J Clin Microbiol 1988;26:2152–6.
5. Su FH, Chung SY, Chen MH, Sheng ML, Chen CH, Chen YJ, et al. Case analysis of purple urine-bag syndrome at a longterm care service in a community hospital. Chang Gung MedJ 2005;28:636–42.
6. Lin CH, Huang HT, Chien CC, Tzeng DS, Lung FW. Purple urine bag syndrome in nursing homes: ten elderly case reports and a literature review. Clin Interv Aging 2008;3:729–34.
7. Harun NS, Nainar SK, Chong VH. Purple urine bag syndrome: a rare and interesting phenomenon. South Med J 2007;100:1048–50.
8. Ting IW, Wang R, Wu VC, Hsueh PR, Hung KY. Purple urine bag syndrome in a hemodialysis patient. Kidney Int 2007;71:956.
9. Chung SD, Liao CH, Sun HD. Purple urine bag syndrome with acidic urine. Int J Infect Dis 2008;12:526–7.
10. Pillai BP, Chong VH, Yong AML. Purple urine bag syndrome. Singapore Med J 2009;50:193–4.

UDHËZIME PËR AUTORËT

Këto të dhëna janë në pajtim me
"Kërkesat uniforme për Dorëshkrimet e Pranuara në Revistat Biomjekësore"
Dokumentin komplet mund ta gjeni në www.icmje.org)

Medicus është revistë ndërkombëtare që boton punime origjinale shkencore, vështrime revijale, punime profesionale, prezentime rasti, kumtesa të shkurtra, recenzione librash, raporte nga tubime shkencore, letra dhe editoriale nga fusha e mjekësisë, stomatologjisë, farmakologjisë si dhe nga fusha tjera të përaferta biomjeksore.

Revista është organ i "Shoqatës së Mjekëve Shqiptarë në Maqedoni."

Gjuha e botimeve është në Gjuhë Shqipe dhe Angleze (këshilli redaktues mund të vendosë nëse botimet do të jenë edhe në gjuhë tjera). Autorëve u kërkohet të lektorojnë dhe të redaktojnë punimin e tyre vetë, në gjuhën përkatëse.

Ju lutemi përdoreni madhësinë standarde të punimit në format: Word për Windows, Times New Roman 12.

Dorëshkrimet dërgohen në format elektronik, qoftë me

CD ose përmes e-mailit tek Kryeredaktori,
Prof. Dr. Nevzat Elezi,
Zyra e Redaksisë, rr. Mehmed Pashë Deralla
nr.16, 1200 Tetovë, apo në
e-mail: shmshm@live.com

Revista për një numër pranon jo më shumë se një artikull nga një autor, dhe jo më shumë se dy si ko-autor.

Autorët duhet të deklarojnë se kontributi i tyre nuk është publikuar apo pranuar për publikim diku tjetër, përderisa nuk përfundon procedura vlerësuese ne Revistën tonë.

Autorët gjatë aplikimit duhet të përmbushin formen e kerkuar nga Komiteti Ndërkombëtar i Redaktorëve të Revistave Mjekësore (ICMJE) për **kriteret e autorësisë**, respektivisht "Kërkesave uniforme për Dorëshkrimet e Pranuara në Revistat Biomjekësore", cilën mund ta gjeni në www.icmje.org .

Revista do të **njoftojë pranimin** e artikullit tuaj brenda shtatë ditësh dhe do t'ju bëjë me dije se kur do të informoheni për vendimin e këshillit redaktues.

Artikujt për t'u botuar në Medicus **do të recensohen**. Këshilli redaktues do të marrë parasysh komentet e recensuesit dhe pastaj mund të kërkojë nga autori ndryshime apo plotësim të punimit.

INFORMATION FOR AUTHORS

These guidelines are in accordance with the
"Uniform Requirements for Manuscripts Submitted to Biomedical Journals"
(The complete document appears at www.icmje.org)

Medicus is an international journal of that publishes papers from all areas of medical research. Furthermore, the journal indends to bring educational material of high quality to its members for continuous medical education (CME), by publishing original research, professional and review papers, case reports, brief communications, literature summary articles and editorials.

The Journal is official organ of the »Association of Albanian Medical Doctors from Macedonia«.

The language of publication is Albanian and English (the editorial board may decide whether other language will be used for publications). Authors are requested to have their paper proof-readed and edited for the respective language.

Please use standard-sized paper and submit your article in the following formate: Word for Windows, Times New Roman 12.

Manuscripts should be submitted in electronic format, either on disc or by e-mail to the Editor-in-Chief,

Nevzat Elezi, MD. PhD
Editorial Office, Str. Mehmed Pashe Deralla,
No 16, 1200 Tetovo,
Email: shmshm@live.com

The Journal allows submission of no more than one article as an author, and at most two, being a co-author per issuance.

The authors attest that their contribution has neither been published nor submitted for publication elsewhere, untill the editorial procedure is over.

Authors should adhere to the International Committee of Medical Journal Editors (**ICMJE**) **authorship criteria** in so far as they apply. These can be found at www.icmje.org.

The Journal will **acknowledge receipt** of your article within seven days and let you know when you will be informed of the editorial board's decision.

Articles to be published in Medicus will be **peer-reviewed**. The editorial board will take into account the reviewer's comments and may then promt the author for changes or further work.

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

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

punim profesional ose punim revyal – deri ne 8 faqe dhe jo më shumë se 4 tabela dhe/ose figura/imazhe;

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

Letër redaksisë - deri 2 faqe

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

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

Tabelat, figurat dhe legjendat (shihni Informacionet plotësuese për autorët)

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

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

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

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

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 afëërt me punimin. Pas emrave të autorëve shkruhet titulli i artikullit; emri i revistës i shkurtuar sipas mënyrës së Index Medicus; viti i botimit; numri i vëllimit; dhe numri i faqes së parë dhe të fundit.

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

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

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

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

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

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

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

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

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

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

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

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

Artikujt e revistave:

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

Librat dhe tekste tjera:

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

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
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.

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

8. Legends for Illustrations (Figures)

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