ISSN 2409-9988

Inter Collegas

Experientia docet

2019

N1(6)

INTER COLLEGAS

2019

Vol. 6 No.1

OFFICIAL JOURNAL OF
KHARKIV NATIONAL MEDICAL UNIVERSITY
ISSN 2409-9988

Recommended for publishing
by Scientific Council of
Kharkiv National Medical
University

18 – Apr.- 2019

Correspondence address:
61022, Kharkiv,
Nauki Avenue, 4
e-mail: collegas@ukr.net
URL:
http://inter.knmu.edu.ua/pub

Periodicity:
4 times a year

Table of Contents

PEDIATRICS

THERAPY

PSYCHIATRICS & MEDICAL PSYCHOLOGY

THEORETICAL MEDICINE

CONNECTIVE TISSUE METABOLISM IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS: 10-YEAR FOLLOW-UP STUDY

Shevchenko N.S.[1, 2], Panko N.O.[1], Rakovska L.O.[1], Holovko T.O.[1]

[1] Department of Pediatrics No. 2, V.N. Karazin Kharkiv National University,
[2] SI "Institute of Children and Adolescences Health Care of National Academy of Medical Science"

Abstract
Introduction. Connective tissue remodeling is essential for progressive course of juvenile idiopathic arthritis (JIA), therefore changes in glucosaminoglycans (GAGs) fractions with time in patients with JIA have been studied during 10-year follow-up. Subjects and Methods. The study involved 22 healthy children (controls) and 83 patients with JIA aged from 2 to 18. The follow up study was yearly held for 10 years and initially included 14 patients with JIA investigated for connective tissue metabolism. Results. Proteoglycans metabolism in children with JIA is characterized by a decrease in the total GAGs, mainly by means of low levels of chondroitin-4-sulfate and highly sulphonated GAGs. This redistribution was more specific for children with prolonged disease duration (more than 5 years). Slowing of proteoglycans metabolism in reducing the excretion of uronic acids was the most common for up to 2 years of disease duration as compared to later stages. Conclusions. The severity of metabolic imbalance of proteoglycans depends on the duration of JIA and has the most unfavorable period of 5 years and later after the onset of the disease.
Keywords: *juvenile idiopathic arthritis, connective tissue metabolism.*

Introduction.

The major clinical presentation of juvenile idiopathic arthritis (JIA) is known to be the persistent synovial inflammation that can lead to irreversible joint destruction and permanent disability in childhood. The complex pathogenesis of JIA has been studied in sufficient detail, but it has not been fully explained yet. Despite significant progress in the treatment of JIA, the risk of disease progression remains high. The findings of the recent investigation have revealed microstructural changes indicative of cartilage damage in JIA patients by new imaging methods, in spite of clinical improvement and before changes in cartilage morphology which can be detected with conventional magnetic resonance imaging [6]. The impact of various mechanisms on the development of cartilage erosion in JIA continues to be the subject of scientific research.

Corresponding Author:
Nataliya Panko, MD, PhD, Associate Professor of Department of Pediatrics No. 2 of V.N. Karazin Kharkiv National University, Ukraine.
E-mail: panko@karazin.ua

Metabolic alterations of extracellular matrix (ECM) components have been shown to play a considerable role in pathological changes in the course of JIA [4, 13, 15, 16].

ECM is a complex and dynamic structure, composed of two main classes of macromolecules: proteoglycans (PGs) and fibrous-forming proteins, such as collagen, elastin, fibronectin, and laminin [2]. PGs consist of a core protein with covalently attached one or more glucosaminoglycans (GAGs) chains of the same or different type [2, 12]. PGs form a hydrated gel that fills the majority of extracellular interstitial space [2]. PGs have been classified according to their core proteins, localization and GAGs composition. The GAGs chains on the protein core are unbranched polysaccharide chains composed of repeating disaccharide units that can be further divided into sulfated and non-sulfated GAGs [2, 16]. Sulfated GAGs include chondroitin sulfate A (or chondroitin-4-sulfate), chondroitin sulfate C (or chondroitin-6-sulfate) and highly sulphonated GAGs (or heparan sulfate and keratan sulfate (KS)).

Hyaluronic acid, chondroitin sulfate (CS) and highly sulphanated GAGs are considered to be the main components of GAGs in humans.

The major PG in cartilage is aggrecan, which is a large proteoglycan bearing numerous CS and KS chains expressed by chondrocytes. A typical aggrecan molecule may contain up to 100 CS chains and a lower number of KS chains. Aggrecan endows articular cartilage with the ability to withstand compressive loads [1, 2]. CS is considered to be an early marker of aggrecan degradation [14].

The disorganization of ECM components' metabolism and structural changes of PGs and collagen is believed to occur in early stages of JIA, and, furthermore, degradation elements of ECM structures have antigenic properties which may maintain progress of immune inflammation and extend the destructive process into deeper structures of the joint [8, 13–16]. Aggrecan degradation products occur in blood, and they are free CS chains or the chains of GAGs bound to core protein fragments [14].

The studies to determine sulphated GAGs in JIA synovial fluids have demonstrated a significantly lower concentration as compared to the levels of fluids in osteoarthritis, juvenile knee injury and knee-healthy reference groups. The authors suggest that unlike other arthritides, aggrecanase cleavage in the aggrecaninterglobular domain might not be a major pathogenic event in JIA [11].

A decreased serum concentration of GAGs resulting from the substantial reduction of sulfated glycans, particularly CS was detected in untreated children with newly diagnosed JIA [13, 14, 17]. The increased levels of dermatan sulfate and hyaluronic acid were also observed in untreated JIA patients [17]. The researchers consider that at the moment of clinical symptoms appearance the total pool of GAGs is significantly reduced, while the processes of ECM components' synthesis do not compensate the degradation of these compounds. In addition, the total amount of GAGs was significantly lower than in healthy children [13]. The low levels of GAGs in blood were accompanied with their decreased urinary excretion [17].

The low concentration of CS recorded in serum of JIA patients with untreated arthroplasty was found to have a negative statistically significant correlation with concentrations of laboratory inflammatory markers, such as C-reactive protein and ESR. Therefore, the researchers have concluded that the concentration of CS in blood of children with arthropathy is directly related to the activity of both inflammatory processes and proteolytic degradation of ECM components [14]. At the same time, the serum level of chondroitin sulfate 846 epitope (CS846) as a biomarker of CS synthesis was increased significantly.

According to the above-mentioned studies the anti-inflammatory treatment of children with JIA leads to clinical improvement, but does not normalize blood GAG concentrations [14, 15]. Despite the increased content of these compounds in treated patients, their level is still significantly lower than in healthy children. The authors believe that increased concentration of GAGs observed during treatment may indicate an ongoing regenerating processes in connective tissue. The observed changes of PG/GAG metabolism in children with JIA are also suggested to be related to the auto-immune mechanisms of the disease, such as presence of GAG-specific antibodies in the systemic circulation and in the synovial fluid of rheumatoid arthritis patients. They come to the conclusion that at the active phase of the disease the levels of anti-GAG antibodies have reduced due to their binding to GAGs, released from the degrading cartilage, resulting in diminishing the general amount of GAGs in plasma [16].

Nevertheless, the qualitative and quantitative evaluation of plasma GAGs of rheumatoid arthritis adult patients in relation to the disease activity has revealed higher levels of total GAGs, CS, heparan sulfate/heparin and hyaluronic acid in patients with high and moderate disease activity than in controls. Total GAGs and CS levels in patients with high disease activity have been elevated in comparison to patients with low disease activity [5]. Thus, plasma concentration of various GAGs types, which reflects tissue alterations of ECM, is suggested to be dependent on the age [14].

It has also been shown that an essential feature of the connective tissue state in children and adolescents with rheumatoid and reactive arthritis is metabolic changes of its structures, accompanied with a progressive loss of basic functionally important components of the extracellular matrix, but with a more pronounced pathological component for juvenile rheumatoid arthritis. The basic reflection of the development of dystrophic changes is the deficiency state of GAGs, mainly due to chondroitin-4-sulfates and highly sulphonated GAGs [9].

Taking into account the essential importance of metabolic alteration of ECM as well as

systemic changes in connective tissue remodeling for progressive course of JIA, changes in GAGs fractions with time in patients with JIA have been studied during 10-year follow-up.

2 Purposes, subjects and methods:

2.1 Purpose – to improve medical care for patients with the progressive course of JIA by 10-year follow-up analysis of changes in GAGs fractions with time.

2.2 Subjects & Methods

The study involved 22 healthy children for the control group and 83 patients with JIA aged from 2 to 18 including 39.60% cases of oligoarthritis, 37.70% off polyarticular form, 20.8% of systemic form, 1.90% of enthesitis-related arthritis. And 61.45 % of them were females, 38.55 % were males. The follow up study was held for 10 years and initially included 14 patients with JIA investigated for connective tissue metabolism. Their examination was repeated yearly. All patients received basic therapy with methotrexate.

Connective tissue metabolism parameters were assessed depending on the disease duration: up to 1 year (14 patients), 1–2 years (11 patients), 2–3 years (11 patients), 3–5 years (13 patients) and 5–10 years (34 patients).

The investigation of connective tissue metabolism implied measurement of the total glucosaminoglycans (GAGs) level, the total chondroitin sulfate level [3, 7], containing chondroitin-6-sulfate and chondroitin-4-sulfate, the level of highly sulphonated GAGs (keratan and dermatan sulfate) in blood [10]; and excretion rate of uronic acid [3, 7]. Clinical and immunological parameters, such as the level of general T-lymphocytes, T-helpers and T-suppressors, the level of circulated immune complexes, spontaneous and induced Nitro Blue Tetrazolium Reduction tests, neutrophil phagocytic activity, the level of interleukin 1β (IL-1β), interleukin 6 (IL-6) and tumor necrotic factor (TNF-a) were assessed.

Statistical analysis was performed using *Statistica*+ software for Windows. The differences between the study groups were assessed by Student's t-test (t). A *p*–value of < 0.05 was considered statistically significant.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available for ethical reasons, as well as privacy reasons, but are available from the authors on reasonable request.

Ethics approval and consent to participate

Approval from medical research ethical committees and data protection authorities was granted according to the regulations of Ukraine. Oral informed assent was obtained from all children. Written informed consent was obtained from parents of children aged < 18 years and from the children if aged ≥14 years of age.

3. Results and discussion

The study of connective tissue components has shown that the children and adolescents with JIA had misbalance of PGs structures. The average total GAGs content, the level of serum chondroitin-6-sulfate and the concentration of uronic acid in daily urine in the investigated patients with JIA were probably no different from those in the similar aged healthy children. The study showed increased content of chondroitin-4-sulphate ((2.76 ± 0.53) units, $p< 0.05$) and highly sulphanated GAGs ((1.32 ± 0.15) units, $p< 0.05$) in patients with JIA in comparison with the control group. That fact indicates the development of dystrophic process and corresponds to destructive changes in connective tissue.

Depending on the gender of children with JIA the following features were established to be more specific for female patients, represented with changes of all types of proteoglycans, except chondroitin-6-sulfate (*table 1*).

Table 1

Connective tissue metabolism parameters in patients with JIA corresponding to gender

Parameters	Patients with JIA n = 58		Control group n = 22	statistically significant difference (p_t)		
	male n = 30	female n = 28				
1	2 M ± m	3 M ± m	4 M ± m	2–3	2–4	3–4
Total GAGs, U	10.46± 0.63	9.14±2. 51	10.01±0.38	< 0.01	>0.05	>0.05
Chondroitin-6-sulphate, U	7.16± 0.39	8.12± 0.95	6.83±0.27	>0.05	>0.05	< 0.05
Chondroitin-4-sulphate, U	2.21± 0.37	3.64±1.23	2.01±0.14	< 0.05	>0.05	< 0.05
Highly sulphonated GAGs, U	1.14± 0.07	1.62± 0.37	1.21±0.09	< 0,01	>0.05	< 0.05
Total CS, g/l	0.13± 0.01	0.67± 0.98	0.12±0.01	< 0.01	>0.05	< 0.01
Uronic acid, mg/d	5.08±0.87	9.02±2.56	7.46±2.14	< 0.01	< 0.05	>0.05

The total level of GAGs was lower ((9.14 ± 2.51) units vs (10.46 ± 0.63) units, p< 0.01) in females as compared to males. Thus, there was significantly higher chondroitin-4-sulfate content, ((3.64 ± 1.23) units and (2.21 ± 0.37) units respectively, p < 0.05) and the level of highly sulphanated GAGs ((1.62 ± 0.37) units and (1.14 ± 0.07) units respectively, p< 0.01). These changes in proteoglycans content in blood were accompanied by higher level of uronic acid excretion in females compared to male patients ((9.02 ± 2.56) mg/d and (5.08 ± 0.87) mg/d, p < 0.01 respectively). This redistribution of proteoglycans content is more common for degenerative processes, such as an initiation of osteoarthritis; it gives a reason to believe female sex is one of the risk factors for early formation of osteoarthritis secondary to JIA. That fact is proved by the correlation of the female sex with chondroitin sulfate content (r = 0.57; p< 0.05), the total level of GAGs (r = -0.56; p< 0.05), chondroitin-6-sulfate (r = 0.55; p< 0.05), chondroitin-4-sulphate (r = 0.72; p< 0.01) and highly sulphanated GAGs (r = 0.58; p< 0.05), the level of excretion of uronic acids (r = 0.62; p < 0.05).

The elevation of levels of general activity of the pathological process is characterized by progressive decreasing of chondroitin-4-sulfate and highly sulphanated GAGs contents with simultaneous increase in uronic acids excretion. This redistribution of proteoglycans components is one of more evidence of the impact of inflammation on the intensity of proteoglycans metabolism and it is different from dystrophic changes.

The radiological progression was established to be accompanied by a redistribution of proteoglycans too. More severe changes in the metabolism of proteoglycans occur in children with JIA, who had radiological stage II, than in patients with radiographic stage I. They were as follows: the reduction of total GAGs ((9.25 ± 0.77) units compared with (13.05 ± 0.07) units, p< 0.001)) and the content of chondroitin-4-sulphate ((1.80 ± 0.42) units compared with (2.75 ± 0.06) units, p< 0.001)) while growing content of highly sulphanated GAGs ((2.65 ± 0.05) units compared with (1.10 ± 0.56) units, p< 0.01).

The significant differences were not determined by the analysis of proteoglycans metabolism according to the disease duration; all values were equivalent (*table 2*). At the same time, due to the comparison with the same parameters of the control group the largest deviations were recorded on the early stages of the disease development, which was associated with the activity of pathological process before or at the beginning of anti-inflammatory treatment.

The content of chondroitin-4-sulfate decreased as the result of increasing disease duration. The patients with disease history exceeding 5 years were found to have the most significant difference as compared to previous years ((1.37 ± 0.12) units and (2.05 ± 0.55) units respectively, p< 0.05)). It might have accompanied the dystrophic processes in the connective tissue.

Table 2

Parameters of connective tissue metabolism corresponding to duration of JIA

Parameters	Duration of JIA (M ± m)						Control group
	Up to 12 months (n =14)	From 13 to 24 months (n =11)	From 25 to 36 months (n =11)	From 37 to 60 months (n =13)	From 61 to 120 months (n =34)	Total number of cases (n = 83)	
Total GAGs, U	10.53 ± 2.28	10.13 ± 0.76	11.00 ± 2.30	10.53 ± 2.28	8.67 ± 0.88[2)4)]	10.24 ± 0.47	10.01 ± 0.38
Chondroitin-6-sulphate, U	6.76 ± 0.97	6.63 ± 0.52	6.20 ± 0.50	6.76 ± 0.97	5.93 ± 0.75[4)]	6.21 ± 0.16	6.83 ± 0.27
Chondroitin-4-sulphate, U	2.13 ± 0.65	2.00 ± 0.21	2.75 ± 1.25	2.05 ± 0.55	1.37 ± 0.12[3)4)]	2.12 ± 0.17	2.01 ± 0.14
Highly sulphonated GAGs, U	1.63 ± 0.23	1.50 ± 0.21[1)]	2.05 ± 0.55	1.63 ± 0.23	1.47 ± 0.19[2)]	1.91 ± 0.31[4)]	1.21 ± 0.09
Total CS, g/l	0.12 ± 0.06	0.07 ± 0.00	0.07 ± 0.02	0.07 ± 0.00	0.10 ± 0.04	0.11 ± 0.01	0.12 ± 0.01
Uronic acid, mg/d	3.65 ± 0.91	2.53 ± 0.84[1)]	3.35 ± 1.05	2.40 ± 0.60	4.20 ± 0.72	3.59 ± 0.34	7.46 ± 2.14

[1)] p_t< 0.05 – the difference between parameters in patients with disease duration from 13 to 24 months and from 25 to 36 months;
[2)] p_t< 0.05 – the difference between parameters in patients with disease duration from 13 to 24 months and from 61 to 120 months;
[3)] p_t< 0.05 – the difference between parameters in patients with disease duration from 37 to 60 months and from 61 to 120 months;
[4)] p_t< 0.05 – the difference between parameters in patients with JIA and healthy children from control group.

Proteoglycans metabolism in children with JIA is characterized by a decrease in total GAGs, mainly by means of low levels of chondroitin-4-sulfate and highly sulphonated GAGs. This redistribution was more specific for children with prolonged disease duration (more than 5 years). It can be assessed as a precondition for the development of osteoarthritis of affected joints.

Slowing of proteoglycans metabolism in reducing the excretion of uronic acids was the most common for up to 2 years of disease duration as compared to later stages ((2.53 ± 0.84) mg/d and (3.35 ± 1.05) mg/d respectively, $p< 0.05$). It was associated with period of more active treatment and the most satisfactory clinical benefits. Along with this, a high content of GAGs as a reflection of inflammatory activity of the disease was detected, reflecting an abnormal inflammatory process.

The duration and activity of the disease have an effect on connective tissue metabolism, that was approved by correlating the duration of JIA with content of chondroitin-4-sulfate ($r = -0.37$; $p < 0.05$); the number of active joints with the level of chondroitin-6-sulfate ($r = -0.39$; $p < 0.05$) and the level of total chondroitin sulfate ($r = 0.37$; $p < 0.05$).

The significance of changes in biochemical homeostasis in patients with JIA is proved by versatility of correlation between indices of immune system and parameters of connective tissue metabolism. The correlations were established between the following parameters of blood: serum calcium correlated with the level of general T-lymphocytes ($r = 0.61$; $p< 0.01$), induced Nitro Blue Tetrazolium Reduction test ($r = 0.58$; $p < 0.02$) and the level of TNF-α ($r = 0.94$; $p < 0.001$); magnesium in blood correlated with blood level of circulating immune complexes ($r = 0.54$; $p < 0.03$); phosphorus blood correlated with T-helpers level ($r = 0.42$; $p < 0.05$), T-suppressors rate ($r = 0.43$; $p < 0.05$); chondroitin sulfates of blood correlated with phagocytes number ($r = 0.65$; $p < 0.001$), T-suppressors rate ($r = -0.84$; $p < 0.001$), the complement content ($r = 0.62$; $p < 0.01$), the level of IgG ($r = 0.50$; $p < 0.05$) and the content of IL-6 ($r = 0.44$; $p < 0.05$); the oxyproline excretion correlated with neutrophil phagocytic activity ($r = 0.45$; $p< 0.05$), spontaneous Nitro Blue Tetrazolium Reduction test ($r = -0.60$; $p < 0.02$). and induced Nitro Blue Tetrazolium Reduction test ($r = - 0.56$; $p<0.01$); the total GAGs level correlated with the level of circulating immune complexes ($r = 0.57$; $p< 0.02$), T-suppressors rate ($r = 0.69$; $p< 0.01$), IgM ($r = 0.47$; $p< 0.05$); the content of highly sulphanated GAGs correlated with T-suppressors rate ($r = 0.49$; $p< 0.05$), the level of circulating immune complexes ($r = 0.91$; $p< 0.001$).

Due to the analysis of correlations almost all studied parameters were involved in correlation the most actively in the period of disease duration from three to five years, confirming polycomponent pathological process. At this stage of the disease cornerstone parameters was the concentration of calcium, phosphorus and to a lesser extent the parameters of collagen metabolism. The isolated correlations were formed involving cholesterol, total GAGs and serum magnesium. It might be a background for the development of osteopenic syndrome and degenerative processes in the connective tissue.

At the time of disease duration over five years among the biochemical indices in creating ties components dominated and were characterized by the structural composition of proteoglycans and magnesium content of blood. It indicates the importance of their deviations in further progression of structural changes in the joints.

Among immunological parameters the most prominent correlation with biochemical parameters was in cell immunity link, T-suppressors were responsible for biochemically-immunological integration during the disease development.

On the other hand, a large number of multiple correlation dependencies at more distant stages of disease duration testify the instability of body systems secondary to the disease development, which leads to insufficient compensation in the event of changes in different parameters of metabolism. It may be a prerequisite for further progression of dystrophic changes in the connective tissue.

Discussion

Information about changes of connective tissue metabolism in patients with JIA was widely published. Plenty of studies showed disorganization of ECM component metabolism and structural changes of PGs and collagen, maintaining progress of immune inflammation and extending the destructive process into deeper structures of the joints [4, 13–17]. As a result of our study, the features of connective tissue metabolism were established to be more specific for female patients, represented with changes of all types of proteoglycans, except, chondroitin-6-sulfate. That fact was proved by the correlation of the female sex of JIA patients with the CS content, the total level of GAGs, the amounts of

chondroitin-6-sulfate, chondroitin-4-sulphate, highly sulphanated GAGs and the level of excretion of uronic acids. The similar results we reported earlier [9]. The decreased serum concentration of GAGs resulting from the substantial reduction of sulfated proteoglycans, particularly CS in untreated children with newly diagnosed JIA [9, 13, 14, 17], the increased levels of dermatan sulfate and hyaluronic acid in untreated JIA patients [9, 17] were recorded before. Cohort of the patients in our research included children with JIA, who were treated with methotrexate initially. In our opinion, it was one of the reasons of difference absence in the average total GAGs content, the level of serum chondroitin-6-sulfate and the concentration of uronic acid in daily urine in the patients with JIA under study generally in comparison with those in the similar aged healthy children. Corresponding to the results of our follow-up study the total amount of GAGs, chondroitin-6-sulfate and chondroitin-4-sulphate in spite of treatment was significantly lower than in healthy children only in patients with disease duration more then 5 years, which corresponded with the reports of our Polish colleagues [13, 17]. On the one hand, the similarity with other researches was recorded regarding the increased levels of highly sulphanated GAGs in JIA patients in comparison with healthy children [17]. On the other hand, our results showed that the level of highly sulphanated GAGs depended on JIA duration, because its content in the group of patients with disease history exceeding 5 years was lower then on previous stages. The significance of changes in biochemical homeostasis in patients with JIA is proved by versatility of correlation between immune system indices and connective tissue metabolism parameters. Serum content of chondroitin sulfates correlated with phagocytes number, T-suppressors rate, the complement content, the level of IgG and the content of IL-6; the content of highly sulphanated GAGs correlated with T-suppressors rate and the level of circulating immune complexes. Corresponding to our research and literature data the anti-inflammatory treatment of children with JIA leads to clinical improvement, but does not normalize connective tissue metabolism [14, 15].

Conclusions

The research has identified a significant imbalance of the structural components of proteoglycans matrix of the connective tissue in children with JIA. These changes are reflective of the presence of the metabolic activity due to the inflammatory process.

The accumulation of dermatan- and keratan-containing fractions of GAGs indicates the disintegration of proteoglycans chains with the possible development of dystrophic changes as early as in childhood secondary to JIA.

Females with JIA are at risk for the possible development of secondary osteoarthritis.

High disease activity is a major predictor of the development of degenerative changes in joints that is proved by the multiple correlation relationships between the indices of proteoglycans metabolism, the inorganic elements and the parameters of immunological homeostasis of the blood.

The severity of metabolic imbalance of proteoglycans depends on the duration of JIA.

The revealed changes can be the basis for pharmacological correction of biochemical composition of connective tissue structures in order to prevent the development of secondary dystrophic changes in the affected joints in children with JIA, and reflect the insufficient effectiveness of the treatment and persistence of subclinical activity of inflammation.

Declarations:

Acknowledgements

First, we thank the children and parents participating in the study. We also thank the scientists and clinicians of hospital of SI "Institute of children and adolescences health care of National Academy of Medical Science".

Funding

This work was supported by administration of SI "Institute of children and adolescences health care of National Academy of Medical Science".

Conflict of interests

There is no conflict of interests.

References

1. Aspberg, A. (2012). The different roles of aggrecan interaction domains. Journal of Histochemistry & Cytochemistry, 60(12), 987-996. doi:10.1369/0022155412464376

2. Frantz, C., Stewart, K. M., Weaver, V. M. (2010). The extracellular matrix at a glance. Journal of Cell Science, 123, 4195-4200. doi:10.1242/jcs.023820.

3. Горячковский, А. М. (2005) Клиническая биохимия в лабораторной диагностике. Одесса: Экология. [Goryachkovskiy A. M. (2005) Klinicheskaya biokhimiya v laboratornoy diagnostike. Odessa: Ekologiya].

4. Hanyecz, A., Olasz, K., Tarjanyi, O., Nemeth, P., Mikecz, K., Glant, T. T., Boldizsar, F. (29 January 2014). Proteoglycan aggrecan conducting T cell activation and apoptosis in a murine model of rheumatoid arthritis. Biomed Research International, Volume 2014, Article ID 942148, 13 pages. http://dx.doi.org/10.1155/2014/942148

5. Jura-P??torak, A., Komosinska-Vassev, K., Kotulska, A., Kucharz, E. J., Klimek, K., Kopec-Medrek, M., Olczyk, K. (10 June 2014) Alterations of plasma glycosaminoglycan profile in patients with rheumatoid arthritis in relation to disease activity. Clinica chimica acta, Volume 433, 20–27. doi:10.1016/j.cca.2014.02.027.

6. Kim, H. K., Laor, T., Graham, T. B., Anton, C. G., Salisbury, S. R., Racadio, J. M., Dardzinski, B. J. (2010). T2 relaxation time changes in distal femoral articular cartilage in children with juvenile idiopathic arthritis: a 3-year longitudinal study. American Journal of Roentgenology, 195(4), 1021–1025. doi:10.2214/AJR.09.4019.

7. Roughley, P. J., Mort, J. M. (2014). The role of aggrecan in normal and osteoarthritic cartilage. Journal of Experimental Orthopaedics, 1(8). doi:10.1186/s40634-014-0008-7.

8. Shevchenko, N. S., Lebec, I. S., Kashkalda, D. A. (2016) Changes of connective tissue biochemical indexes in children and adolescents with inflammatory diseases of joints. The Journal of V.N. Karazin Kharkiv National University, Series: biology, Issue 26, 11–15.

9. Штерн, М. Р., Тимошенко, О. П., Леонтьева, Ф. С., Клюева, Г. Ф. Способ определения глюкозаминогликанов в сыворотке крови. Патент A.s. 960626 SSSR, M. Kl 3.G 0,1 № 33148. SSSR. – №2998857128 – 13, Бюллетень № 35, 2 с. [Shtern M.P., Timoshenko O.P., Leontyeva F.S., Klyueva G.F. Sposob opredeleniya glikozaminoglikanov v syvorotke krovi. A.s. 960626 SSSR, M. Kl 3.G 0,1 № 33148. SSSR. – №2998857128 – 13; Zayavl. 23.10.80. Opubl. 23.09.82. Byul. №35. 2s.]

10. Struglics, A., Lohmander, L. S., Last, K., Akikusa, J., Allen, R., Fosang, A. J. (08 August 2012). Aggrecanase cleavage in juvenile idiopathic arthritis patients is minimally detected in the aggrecaninterglobular domain but robust at the aggrecan C-terminus. Arthritis & Rheumatism, Volume 64, Issue 12, 4151–4161. https://doi.org/10.1002/art.34665.

11. Theocharis, A. D., Skandalis, S. S., Gialeli, C., Karamanos, N. K. (1 February 2016). Extracellular matrix structure. Advanced Drug Delivery Reviews, Volume 97, 4–27. http://dx.doi.org/10.1016/j.addr.2015.11.001.

12. Winsz-Szczotka, K., Komosicska-Vassev, K., Kuznik-Trocha, K., Gruenpeter, A., Lachyr-Motyka, I., Olczyk, K. (June 2014) Influence of proteolytic-antiproteolytic enzymes and prooxidative-antioxidative factors on proteoglycan alterations in children with juvenile idiopathic arthritis. Clinical Biochemistry, Volume 47, Issue 9, 829–834. https://doi.org/10.1016/j.clinbiochem.2014.01.027.

13. Winsz-Szczotka, K., Komosicska-Vassev, K., Kuznik-Trocha, K., Jura-PyBtorak, A. (January 2016). Laboratory Indicators of Aggrecan Turnover in Juvenile Idiopathic Arthritis. Disease Markers, Volume 2016, Article ID 7157169, 7 pages. https://www.hindawi.com/journals/dm/2016/7157169/.

14. Winsz-Szczotka, K., Komosicska-Vassev, K., Kuznik-Trocha, K., Siwiec, A., Эeglec, B., Olczyk, K. (2015). Circulating keratan sulfate as a marker of metabolic changes of cartilage proteoglycan in juvenile idiopathic arthritis; influence of growth factors as well as proteolytic and prooxidative agents on aggrecan alterations. Clinical Chemistry and Laboratory Medicine, 53(2): 291–297. doi:10.1515/cclm-2014-0441.

15. Winsz-Szczotka, K., Mencner1, L., Olczyk, K. (2016). Metabolism of glycosaminoglycans in the course of juvenile idiopathic arthritis. Advances in Hygiene and Experimental Medicine, 70, 135–142. doi:10.5604/17322693.1196355.

16. Winsz-Szczotka, K., Kuznik-Trocha, K., Komosicska-Vassev, K., Wisowski, G., Gruenpeter, A., Lachyr-Motyka, I., Эeglec, B., Lemski, W., Olczyk, K. (2015). Plasma and urinary glycosaminoglycans in the course of juvenile idiopathic arthritis. Biochemical and Biophysical Research Communications, 458(3), 639-643. doi:10.1016/j.bbrc.2015.02.018.

Received: 20-Dec-2018
Accepted: 11-Mar-2019

SCHOOL-AGE CHILDREN AWARENESS OF THE CAUSES OF OBESITY AND ITS HEALTH RELATED OUTCOMES

Chaychenko T.V., Gonchar M.O., Chumachenko T.O., Klymenko V.A., Samsonenko T., Kharkova M.O

Kharkiv National Medical University, Ukraine

Abstract

Childhood obesity is a serious medical condition affecting children and adolescents that can be prevented by life style modification. Therefore, school-age children awareness of the causes of obesity and its health related outcomes is very importan. Subjects Methods This work is a part of the complex project "Assessment of the current nutritional status, nutrition-related health problems in school-age children in Ukraine". The total number of participants is 392 school-age children who were grouped by the age: primary school (75 children aged 6–9), secondary school (202 children aged 10–14) and high school (115 children aged 15–18). Original questionnaire was elaborated for the survey, consisting of both multiple choice questions and "open questions" that encouraged children to give their own idea with the purpose of understanding a real awareness of the problem. Answers to the open questions about the causes and effects of obesity were assessed. Results One third of respondents regardless of age (primary school, – 29.31%, secondary school – 29.21%, high school – 33.04%, p>0.05) understood that obesity can cause serious health problems and the most detrimental changes can occur in the cardiovascular system. It was established that self-controlled situations were named as the main causatives of the obesity by more than half of surveyed children (53.33% of primary school, 53.46% of secondary school children and 41.74% high school children, p>0.05). We established that less than 10% of children were not aware of the causes of obesity and possible outcomes. Meantime, 30% of respondents were not prone to give any answer. Conclusions: Regardless of age school-children are aware of health-related problems caused by obesity. Special education programs are necessary for all school-age children with the purpose of developing the responsibility for the health in their adult life.

Key words: *Obesity, causes of overweight, school-age children, social education program.*

Introduction

Number of overweight people is about 2.1 billion around the world. It exceeds the amount of starving people by 2.5 times [1]. There is a tendency to an increase in obesity rate not only in adult, but in pediatric population as well. The incidence of pediatric obesity increased dramatically within one generation [2]. Thus, 42 billion of children under 5 years are overweight or obese [3].

The main feature of this epidemic is that it can be prevented by life style modification [4], that may well lead to the cardiovascular risk reduction by the improvement of the metabolic parameters [5]. According to the WHO [4] and AHA [6], diet together with exercising are effective tools for the prevention of cardiovascular problems.

17.77% children in Ukraine are obese [7]. There is a tendency to the growing number of over non-medication interventions depends on different factors [9] but still is a treatment of choice of pediatric obesity [4].

Thus, study of school-age children awareness of the causes of obesity and its health related outcomes is crucial for the education programs.

2. Purposes, subjects and methods:

2.1 Purpose – to study school-age children awareness of the causes of obesity and its health related outcomes.

Corresponding Author:
Tetyana Chaychenko, MD, PhD, Professor
of Department of Pediatrics 1 and Neonatology
of Kharkiv National Medical University, Ukraine.
E-mail: tatyana.chaychenko@gmail.com

2.2 Subjects & Methods

This work is a part of the research "Assessment of the current nutritional status, nutrition-related health problems in school-age children in Ukraine", conducted at Kharkiv National Medical University for the development and further implementation of social education program for prevention of non-communicable diseases.

A cross-sectoral study was conducted in three different geographic regions of Ukraine. The present data provides survey results of children in Kharkiv region (as a representative of eastern part of country).

Survey assessment of current nutritional status in school-age children of 3 age groups (aged 6–9, 10–14, 15–18), who were randomly selected in urban and rural areas of region, was performed.

The total number of participants was 392 school-age children who were grouped by the age.

The high school group (aged 15–17) consisted of 115 children aged 15.28 + 1.47 that included 29 (25.22%) boys and 86 (74.78%) girls.

The secondary school group (aged 10–14) consisted of 202 children aged 12.55 + 1.40 that included 95 (47.03%) boys and 102 (52.97%) girls.

The primary school group (aged 6-9) consisted of 75 children aged 8.20 + 1.27 that included 43 (57.33%) boys and 32 (42.67%) girls.

For the survey the original questionnaire (adapted according to the FAO recommendations) was elaborated for evaluation of broader context (economic, social, environmental factors) that influences nutrition. Questionnaire consists of both multiple choice questions and "open questions" that encouraged children to give their own idea with the purpose of understanding real awareness of the problem. Survey was conducted in the comfortable atmosphere with no pressure from peers, parents or tutors.

Results of the provided data concerning causes and outcomes of obesity were grouped by the self-control (self-controlled, uncontrolled), affected body system and health risk.

Self-controlled causes include such answers as "wrong nutrition", "sedentary lifestyle", "continuous consumption of food", "increased appetite to the tasty food", "habitual eating", "consumption of bakery products", "consumption of sweets", "tasty food", "don't understand that it's a problem", etc.). Uncontrolled causes include such answers as: "stress", "hormonal problems", "diseases", "heredity", "metabolic problems" etc.).

Potential outcomes of obesity were grouped by the body systems.

• Cardiovascular problems: "myocardial infarction", "high blood pressure", "blocked vessels", "tachycardia", "stroke", "heart problems", etc.

• Orthopedic problems: "pain in legs", "difficulty in walking", "joint pain", "posture problems", etc.

• Gastrointestinal problems: "liver disorders", "stomachache", "nausea", "abdominal pain", "digestion problems"

• Endocrine problems: "high blood sugar", "diabetes", "infertility", etc.

• General well-being problems: "weakness", "tiredness", "poor sleeping", "headaches", "depression", etc.)

Potential outcomes of obesity were grouped by the health risk:

• Death or disability associated: "premature death", "myocardial infarction", "stroke", "tumors", etc.

• Chronic diseases: "diabetes", "joint problems", "dyspnea", "liver disorders", "digestion problems", "heart diseases"

• General well-being problems: "weakness", "tiredness", "poor sleeping", "headaches", "depression", etc.)

The study was approved by the institutional Committee in Ethics and Bioethics of Kharkiv National Medical University. Written consent from parents and children was obtained for every participant.

Standard statistics was used for the data analysis.

Conflict of interests. There is no conflict of interests.

3. Results and discussion

Children in all groups have chosen self-controlled causes of obesity as the most significant (53.33% of primary school, 53.46% of secondary school children and 41.74% high school children).

Number of children who do not know the answer to this question is growing from primary to secondary and declining from secondary to high school age. The number of those who did not respond was statistically higher in high-school group (*table 1*). This might be suggestive for the substitution of the problem by the non-primary school children whereas they are able to understand the real causes. On the other hand this tendency could be a feature of teenager's behavior.

Recent studies show that more than 60% of children are aware of childhood obesity and about 40% know that overeating, decreased outdoor play, spending more time in front of screen (TV, mobile, and laptop) can contribute to it [10]. 75% of parents in this study to 85% of obese children's parents are informed about causes of the

Table 1

Number of children who did not know the answer or did not respond to the question concerning causes of overweight (% of respondents)

Age group	"I do not know" answer	No answer
Primary school, n=75	2.67	34.67
Secondary school, n=202	12.38	24.75
High school, n=115	4.35	40.87
Difference	P_{13} = 0.01 P_{23} = 0.01	P_{23} = 0.002

excessive weight, meantime they do not practice this knowledge in parenting their children [11]. It is worth mentioning that the vast majority of them originate from the socioeconomic level. This could be suggestive for the pure family control. Moreover, we have our own data that reflect pure life style control in families with overweight children in forms of episodes of hyper-dominant behavior and complete neglecting of the problem [8]. On the other hand, school-age children are able to keep recommendations on the diet and develop appropriate food priorities [12]. Thus, it is necessary to develop programs for the education of children with no direct involvement of family members due to potential low compliance.

The cornerstone of any educational program is motivation that could be raised by the appreciation of potential outcomes of the problem [13]. Our comparative analysis of the awareness concerning outcomes of overweight demonstrates that children may well understand potential problems, associated with different parts of the body. Meanwhile, the third part of respondents despite of age (primary school, – 29.31%, secondary school – 29.21%, high school – 33.04%, p>0.05) consider cardiovascular problems as the most significant. It is an important issue as according to our studies, even overweight and metabolically healthy children are under the risk of cardiovascular problems [14].

About 10% of population associate obesity with decreased well-being (primary school – 12%, secondary school – 10.89%, high school – 13.91%, p>0.05). And the same amount – with GIT disorders (primary school – 10.67%, secondary school – 13.87%, high school – 12.17%, p>0.05).

Just 5-8% of respondents are able to see probable link between excessive weight and orthopedic problems (primary school – 8%, secondary school – 7.43%, high school – 5.22%, p>0.05).

Number of those who did not know the answer did not differ in groups. Whereas, about quarter of respondents regardless of age were not prone to answer the question about the body system most affected by overweight (*table 2*).

Table 2

Number of school-age children who did not respond and were unaware of body systems potentially affected by overweight (% of respondents)

Age group	"I do not know" answer	No answer
Primary school, n=75	4	34.68
Secondary school, n=202	8.91	24.75
High school, n=115	4.35	25.22
Difference	>0.05	> 0.05

Answers of children to the question about overweight outcomes were grouped by the degree of risk for the health and life. We have revealed that children in all age groups understand the link between obesity and acute cardiovascular events, diabetes and cancer (primary school – 20%, secondary school – 28.71%, high school – 29.57%, p>0.05). They also understand that excessive body mass can cause general weakness, tiredness, sleep disorders and headache (primary school – 20%, secondary school – 15.35%, high school – 12.7%, p>0.05). This findings suggest appropriate awareness of the problem which is greater than in other middle-income countries [10, 11, 16]. Simultaneously, the number of unreplied subjects varies from 20 to 40% that is really significant and attracts a particular attention.

Conclusions

1. School-age children understand that obesity can cause problems with a general well-being, leading to the chronic diseases, disability and even death. Regardless of age children consider that the most detrimental changes can occur in the cardiovascular system (primary school – 29.31%,

secondary school – 29.21%, high school – 33.04%, p>0.05).

2. Self-controlled situations (wrong nutrition, sedentary life style, etc.) were named as the main causatives of obesity by more than half children regardless of age (primary school – 53.33%, secondary school – 53.46%, high school – 41.74%).

3. The number of children who are not aware of obesity causes and potential outcomes is less than 10%. Whereas about 30% of respondents were not prone to give an answer that is suggestive for the psychological substitution of the problem. Thus, education is necessary for all school-age children with the purpose of developing the responsibility for health in their adult life.

References

1. Roberto, C. A., Swinburn, B., Hawkes, C. (2015). Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. Lancet. 385(9985):2400 -2409. doi: 10.1016/ S0140–6736(14)61744-X.

2. Lobstein, T., Jackson-Leach, R., Moodie, M.L. (2015). Child and adolescent obesity: part of a bigger picture. Lancet. 385(9986): 2510-2520. doi: 10.1016/S0140–6736(14)61746-3

3. World Health Organization Fact sheet № 311. Obesity and overweight (2016). Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

4. WHO Report of the Commission on Ending Childhood Obesity.World Health Organization (2016). 68 P.

5. Ho, M., Garnett, S.P., Baur, L., Burrows, T., Stewart, L., Neve, M., Collins, C. (2012). Effectiveness of life style interventions inchild obesity: systematic reviewwithmeta-analysis. Pediatrics, 130(6), 1647–71. doi: 10.1542/peds.2012-1176.

6. American College of Cardiology/American Heart Association Task Force on Practice Guidelines OEP. Expert panel report: Guidelines (2013) for the management of overweight and obesity in adults. Obesity (Silver Spring). 2014;22 Suppl 2:S41–S410. doi: 10.1002/ oby.20660.

7. Zelins`ka N. B., Rudenko N. G. (2015) Stan nadannya medy`chnoyi dopomogy` dityam z endokry`nnoyu patologiyeyu v Ukrayini u 2014 roci [The state of medical care for children with endocrine pathology in Ukraine in 2014]. Ukrayins`ky`j zhurnal dy`tyachoyi endokry`nologiyi, no 2, pp. 5–13.

8. Chaychenko, T., Rybka, O., Georgievska, N., Buginska, N. (2016) Trends of nutrition of eastern Ukrainian children: tendency to overweight, dehydration and impaired social adaptation. Horm Res Pediatr, 86 (S1): 1–556 doi:10.1159/000449142

9. Chaychenko T. (2015) Efekty`vnist` nemedy`kamentozny`x intervencij u ditej z ozhy`rinnyam [Efficacy of non-drug interversion in obese children]Ukrayins`ky`j zhurnal dy`tyachoyi endokry`nologiyi, no 1 (13), pp. 31–35.].

10. Pradeepa, S., Elango, S., Andrews, M., Hanan, R.A., Amritha, S., Ambica, G. (2018). Awareness on childhood obesity among mothers attending pediatrics outpatient department at tertiary care teaching hospital. Int J Med Sci Public Health, 7(9), 760–764.

11. Mabiala Babela, J. R., Nika, E. R., Nkounkou Milandou, K. G., Missambou Mandilou, S. V., Bouangui Bazolana, S. B., Monabeka, H. G., & Moyen, G. (2016). Knowledge, Attitudes, and Practices of Parents Facing Child and Adolescent Obesity in Brazzaville, Congo. Global pediatric health, 3, 2333794X16675546. doi:10.1177/2333794X16675546

12. Waters, E., de Silva-Sanigorski, A., Hall, B.J., Brown, T., Campbell, K.J., Gao, Y. (2011) Interventions for preventing obesity in children. Cochraine Database Syst. Rev, 12 CD 001871

13. Deforche, B., Haerens, L., Ilse de Bourdeaudhuij (2011) How to make overweight children exercise and follow the recommendations, International Journal of Pediatric Obesity, 6:sup1, 35–41. doi: 10.3109/ 17477166.2011.583660

14. Chaychenko, T. (2016).Risk related cardiovascular changes in metabolically healthy obese adolescents. Polish Annals of Medicine,23, 2, 87-91. doi:10.1016/j.poamed.2016.01.006

15. Aceves-Martins, M., Llaurady, E., Tarro, L., Sola, R., & Giralt, M. (2016). Obesity-promoting factors in Mexican children and adolescents: challenges and opportunities. Global health action, 9, 29625. doi:10.3402/gha.v9.29625

Received: 02-Feb-2019
Accepted: 14-Mar-2019

DISORDERS OF HAEMOSTASIS, COMPLICATIONS AND THEIR CORRECTION IN CHILDREN WITH ACUTE LEUKEMIA

Makieieva N. I., Gubar S.O., Koval V. A., Zharkova T. S.

Kharkiv National Medical University, Ukraine

Abstract

To study the significance of capillarotrophic disorders in the development of complications of chemotherapy in children with acute leukemia and the effectiveness of the treatment and prevention of these complications. Subjects and methods. Parameters of hemostasis system (plasma, platelet and vascular chains) have been studied in 86 children aged 1–17 years with acute leukemia in the follow-up of the condition, before the start and secondary to chemotherapy during the development of infectious and non-infectious complications. The patients receiving standard therapy in compliance with the BFM protocols were divided into two groups according to the difference in the substitution therapy: Group 1 included patients who did not receive platelet replacement therapy; Group 2 comprised patients who received replacement therapy, including preventive platelet transfusion. The effectiveness of therapy was accessed by comparing the number of complications in patients of both groups. Results. Severe myelosuppression was observed in 100% of patients. A decrease in the number of platelets in the blood lower than 20*109/l was found in 43% of patients, agranulocytosis was found in 35%. Group 1 patients had bleeding in 33% of cases, stage II-III anemia in 76%, gastroenterologic inflammation in 21%, respiratory distress syndrome in 33%, pneumonia in 47% , sepsis in 14%, other localization of infection in 13%. In Group 2 patients the incidence of complications of chemotherapy and their severity decreased by 2–6 times. The concept of the leading role of thrombocytopenia in the development of stages of capillarotrophic disorders is presented. Conclusions. The results indicate the important role of severe thrombocytopenia and capillarotrophic disorders in the development of infectious and non-infectious complications of chemotherapy in patients with acute leukemia. Adequate replacement therapy with donor platelets reduces the incidence and severity of complications, increases the effectiveness of treatment.

Key words: *acute leukemia, children, complications, correction, hemostasis.*

Introduction

Disorders in the system of hemostasis in patients with acute leukemia occur due to underlying disease, but even more often they occur as a result of myelodepression as a complication of polychemotherapy (PCT). Hemorrhagic syndrome and neutropenia are severe complications of PCT, that worsen the course and prognosis of the disease [1–6]. Due to modern therapy of acute leukemia (AL) according to BFM protocols remission is achieved in 80–90% of patients [3, 7, 8]. However, the use of high-dosage, multi-component, prolonged PCT is accompanied by numerous complications affecting prognosis of the disease [1, 7, 9, 10]. Improvement of supportive therapy, prediction and timely elimination of these complications allows to improve the final result of therapy [7, 8, 11].

Corresponding Author:
Nataliya Makieiva, MD, PhD, Professor,
Head of the Department of Pediatrics No.2
of Kharkiv National Medical University, Ukraine.
E-mail: makeevanataly313@gmail.com

2 Purposes, subjects and methods:

2.1 Purpose – study the parameters of the hemostasis system in children with acute leukemia at various stages of the disease, to determine the importance of thrombocytopenia in the development of capillarotrophic disorders and complications of PCT, and the role of transfusion of platelets as substitution therapy.

2.2 Subjects & Methods

The parameters of platelet, plasma, vascular components of the hemostasis system were studied in 86 children aged 2 to 18 years with

acute leukemia (AL) using autocoagulation test (ACT) according to Z.S. Barkagan [12], prothrombin index, fibrinogen level, total protein in the blood serum, platelet count in peripheral blood, permeability of capillaries (PC) according to Kaznacheev [12]. The studies were carried out before the start of treatment and secondary to PCT with complications. An analysis of the complications of PCT and a comparison of their frequency and severity in two groups of AL patients of intensive care unit of Kharkiv Municipal Children Hospital No. 16 has been performed. Group 1 included patients (n = 42) with acute lymphoblastic leukemia (ALL), who underwent PCT and supportive therapy according to the protocol of treatment. Group 2 included patients with ALL (n = 32) and acute myeloblastic leukemia (AML) (n = 12) who, in addition to protocol treatment, underwent transfusion of platelets.

Standard statistics was used for the data analysis.

Conflict of interests. There is no conflict of interests.

3 Results and discussion

All the patients under study were found to have a decreased platelet count in the blood, which was due to the replacement of the megakaryocytic bone marrow lineage with tumor cell clones. It was confirmed by bone marrow examination. The level of platelets in ALL patients ranged from $24*10^9$/l to $107*10^9$/l and averaged 46.0± $17.7*10^9$/l. In patients with AML, the platelet count ranged from $42.0*10^9$/L to $73.0*10^9$/L and averaged $55.3±7.4*10^9$/L, that was significantly higher than in ALL patients ($p<0.05$). The bleeding time in ALL patients was 4.8±1.7 minutes and 6.6±2.3 minutes in AML patients. The prothrombin index in patients of both groups did not differ significantly, and in the majority of patients it was within the norm or exceeded it.

The parameters of autocoagulation test (ACT) in patients with ALL and AML before PCT are presented in *Table. 1*.

According to the ACT in both group of patients, there was an increase in the coagulation potential and a moderate inhibition of fibrinolysis, but there were no significant differences in the parameters in the groups. Permeability of capillaries for water and protein in 14 examined patients did not differ from the normal ones. In 8 patients with a very low level of platelets, an increase in the permeability of capillaries to water was 5.2±1.1 ml (normal level: 2.3±1.8 ml). In patients with AL, the initial state of the hemostasis system was characterized by a decrease in the platelet level, and normal or, in some patients, an elevated plasma factor level of the blood coagulation system indicated compensatory responses. Five patients with severe hemorrhagic syndrome in the onset of the disease were found to have platelet levels below critical values ($<20*10^9$/l), as well as hypocoagulation and activation of fibrinolysis according to ACT (decrease in fibrinogen, prothrombin index, IIT, decrease in fibrinolysis time). There were no significant differences in the parameters of the hemostatic system in patients with ALL and AML before the onset of PCT. It allowed us to include these patients and those, who received thromboconcentrate substitution therapy, into one group.

Modern therapy for acute leukemia includes prolonged high-dose PCT. This leads to the development of numerous complications of hemopoiesis, gastrointestinal tract, immune system, lungs, etc.[9, 13, 14].

Thus, all patients developed severe myelodepression with inhibition of three hematopoietic germs as a result of chemotherapy. The most dangerous is leukopenia (agranulocytosis), which leads to the development of purulent complica-tions, sepsis, infectious-toxic shock (ITS) [5, 14, 15], as well as thrombocytopenia and, as a result, a number of hemostasis disorders and bleeding The platelets count in 43% of ALL patients decreased due to myelodepression below the critical level ($<20*10^9$/L), in others was not

Table 1

ACT data in patients with ALL and AML before the start of PCT (M±m)

Parameters / ACT Patients with AL	A (min)	T1 (min)	T2 (min)	M A (min)	IIT units	Fibrinolysis (min)	Fibrinofen (g/l)	PTI (%)
ALL (n=74)	21.7±2.4	3.7±0.5	9.1±1.6	96.5±4.6	2.1±0.2	58.7±4.7	3.1±0.4	97.6±3.7
AML (n=12)	18.2±2.1	3.9±1.0	9.4±0.7	88.7±3.3	1.8+0.2	56.2±2.7	2.4±0.28	89.3±3.1

more than 35*10^9/L. Data of disorders in the hemostasis system secondary to therapy are presented in *Table. 2*.

In 7 patients, long-term and massive bleeding led to severe anemia.

The severity of the condition of patients

Table 2

ACT (M ± m) parameters in patients with AL with myelodepression with and without complications as a result of polychemotherapy

Parameters / ACT Patients with AL	A (min)	T1 (min)	T2 (min)	M A (min)	IIT units	Fibrinolysis (min.)	Fibrinogen (g/l)	PTI (%)
AL with myelo-depression without complications (n = 24)	14.7±3.3	3.63±0.22	8.66±1.12	94.8±2.2	1.92±0.14	54.6±2.3	1.94±0.16	76.6±4.9
AL with myelo-depression with complications (n = 49)	11.4±3.1	3.5±0.4	8.28±1.06	88.5±2.6*	1.61±0.12*	51.7±2.8	1.30±0.21*	58.9±3.2*

Note. * significant differences ($p < 0.05$) in parameters of AL patients with myelodepression without complications and with complications.

We compared the parameters of the hemostatic system in patients with AL who received chemotherapy and had no complications except myelodepression with hemostatic parameters of patients with purulent and non-infectious complications.

Patients who did not have severe complications of therapy, were shown to have a moderate decrease in the coagulation potential of the blood, confirmed by a decrease in IIT, MA, as well as activation of fibrinolysis, a decrease in the serum fibrinogen level. The coagulation time was 6.7±1.8 minutes. These changes in the parameters of the hemostasis system did not have its clinical manifestation. There was no hemorrhagic syndrome, and only in certain patients petechiae and mild bleeding were observed in disorders of the integrity of the skin and mucous membranes. Patients with numerous complications, both infectious and non-infectious, had more significant disorders of the hemostatic system, compared with the patients before PCT and patients who did not have numerous complications.

For example, the parameters of the prothrombin index, fibrinogen, IIT were significantly lower ($p<0.05$), fibrinogen-B, fibrin degradation products were most often detected, A and MA parameter decreased, which indicated the development of disseminated intravascular coagulation syndrome in these patients in phase of consumption. Clinical manifestations were characterized by the development of spontaneous hemorrhages in the skin, mucous membranes, nasal, gastrointestinal, uterine (in girls) bleeding. depended not only on the degree of myelodepression, but also on its duration and the number of other complications and, above all, infectious ones. The relationship between the severity of disorders of hemostatic parameters, organ and infectious complications in children with oncohe-matological diseases was presented in a number of studies [15, 16]. An analogous dependence was also determined with the degree of impairment of capillary permeability. The maximal disorders of the permeability of capillaries for water (6.7± 1.1 ml/100 ml of arterial blood (normal level: 4.8±0.37) and protein P% = 7.8±0.63%, normal level: 4.6±0.93%) were observed in patients with severe complications, multiple organ failure, as well as in patients with myelodepression and critical thrombocytopenia of 7–10 days or more. As a rule, myelodepression with hemorrhagic manifestations was accompanied by a large number of complications.

Our study allowed us to develop a concept of stages of capillarotrophic disorders in patients with acute leukemia. In case of severe prolonged thrombocytopenia, capillary trophism is disrupted, triggering edema and endothelial dysfunction. At this stage, clinical manifestations of capillarotrophic disorders are absent, but laboratory tests detected an increase in the permeability of capillaries to water. Then there was a syndrome of "leakage" of capillaries or extravasations of fluid, electrolytes, protein, other plasma components to interstitial space. The patients were found to have positive water balance during the infusion therapy, relative oliguria, weight gain, edema of tissues, impaired

capillary permeability for protein, progressive hypoproteinemia. Furthermore, there were disorders of Frank-Starling mechanism, a decrease in effective oncotic pressure and an increase in extravasation of the fluid. Administration of plasma, albumin was not very effective at this stage, and the use of diuretics (saluretics) can be unsafe because of deterioration of tissue perfusion and transcapillary exchange. The decrease in blood volume, activation of renin-angiotensin-aldosterone system, antidiuretic hormone and retention of water and sodium in the body were observed. Decrease in blood volume and anemia resulted in disorders of tissue perfusion and oxygen delivery. Then the process progressed and led to organ disorders: edema of the interstitium of soft tissues, internal organs, hypoxia, acidosis. Clinically, it is clearly manifested in the lungs with formation of acute respiratory distress syndrome (ARDS) and in the gastrointestinal tract with formation of stomatogastroenterocolitis, edema, ischemia of the intestinal wall, activation of intestinal microflora, diarrhea. Similar changes develop in all tissues of the body at the stage of transcapillary exchange disruption. Lungs and intestines are a frequent gateway to infection, acting as a pacemaker and promoting the development of the systemic inflammatory reaction syndrome and sepsis, which reflects the stage of tissue barrier disorders. Diapedesis of blood constituents beyond the vascular system and bleeding are the top of the "iceberg" of capillarotrophic disorders.

The supposition of a significant role of hemostasis system disorders in the development of complications was based on the following factors. Firstly, they are based on the physiological significance of this system in ensuring the aggregate state and viscosity of blood, the integrity of the vascular system, preservation of blood volume, transcapillary exchange (capillary permeability, capillarotrophic function of platelets). Secondly, our long-term experience in the treatment of patients with AL children, indicated that in cases of possibility of providing reliable hemostasis, the course and prognosis of the disease improved [17–19]. This fact was confirmed in patients with acute myeloid leukemia (AML), in which the level of blood platelets was maintained at the level of at least $70*10^9$/L by multiple transfusions of platelet concentrate, regulated by the protocol of treatment. None of these patients had severe hemorrhagic syndrome or polyorganic disorders requiring intensive therapy, so better preservation of organs and systems during PCT was registered. This is consistent with research data [15, 20–23] confirming the high efficiency of prevention and treatment of hemorrhagic syndrome in patients with acute leukemia and severe myelodepression. The main variants and incidence of infectious and non-infectious complications in the patients with ALL who did not receive transfusions of platelet concentrate (Group 1) are presented in *Table 3*.

Patients admitted to the intensive care unit were found to have from 3 to 7 complications of PCT (*Table 3*). We have tested the use of donor thrombocyte concentrate for the correction of thrombocytopenia and angiotrophic disorders. Thrombocyte concentrate from the donor was obtained with the help of the COBE SPECTRA blood fractionator. It is used to obtain high quality thrombocyte concentrate. Indications for thrombocyte concentrate transfusion were bleeding or thrombocytopenia below the critical level. Bleeding was arrested after 1–2 transfusions of thrombocyte concentrate in all patients, in 36% of patients the platelet count continued to increase, and they quickly recovered from myelodepression

Table 3

Types and incidence of complications of chemotherapy in patients who did not receive transfusions of platelet concentrate *

Non-infectious complications	%	Infectious complications	%
Neutropenia	100	Pneumonia	47
Agranulocytosis	35	(including destructive)	7
Thrombocytopenia <20*10 ^{9}/л	43	Dysbacteriosis of the intestine	17
Bleeding	33	Pneumonia + other infectious focuses	
Hemorrhagic shock	2		11
Stage II-III anemia	76		
Gastrointestinal disorders	21	Sepsis	14
Acute respiratory distress syndrome (ARDS)	33	Other infectious complications (otitis media, pyelonephritis, phlebitis, meningitis)	13

*The incidence of complications is expressed in % in relation to the total number of patients with acute leukemia who did not receive transfusions of platelet concentrate.

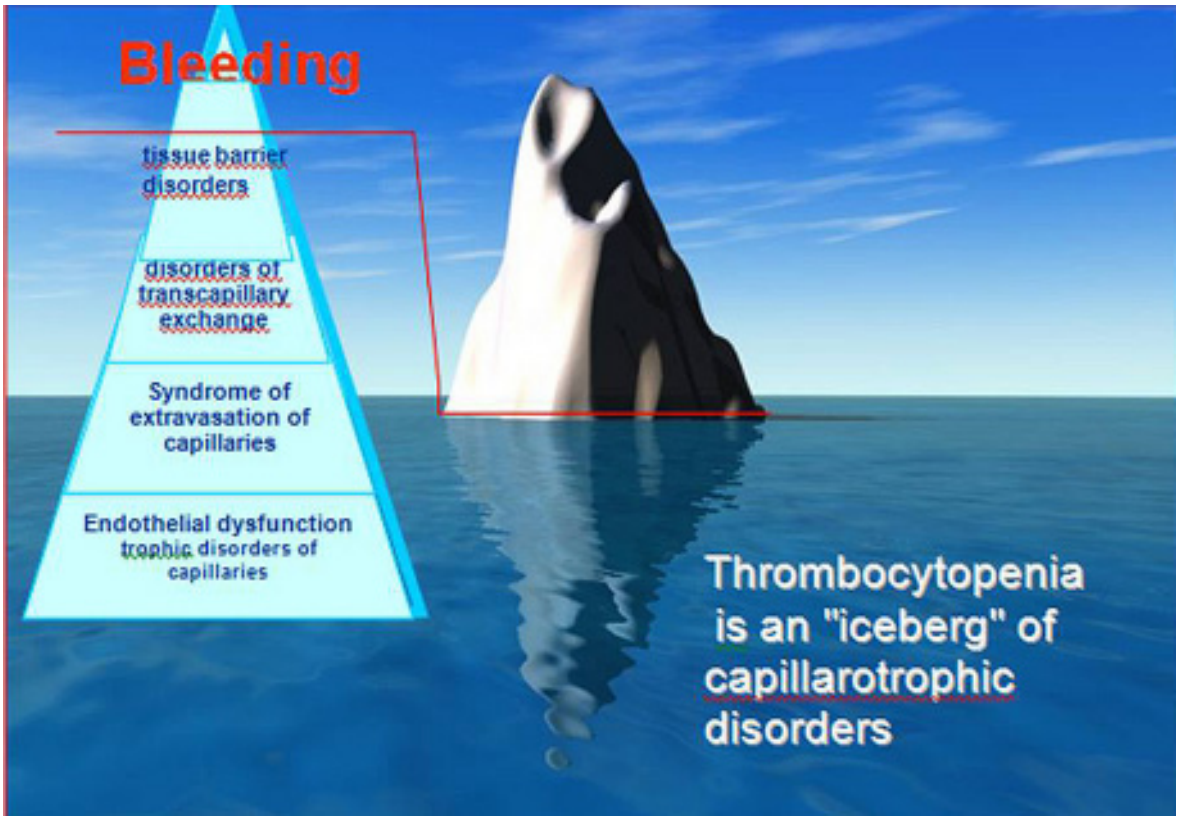
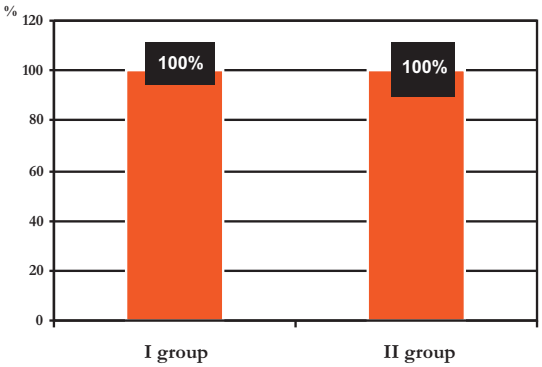


Fig.1. Stages of capillarotrophic disorders in the form of an iceberg with hemorrhagic syndrome as its top

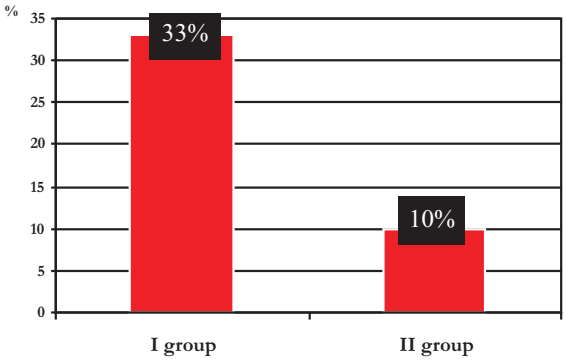
and complications. Moreover, 64% of patients had myelodepression and during the day the platelets again decreased to a critical level. Such patients underwent an intensive course of thrombocyte concentrate replacement therapy (Group 2) daily or at intervals of 1 to 2 days, depending on the therapeutic effect and management of myelodepression.

Evaluation of the effectiveness of thrombocyte concentrate substitution therapy was performed according to clinical data (reduction or elimination of hemorrhagic syndrome and other complications), and by laboratory parameters, blood coagulation time, bleeding time, platelet count, capillary permeability for water and protein, auto-coagulation test, fibrinogen, products degradation of fibrin, a common protein of blood. The final result of the introduced method of treatment and prevention of complications of PCT was assessed by the number and severity of complications in comparison with patients who were treated without the use of thrombocyte concentrate (group I).

Comparison of the frequency of complications of chemotherapy in patients of Groups 1 and 2 showed that myelodepression is the only complication that was registered with the same frequency (100%), infectious and non-infectious complications were less often observed in Group 2 patients. Thus, bleeding occurred 3.3 times less frequently and there were no cases of hemorrhagic shock, respiratory distress



2-A. Myelodepression



2-B. Bleeding

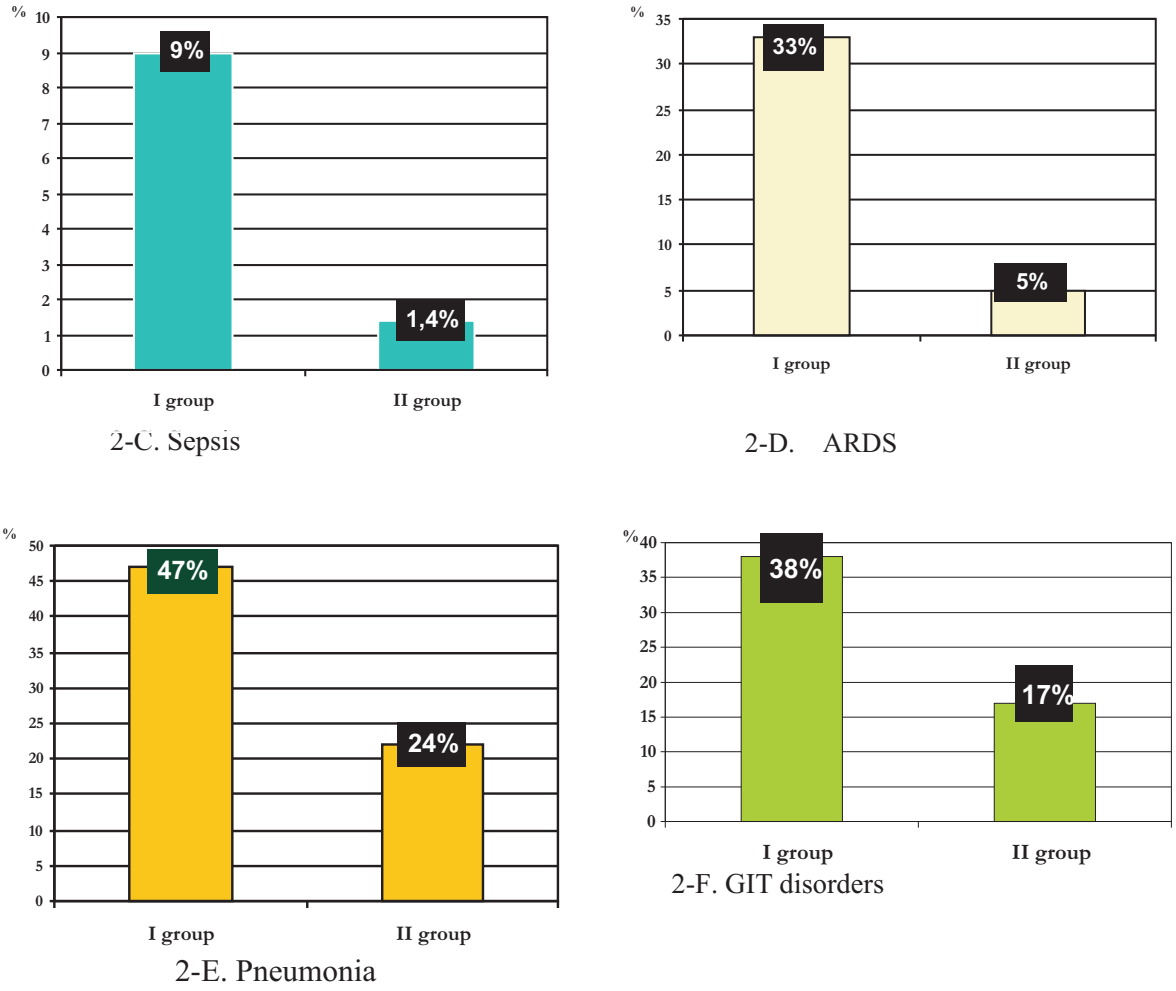


Fig. 2. The frequency of complications of chemotherapy in patients of Groups 1 and 2 (the indices are presented as a percentage of the total number of patients in groups)

syndrome (ARDS) was 6.8 times less frequent, dento-esophagogastroenteropathy, enterocolitis was 2 times less frequent, pneumonia was 2.3 times less frequent, sepsis 6 times less often in Group 2. The presented complications in Group 2 patients were less severe and were eliminated earlier in comparison with the patients of the control group.

Mortality at the hospital No. 16 in Kharkov, which was most commonly caused by oncohematological disorders, has decreased over the last 10 years from 2% to 0.2–0.3%.

Conclusions

Patients with AL at the beginning of the disease, before the onset of PCT, were found to have thrombocytopenia, increased plasma clotting factors, normal permeability of capillaries in most children.

Secondary to myelosuppression, critical thrombocytopenia was detected, lasting 7–10 days, accompanied by clinically significant capillarotrophic disorders, which contributed to the development or progression of numerous infectious and non-infectious PCT complications.

Substitution therapy with donor thrombocyte concentrate demonstrated the high effectiveness of treatment of complications of chemotherapy in patients with myelodepression, reduces the frequency and severity of their manifestations.

To prevent the onset and severe course of complications, patients with a critical level of platelets should have preventive, substitution therapy with thromboconcentrate prior to the development of bleeding and capillarotrophic disorders.

References

1. Pavlova M.P., Aleynikova O.V. (1996) Gematologicheskie bolezni u detey [Hematologic diseases in children]. Minsk, 283–292.

2. Ching-Hon P., William L. C., Soheil M., Arceci R. J. (2011). Biology, Risk Stratification, and Therapy of Pediatric Acute Leukemias: An Update. Clin Oncol, 29(5): 551–565. doi: 10.1200/ JCO.2010.30.7405

3. Sousa D.W., Ferreira F.V. , F?lix F. H. , Lopes M.V. (2015). Acute lymphoblastic leukemia in children and adolescents: prognostic factors and analysis of survival. Rev Bras Hematol Hemoter,37(4):223–229. doi: 10.1016/ j.bjhh.2015.03.009.

4. Cooper S.L., Brown P.A.(2015). Treatment of Pediatric Acute Lymphoblastic Leukemia. Pediatr Clin North Am. ,62(1): 61–73. doi: 10.1016/j.pcl.2014.09.006.

5. Dayyani F., Mougalian S.S., Naqvi K., Shan J., Ravandi F., Cortes J., …Garcia-Manero G. (2011). Prediction model for mortality after intracranial hemorrhage in patients with leukemia. Am J Hematol, 86(7): 546–549. doi: 10.1002/ajh.22031.

6. Dmitriev V.V., Dunaev I.A. (2012) Prognozirovanie gemorragicheskih oslozhneniy na etapah programmnogo lecheniya detey so zlokachestvennyimi novoobrazovaniyami i gemoblastozami [Prediction of hemorrhagic complications at the stages of programmed treatment of children with malignant neoplasms and hemoblastosis]. Onkogematologiya [Oncohaematology], 7(1), 15–21.

7. Balasheva I.I., Maevskaya Z.A., Desyatova L.F. (1996) Predvaritelnyie rezultatyi lecheniya detey, bolnyih ostryim limfoblastnyim leykozom po protokolu BFM-90 [Preliminary results of treatment of children with acute lymphoblastic leukemia according to the BFM-90 protocol]. Trudyi uchastnikov konferentsii po protivoopuholevoy terapii [Proceedings of the participants of the conference on antitumor therapy]. Moscow, p. 44.

8. Jimйnez-Hernбndez E., Jaimes-Reyes E. Z., Arellano-Galindo J., Garcнa-Jimйnez X.,Tiznado-Garcнa H.M, Duecas-Gonzбlez M.T.,…Mejнa-Arangurй J. M. (2015). Survival of Mexican Children with Acute Lymphoblastic Leukaemia under Treatment with the Protocol from the Dana-Farber Cancer Institute. Biomed Res

Int. 2015: 576950. doi: 10.1155/2015/576950.

9. Sotnikov A.V. (2014) Zhizneugrozhayuschie oslozhneniya u detey posle himioterapii po povodu onkologicheskih zabolevaniy. Dissertatsiya. d.med.n., "Rossiyskiy onkologicheskiy nauchnyiy tsentr im. N.N. Blohina" [Life-threatening complications in children after chemotherapy for cancer. Thesis. Doctor of Medical Sciences, "Russian Cancer Research Center named by N.N. Blokhin "], Moscow, 360 p.

10. Valchevskaya E.V., Kolomenskaya S.A., Marchenko E.N. (2014) Ostryiy leykoz u detey [Acute leukemia in children]. Zdorove rebenka [Child's health], 6(57), 113–118.

11. Aleskerova G.A. (2016) Lechenie ostrogo limfoblastnogo leykoza u detey [Treatment of acute lymphoblastic leukemia in children]. Meditsinskiy sovet, 1, 172–176.

12. Veltischev Yu.E., Kislyak N.S.. (1979) Spravochnik po funktsionalnoy diagnostike v pediatrii [Handbook of functional diagnostics in pediatrics]. Moscow, 259–260.

13. Inaba H, Pei D, Wolf J, Howard SC, Hayden RT, Go M, Varechtchouk O, Hahn T at al. (2017) Infection-related complications during treatment for childhood acute lymphoblastic leukemia. Annals of Oncology, 28(2), 386–392. doi: 10.1093/annonc/mdw557.

14. Garcia-Vidal C., Cardozo-Espinola C., Puerta-Alcalde P., Marco F., Tellez A., Agьero D., ... Soriano A. (2018) Risk factors for mortality in patients with acute leukemia and bloodstream infections in the era of multiresistance. PLoS One. 2018; 13(6): e0199531. doi: 10.1371/journal.pone.0199531. D:PMC 6023133.

15. Middelburg R.A., Kerkhoffs J.-L. H., van der Bom J.G. (2018). Thrombocytopenia and bleeding in myelosuppressed transfusion-dependent patients: a simulation study exploring underlying mechanisms.Clin Epidemiol, 10: 401–411. doi: 10.2147/CLEP.S149926.

16. Marta Zapata-Tarrйs, Miguel Klьnder-Klьnder, Carlo Cicero-Oneto, Roberto Rivera-Luna, Fernando Ortega-Rнos Velasco, Gabriel Cortйs Gallo, and Elisa Dorantes-Acosta (2012) Analysis of complications during treatment of children with acute lymphoblastic leukemia. Boletнn Mйdico del Hospital Infantil de M?xico, 69(3), 208–215.

17. Stanworth S.J., Dyer C., Choo L., Bakrania L., Copplestone A., Llewelyn C., …Murphy M.F.(2010). Do all patients with hematologic malignancies and severe thrombocytopenia need prophylactic platelet

transfusions? Background, rationale, and design of a clinical trial (trial of platelet prophylaxis) to assess the effectiveness of prophylactic platelet transfusions. Transfus Med Re, 24:163–71.

18. Stanworth S.J., Hyde C., Heddle N., Rebulla P., Brunskill S., Murphy M.F. (2004). Prophylactic platelet transfusion for haemorrhage after chemotherapy and stem cell transplantation. Cochrane Database Syst Rev. 2004CD004269

19. Slichter S.J., Kaufman R.M., Assmann S.F., McCullough J., Triulzi DJ, Strauss R.G., Granger S. (2010). Dose of prophylactic platelet transfusions and prevention of hemorrhage. N Engl J Med, 362:600–6

20. Cannas G.,Thomas X.(2015).Supportive care in patients with acute leukaemia: historical perspectives Blood Transfus,13(2):205–220. doi: 10.2450/2014.0080-140

21. M.Stolla, M. A. Refaai, J.M. Heal, Sh. L. Spinelli, O. Garraud, R.P. Phipps, N.Blumberg.(2015). Platelet Transfusion – The New Immunology of an Old Therapy. Front Immunol, 6: 28. doi: 10.3389/fimmu.2015.00028 PMCID: PMC4313719

22. Cid J., Harm S.K., Yazer M.H. (2013). Platelet Transfusion – the Art and Science of Compromise Transfus Med Hemother, 40(3): 160–171. doi: 10.1159/000351230 PMCID: PMC3725020.

23. Wandt H., Sch?fer-Eckart K., Greinacher A.(2014). Platelet Transfusion in Hematology, Oncology and Surgery. Dtsch Arztebl Int, 111(48): 809–815. doi: 10.3238/arztebl.2014.0809.

Received: 27-Dec-2018
Accepted: 14-Mar-2019

CONGENITAL CARDITIS IN A NEWBORN (CASE REPORT)

Gonchar M.O., Senatorova A.V., Matsiyevskaya N.K., Zatoloka D.V.

Kharkiv National Medical University, Ukraine

Abstract
Diagnosis of carditis in newborns presents a number of difficulties, even with the results of high-technology research methods. Carditis is characterized by the absence of specific diagnostic criteria, similarity of clinical manifestations of cardiovascular and respiratory failure in young children, including secondary to generalized infectious diseases. The article presents a case of an atypical clinical presentation of carditis in a child with a confirmed intrauterine infection.
Key words: *newborns, carditis, intrauterine infection.*

Difficulties in diagnosing carditis in pediatric practice, especially in newborns, are due to the lack of specific diagnostic criteria, similarity of clinical manifestations of cardiovascular and respiratory failure in young children, especially secondary to generalized infectious diseases [1, 7].

The incidence of carditis is not exactly established. According to autopsy, it develops in 3–8% of children. Two thirds of newborns with carditis have a fulminant course, and the mortality rate is high, in 50% or more [3].

Mothers of newborns with carditis often have signs of infection during pregnancy, manifestations of heart failure can be registered in utero or in the maternity hospital. The risk of horizontal or vertical transmission from mother to newborn is high [7].

There is no generally accepted classification of carditis. It is a common practice to differentiate congenital (antenatal) and acquired (postnatal) carditis of newborns [2].

Carditis is considered reliably congenital in the presence of severe clinical symptoms of prenatal generalized infection, early manifestation of severe HF and cardiomegaly of varying severity in combination with damage to many organs and systems, and with appropriate reliable instrumental and laboratory (virological, bacteriological, immuno-biochemical) markers of myocardial damage. Congenital carditis is considered probable if HF and cardiomegaly are detected in the first 6 months of life (less frequently at the age of 2–3 years) without a prior intercurrent disease of the child, but with indications of the mother's disease during pregnancy in history. Congenital carditis is classified into early and late forms, depending on the expected timing of the intrauterine onset of the process and differences in the morphological substrate of pathology. The condition is characterized by endomyocardial fibroelastosis in the fetus with an infection up to 28 weeks of gestation and the usual phasic inflammatory process at later stages.

Acquired (postnatal) carditis in newborns and infants more often has viral etiology and acute course. The presence in the history of previous infections of the upper respiratory tract, febrile fever, diarrhea syndrome in the mother and the newborn is of great importance in the diagnosis. There can also be nosocomial infections.

The course of carditis can be acute (up to 3 months), subacute (up to 18 months), chronic (more than 18 months, relapsing and primary chronic). Subacute course is not typical for carditis manifesting in the neonatal period.

The most common cause of carditis in newborns are Coxsackie enterovirus (types B and less often A) and ECHO, a number of cardiotropic poliomyelitis viruses, some types of influenza virus, herpes simplex virus I and II, adenovirus, CMV

Corresponding Author:
Anastasiya Senatorova, MD, PhD,
Professor asssistant of Department of Pediatrics 1 and Neonatology of Kharkiv National Medical Univeristy, Ukraine.
E-mail: anastasya.senatorova@gmail.com

and toxoplasma infection. This is explained by the cardiotropic nature of these viruses and the imperfection of immunological protection of newborns and young children predisposed to this heart disease [7].

Myocarditis and pancarditis can be a complication of any infectious disease (of bacterial, fungal, rickettsial and parasitic etiology) or a consequence of toxic effects (medication, ionizing radiation, chemical). In recent years, there have been cases of congenital carditis in newborns as one of the symptoms of the visceral form of early congenital symptomatic syphilis. There are single descriptions of Kawasaki disease with myocarditis, coronaritis, acute HF in the 1st month of life.

According to the literature, the introduction of virus into the cell is most likely important in the pathogenesis of carditis only when associated with disorders of the immune system. This stage is accompanied by a violation of myocardial metabolism, dystrophic and necrotic changes, development of an immunological imbalance. Protection mechanisms become effective only after the peak of virus replication on the 3rd or 4th day and are due to the combined participation of the macrophage defense system, T-lymphocytes and B-lymphocytes and interferon in virus elimination. Lymphocyte-macrophage inflammatory infiltration is accompanied by lysis of myofibrils infected with cytotoxic T-lymphocytes with fibroblast production, increased production of pro-inflammatory cytokines. Thus, myocardial damage is the result of both direct and indirect cytotoxic effects. The developing HF is accompanied by hyperproduction of neurohormones and a further increase in the secretion of proinflammatory cytokines (TNF-2, IL-1, IL-6, IL-8), which initiate remodeling and progressive myocardial dysfunction. The mechanism of action of cytokines in inflammation and HF comprises negative inotropic action, cardiac remodeling, impaired endothelium-dependent arteriole dilatation (due to activation of endogenous nitric oxide synthase) and increased cardiomyocyte apoptosis. Clinically, this correlates with impaired left ventricular function, contractility, cardiomegaly, severity of clinical manifestations and prognosis of the disease [2, 3].

Clinically, in congenital carditis, symptoms of the disease develop in utero or in a maternity hospital. In acquired (postnatal) carditis, symptoms develop on the 5th–7th day of a viral infection, after contact with a sick mother, relatives, and sometimes in nosocomial contacts. The severity of the condition progressively increases and depends on the severity of infectious toxicosis, severity of myocardial damage, CH mainly of the left ventricular and/or right ventricular type, the presence of circulatory collapse.

In moderate forms only moderate cardiomegaly, electrophotographic and ECHO changes, and moderately elevated concentrations of biochemical markers serve as criteria for myocarditis.

In severe course, symptoms of acute left ventricular and then right ventricular insufficiency with dyspnea, cyanosis of the mucous membranes, tachycardia, palpitations, congestive moist rales in the lungs, enlarged liver, less often splenomegaly, and limb pastosity develop quickly. Edema of the limbs, polyserositis and ascites appear in the terminal stage. Extracardiac manifestations may include symptoms of enterocolitis, meningitis, encephalitis [3, 4].

Newborns are found to have manifestations of intrauterine growth retardation. Fever, acrocyanosis or general cyanosis, fatigue during feeding up to anorexia, shortness of breath are possible. On examination, there are no chest deformity in the form of a heart hump and visual abnormal pulsations. Percussion reveals varying degrees of heart enlargement, up to cardiomegaly. The apical impulse is not changed or moderately weakened, shifted to the left depending on the degree of heart enlargement.

Physical changes are characterized by varying degrees of tachycardia, muffled heart sounds, sometimes weakening of I tone, embryocardia, development of myocardial cantering rhythm (most often diastolic or presystolic as a symptom of pressure increase in the atria or valvulitis of the mitral valve) at the apex. Systolic murmur of muscular character is typical, somewhat later patient develop systolic murmur of relative insufficiency of atrioventricular valves, mainly mitral, with a maximum volume at the apex of the heart. Rhythm and conduction disturbances are observed quite frequently.

In some newborns, myocarditis is associated with pericarditis, which is clinically accompanied by a sharp deafness of heart tones up to aphonia [1, 6].

Routine laboratory tests in the diagnosis of carditis are not sufficiently informative, non-specific and have diagnostic value only in combination with clinical findings and functional research data.

The increase in the activity of cardiac isoenzymes CPK-MB, LDH1 and LDH2 is more specific (there is evidence of an increase in their activity in the acute phase to values comparable to those in myocardial infarction).

In recent years, troponin and its isoenzymes (troponin I and troponin T) are considered to be a rather informative biochemical marker of myocardial damage. In absence of clinical or ECG signs of ischemia, an increase in troponin I or troponin T in blood indicates non-coronary damage (necrosis), which is very important for pediatrics and neonatology.

Bacteriological and virological studies of blood and other biological fluids (in particular, pericardial effusion), serological and enzyme immunoassay methods establish the bacterial or viral etiology of the disease. Ig M antibodies (AT) have diagnostic value for acute carditis. AT titres usually increase four times in the recovery period compared with the acute period. Polymerase chain reaction is informative. In recent years, data have appeared on the correspondence of the increase in AT titres to various structures of the myocardium (to cardiomyocytes, the conduction system, endothelium, and other structures) to different clinical manifestations of carditis [2, 6].

An x-ray study determines an increase in the size of the heart (up to cardiomegaly), with an increase in the cardio-thoracic index of more than 0.6–0.7. Patients are typically found to have changed shape of heart (pathological remodeling) with smoothness of contours and development of sphericity, occasionally signs of venous congestion in the lungs or moderate pleural effusion.

ECG changes depend on the degree of myocarditis activity and are characterized by transient unstable non-specific changes in repolarization in the form of isoelectricity or depression (when combined with pericarditis in the form of elevation) in more than three leads of the ST segment, in the form of amplitude reduction, isoelectricity, T wave inversion. Patients are often found to have a decrease in QRS complex voltage. Pseudo-infarction changes and pronounced signs of subendocardial ischemia can be signs of coronaritis. Early changes may include different types of blockades of the bundle of the His branch, AV blockades. Extrasystole is observed in 60% of cases, less frequently paroxysmal tachycardia, atrial fibrillation. High scale extrasystole, ventricular arrhythmia and alorrhythmia are prognostically unfavorable. Rhythm disorders can be persistent and difficult to treat with metabolic and antiarrhythmic agents before the onset of the clinical effect of anti-inflammatory therapy. The severity of signs of overload (hypertrophy) of the left heart chambers is variable. Development of HF with congestion in the pulmonary and systemic blood circulation is characterized by signs of overload of both the atria and the right ventricle [4, 6].

ECHO shows myocardial edema, moderate dilation of the heart cavities, a decrease in pumping indices (left ventricular ejection fraction) and contractile function of the myocardium. Doppler examination determines relative mitral and tricuspid insufficiency, impaired left ventricular diastolic function. If there are signs of pericarditis, a pericardial effusion is quantified (1 mm of pericardial separation corresponds to approximately 10 ml of effusion) [7].

Radionuclide methods of examination and especially new radiological methods of simultaneous study of metabolism and myocardial function are sufficiently informative for the differential diagnosis of reversible (inflammatory and ischemic) and irreversible (destructive) myocardial changes, clarification or diagnosis. These studies are just beginning to be used in pediatric practice.

Case report

A boy was born in the perinatal center from the 2nd pregnancy, 1st labor at the gestation term of 39 weeks by caesarean section. The mother has a high degree of disturbance of fetal hemodynamics with the formation of ascites. At 11 weeks, she was found to have positive titres of Ig G antibodies to cytomegalovirus, herpetic, toxoplasmic infections. Prenatal examination of the fetal Doppler echocardiography revealed a marked predominance of the right heart chambers, ventricular myocardial hypertrophy and interventricular septum; moderate tricuspid regurgitation.

The function of fetal communications is not impaired, the Botallo's duct is narrowed to 1.4 mm, the aorta at the base is narrowed to 7 mm, the PA at the valve level is 11.8 mm, the left ventricle is reduced in size; ascitic strip of fluid up to 20 mm. Fetal-placental blood flow is normal, pulsation index in the umbilical artery is 1.05 (68‰); systolic-diastolic ratio is (S/D) is 2.57. Fetal blood flow is decompensated - reverse blood flow in the venous duct. The pulsation index PI in the middle cerebral artery (MCA) is 1.09. There is two-phase pulsation in the umbilical vein. The uterine-placental blood flow is impaired – highly resistant PI in the right uterine artery (UA) is

1.34, PI in the left UA is 0.69, average PI is 1.17 (98‰) (*Fig. 1.1*).

The child was born with a mass of 2380 g, height 47 cm, head circumference 33 cm, chest circumference 31 cm. Apgar score is 7–8 points. At birth, the general condition is satisfactory, flexor position, loud cry, muscular hyper tone, body temperature 37.1°C. The frequency of respiratory movements is 46/min, heart rate is 142/min. Heart sounds are rhythmic, systolic murmur. The abdomen is soft and palpable. Acid-base indices at birth: pH – 7.19, pCO_2 – 68.7 mmHg, pO2 – 41 mmHg, HCO_2 – 28.8, BE 3.6 mmol/l – compensated respiratory acidosis. Blood count and biochemical blood count (total cord blood bilirubin, direct bilirubin, glucose): without abnormalities. The child was transferred to the department of joint residence with the mother, where he stayed for 8–10 days.

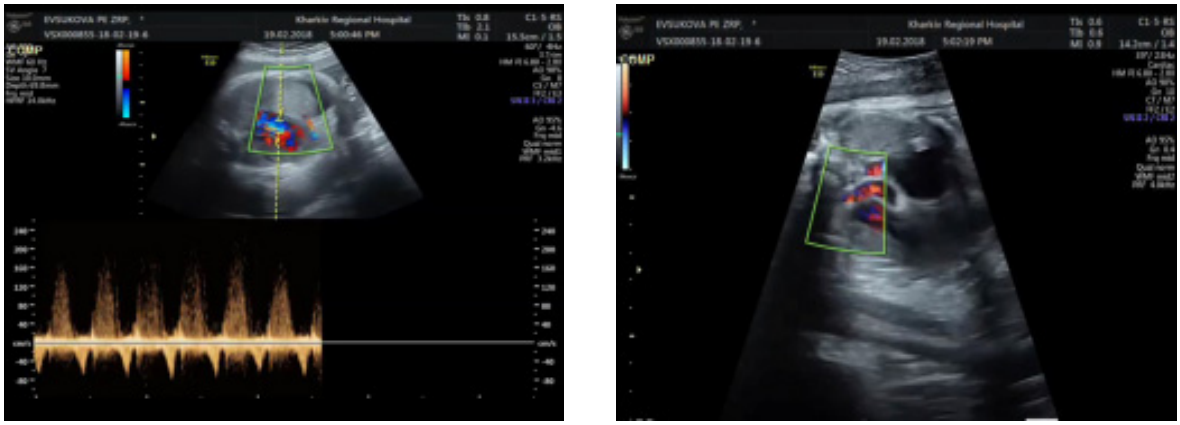


Fig. 1. Fetal Doppler echocardiography, gestation term of 39 weeks

During the first days of life the general condition of the child is without impairments. His cry is loud. Spontaneous motor activity is sufficient. The skin is pink, clean and dry. Elasticity and skin turgor aare reduced. Breathing is spontaneous, rhythmic, with intercostal retraction. On auscultation: breathing in the lungs is carried out in all departments on both sides. Breathing rate – 44/min. On auscultation heart sounds are rhythmic, muffled. Heart rate – 140/min. The abdomen is soft. Liver + 1.5 cm below the edge of the costal arch. Urination is sufficient. Clinical blood assay did not show any abnormalities.

Doppler echocardiography in the first day of life: diastolic diameter of the left ventricle (DdLV) – 14.3 mm (norm – 20.0mm), thickness of the posterior wall of the left ventricle (Tpwlv) – 6.0 mm (norm – 4.0mm), ejection fraction (EF) – 72% (norm – up to 65–75%), ΔD – 40% (norm – up to 45%), diameter of the left atrium (DLA) – 9.0 mm (norm – up to 12 mm), diastolic diameter of the right ventricle (DdRV) – 15.7 mm (norm – up to 8.0 mm), diameter of the right atrium (DRA) – 13.1 mm (norm – up to 9.0 mm), aortic diameter (Ao) – 9.0 mm (norm – to 10.0 mm), diameter of the pulmonary artery (PA) – 12.0 mm (norm – up to 10.0 mm), Δp of Ao valve – 6.3 mmHg (norm – up to 10.0 mmHg), Δp of PA valve – 7.4 mm Hg (norm – to 10.0 mmHg), average pressure in the PA trunk – 43 mmHg (norm – to 25 mmHg). Conclusion: LV hypoplasia, RV hypertophy, dilation of right chambers. Patent foramen ovale, diameter – 3.2 mm, left-right shunt. Open arterial duct, diameter is 1.0 mm. The blood flow in the abdominal aorta is pulsating.

Cardiac surgeon's conclusions: Congenital heart disease (persistent ductus arteriosus, patent foramen ovale). Pulmonary hypertension. Follow-up Doppler echocardiography is recommended.

In the follow-up observation the child's condition is stable. Biochemical blood assay: ALT – 307.9 U / l (norm – up to 45 U / l), ACT – 176.1 U/l (norm – up to 75 U/l), total bilirubin – 63.5 μmol / l (normal – up to 21 μmol / l), direct bilirubin – 10.5 μmol / l (norm – up to 6.8 μmol /l), indirect bilirubin – 53 μmol/l (norm – up to 14.2 μmol /l), CPK – 364 U/l (norm – up to 190 U/l), CPK-MB – 251.3 U/l (norm – up to 25 U/l), LDH – 1200,1 U/l (norm – up to 750 U/l), blood urea – 6.8 mmol/l (norm – 2.5–4.4 mmol/l), C-reactive protein – 10.49 mg/l.

Doppler echocardiography findings on the third day of life: DdLV – 14.0 mm (norm – 20.0 mm), EF 75% (norm – up to 75%), ΔD – 40% (norm – up to 45%), DLA – 9.0 mm (norm – to 10.0 mmHg), DdRV – 15.6 mm (norm – to 10.0 mmHg), DRA –13.0 mm (norm – to 10.0 mmHg), Ao diameter – 9.0 mm (norm – up to 10.0 mmHg), PA diameter – 4.0 mm (norm – up to 10.0 mmHg), Δp of Ao valve – 7.0 mmHg, Δp of PA valve – 7.1 mmHg (norm – up to 10.0 mmHg), Δp of asc. Ao – 7.7 mmHg (norm – to 10.0 mm Hg), the average pressure in PA trunk – 27 mmHg

(norm – up to 30 mmHg). Conclusion: severe hypertrophy of the RV. Dilatation of right chambers, 1st–2nd degree tricuspid regurgitation. Pulmonary hypertension. Open oval window, diameter – 3.0 mm, with left-right shunting. Open arterial duct, diameter – 1.2 mm. The blood flow in the abdominal aorta is pulsating (*Fig. 2, Fig. 3*).

An ECG study was performed: overloading of the right chambers, myocardial hypertrophy of the interventricular septum and right ventricle. Slowing down of AV conduction. Incomplete blockade of the right bundle of His. Violation of repolarization processes (*Fig. 4*).

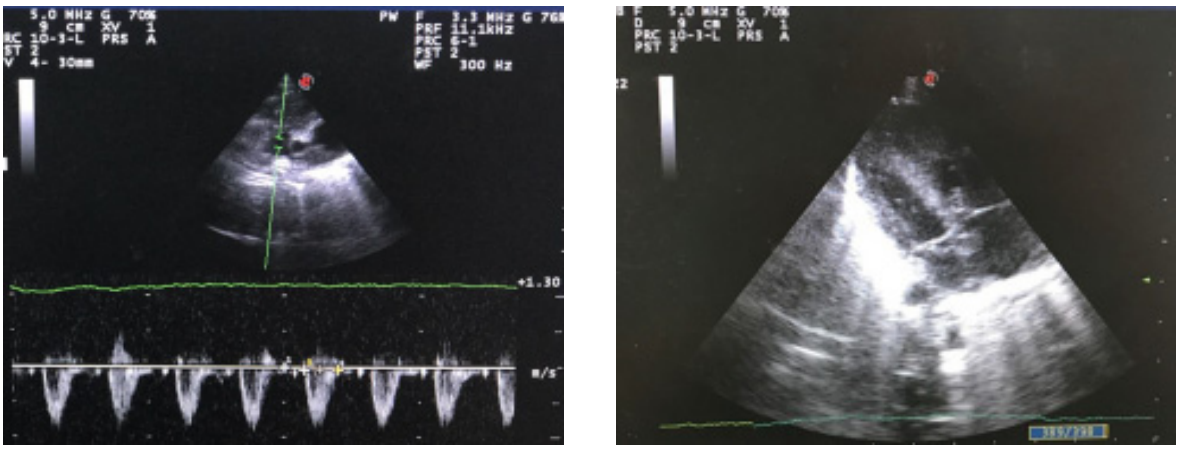


Fig. 2. Doppler echocardiography (M-mode) of a newborn (boy) on the 3rd day of life

Holter heart rate monitoring: during the day heart rate (HR) without abnormalities. Arrhythmias are not registered. Episodes of sinus "tachy-brady" arrhythmia. The patient was found to have 21 episodes of ST depression.

The child underwent immunoassay for antibodies to infectious agents:

Cytomegalovirus infection IgM 0.01 (norm – 0.384), IgG 1.75 (norm – 0.3) positive; herpes simplex IgM 0.046 (norm – 0.287), IgG 2.25 (norm – 0.215) positive; Toxoplasma IgM 0.012 (norm – 0.412), IgG 0.025 (norm – 1.21) negative. Hepatitis B and C markers are negative.

The mother refused to perform any PCR tests for the newborn. Diagnosis: intrauterine viral infection (carditis, hepatitis). 1st degree Pulmonary hypertension.

The newborn received antiviral treatment according to the protocol [4, 5, 7].

In the follow-up observation on the 10th day C-reactive protein normalized to 4.1 mg/l. Biochemical blood assay: total bilirubin 28.3 μmol/l, direct 9.8 μmol/l, ALT 42.4 U/l (normal), AsT 56.1 U/l (normal).

Repeated ECG studies: sinus rhythm. Overloading of the right chambers, myocardial hypertrophy of the interventricular septum and right ventricle. Slowing down of AV conduction. Incomplete blockade of the right bundle of His. Disruption of repolarization processes (*Fig. 5*).

Doppler echocardiography on the tenth day of life: DdLV – 15.3 mm (norm – 20.0mm), Tpwlv – 7.0 mm (norm – 2.0mm), EF – 70% (norm – up to 75%), DΔ – 40% (norm – up to 45%), DLA – 8.0 mm (norm – up to 12 mm), DdRV – 15.7 mm (norm – up to 8.0 mm), DRA – 13.4 mm (norm – up to 9.0 mm), Ao diameter – 9.0 mm

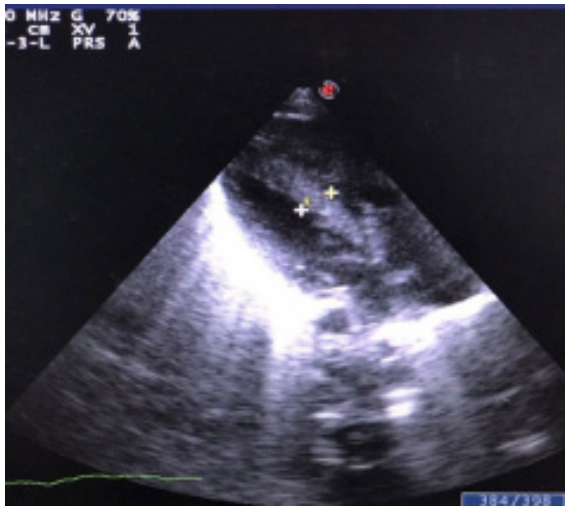


Fig. 3. Doppler echocardiography (M-mode) of a newborn (boy) on the 3rd day of life

(norm – up to 9.0 mm), PA diameter – 11.0 mm (norm – up to 9.0 mm), Δp of Ao valve – 5.2 mmHg (norm – to 10.0 mm Hg), Δp PA valve – 6.4 mmHg (norm – up to 10.0 mmHg), the average pressure in the PA trunk – 29 mmHg (norm – up to 30 mmHg). Conclusion: LV hypoplasia, RV hypertophy, dilation of right chambers. Open oval window, diameter – 3.2 mm, left-right shunt. The open arterial duct diameter is 1.0 mm. The blood flow in the abdominal aorta is pulsating.

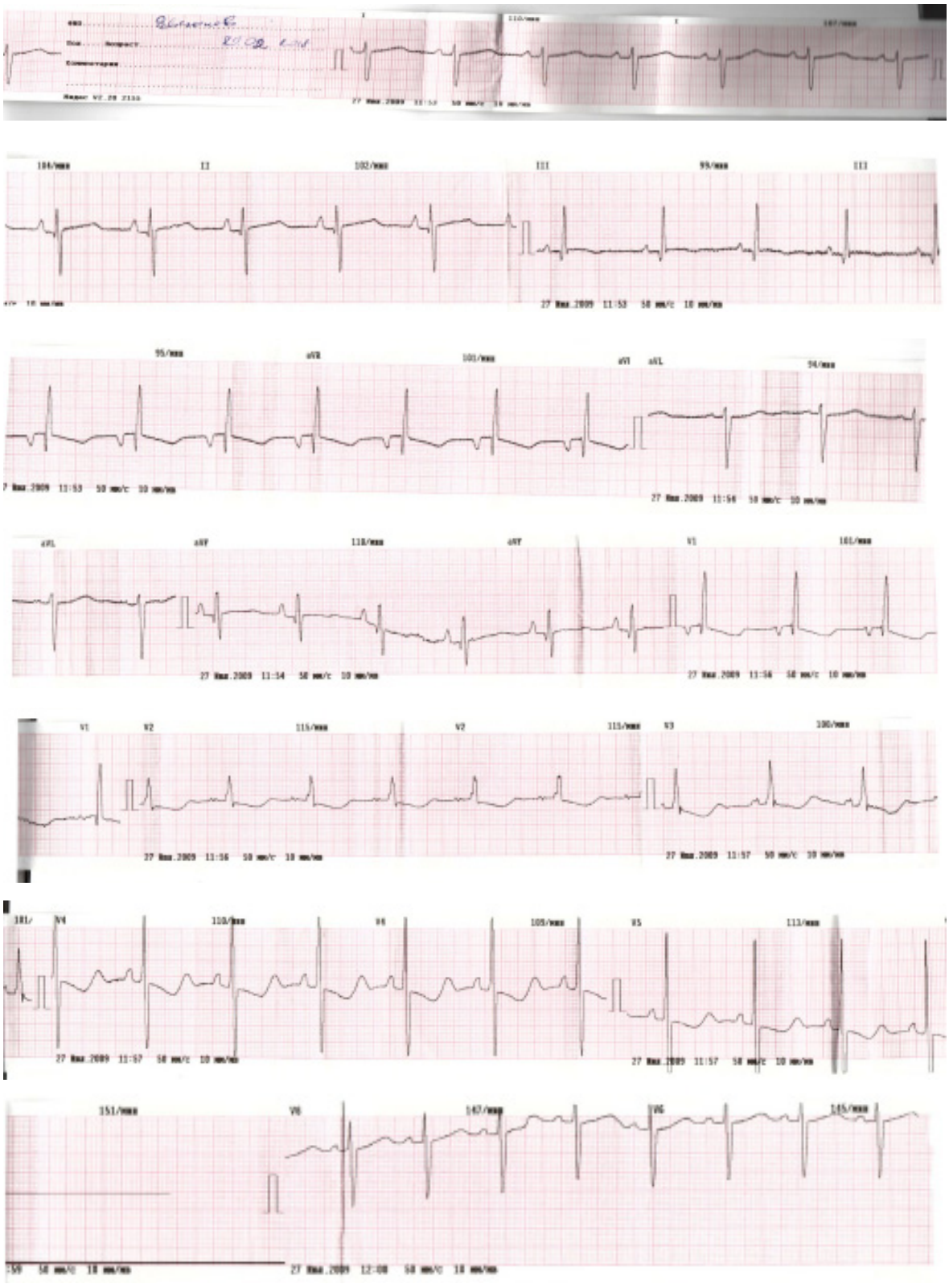


Fig. 4. ECG of a newborn (boy) on the 1st day of life

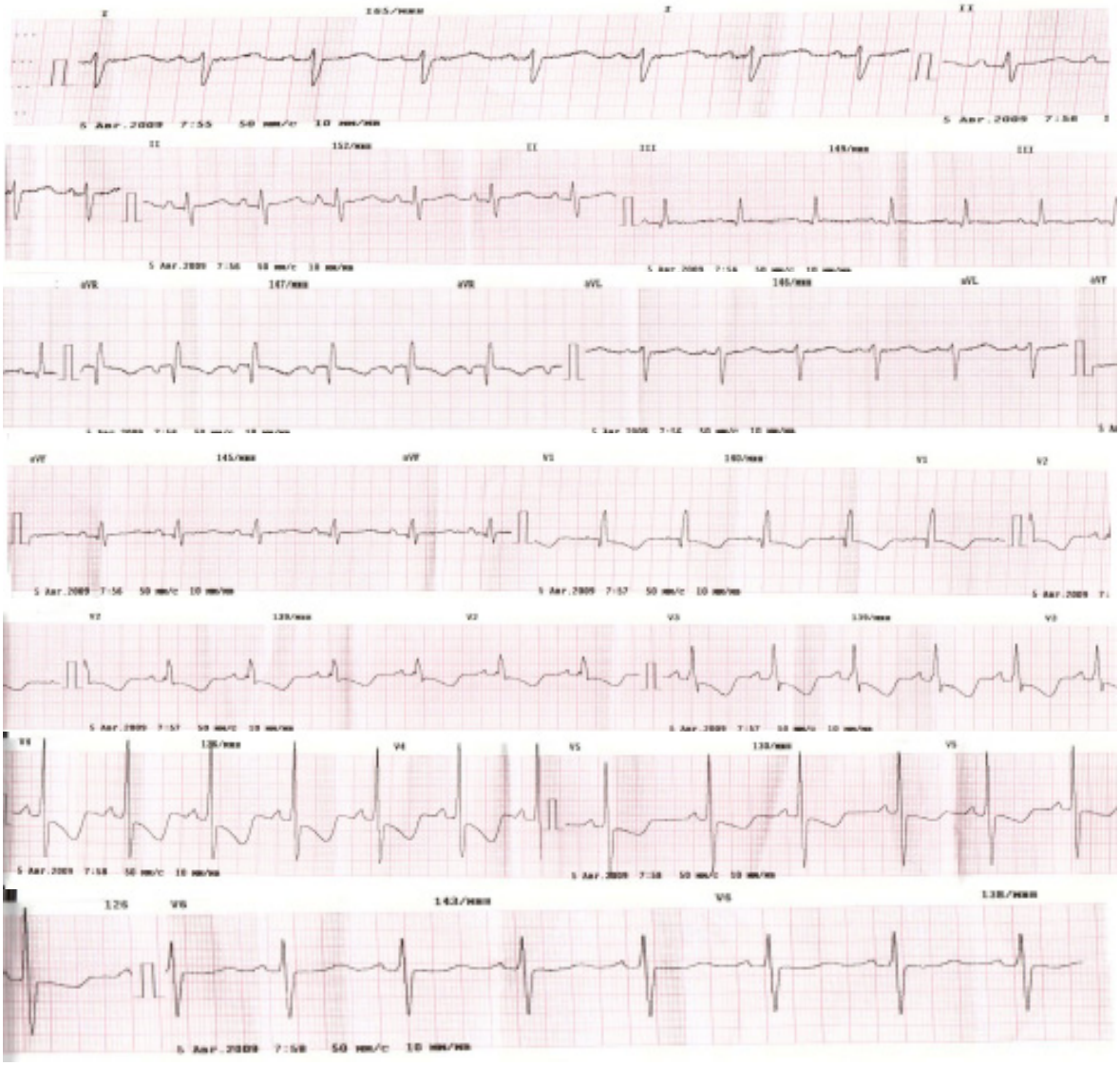


Fig. 5. ECG of a newborn E. (boy) on the 10th day of life

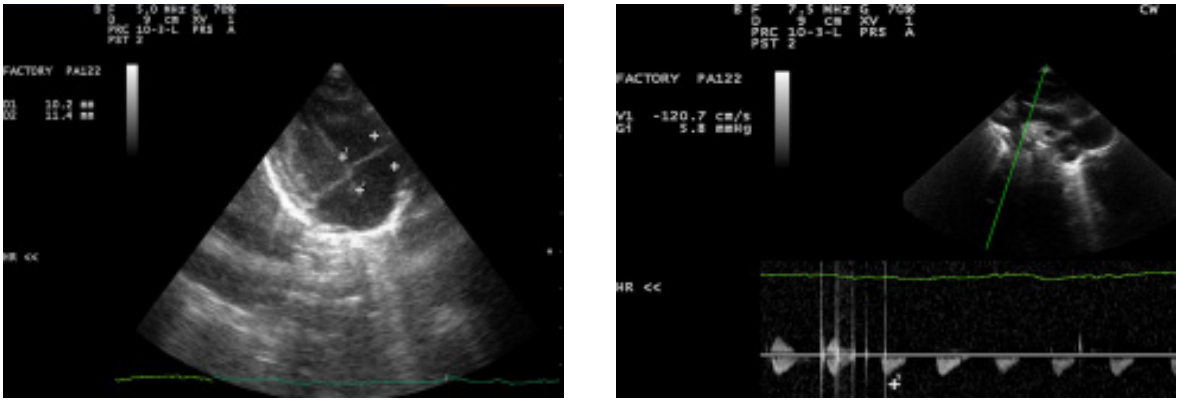


Fig. 6. Doppler echocardiography of a newborn E. (boy) on the 10th day of life

Conclusions:

Carditis in a newborn with an intrauterine viral infection may be manifested by significant hypertrophy of the right chambers. Diagnosis of carditis requires the exclusion of congenital heart disease, premature closure of the ductus arteriosus.

References

1. Bergmann K.R., Kharbanda A., Haveman L. (2015). Myocarditis and pericarditis in the pediatric patient: Validated management strategies. Pediatr. Emerg. Med. Pract., 12, 1–22.

2. Camargo P.R., Okay T.S., Yamamoto L., Del Negro G.M., Lopes A.A. (2011). Myocarditis in children and detection of viruses in myocardial tissue: Implications for immunosuppressive therapy. Int. J. Cardiol., 148, 204–208.

3. Ines T. F., Joana O. M. (2016) Myocarditis in Paediatric Patients: Unveiling the Progression to Dilated Cardiomyopathy and Heart Failure J. Cardiovasc., 3, 31–49. doi:10.3390/jcdd3040031.

4. Guidelines for Diagnosis and Treatment of Myocarditis. JCS Joint Working Group. Circ J (2011), 75, 734–743.

5. Jensen L.D., Marchant D.J. (2016). Emerging pharmacologic targets and treatments for myocarditis. Pharmacol.Ther., 161, 40–51.

6. Shauer A., Gotsman, I., Keren A., Zwas D., Hellman Y., Durst R., Admon D. . (2013). Acute viral myocarditis: Current concepts in diagnosis and treatment. Isr. Med. Assoc. J, 15, 180–185.

7. Tzialla C, Civardi E, Borghesi A, Sarasini A, Baldanti F, Stronati M. (2011). Emerging viral infections in neonatal intensive care unit. J Matern Fetal Neonatal Med, 24, 156–158.

8. Jack F. (2011) Price Unique Aspects of Heart Failure in the Neonate. – R.E. Shaddy (ed.), Heart Failure in Congenital Heart Disease: Rrom Fetus to Adult, 123, 205–207.

9. Yuansheng Gao (2010). J. Usha Raj. Regulation of the Pulmonary Circulation in the Fetus and Newborn. Physiological Reviews, 90(4), 1291–1335.

Received: 20-Jan-2019
Accepted: 19-Mar-2019

NUTRITIONAL RICKETS IN CHILDREN (CASE REPORT)

Chaychenko T.[1], Shulha N.[2], Kharkova M.[1], Rybka O.[1], Buginskaya N.[1], Chercun A.[2]

[1]Kharkiv National Medical University, Ukraine
[2]Municipal nonprofit enterprise of the Kharkiv Regional Council "Regional children clinical hospital"

Abstract
Nutritional rickets (NR) caused by vitamin D and/or dietary calcium deficiency remains a significant global, public health problem. The main causes of NR are discussed with a focus on the investigations, management and prophylaxis by the Global Consensus Recommendations on Prevention and Management of NR (2016).
The article presents a clinical case of NR in a girl aged 4 years and 3 months admitted to our hospital with severe deformation of low extremities. She was found to have vitamin D-deficient state with extremely high alkaline phosphatase, suggestive for massive bone resorption. NR was diagnosed following comprehensive examination and therapy according to the protocol was initiated.
Conclusions: NR rate tends to the incline in both low-income and industrialized countries, which requires special attention of pediatricians to the classical clinical presentation with particular focus on the risk group.
Key words: *Nutritional rickets, vitamin D, children, deformity of extremities.*

Nutritional rickets (NR) is still the most common form of growing bone disease despite of the efforts of health care providers to reduce the incidence of the disorder. Recent evidence suggests that in addition to its short- or long-term effects on skeletal development, vitamin D (VitD) deficiency during infancy may predispose the patient to diseases such as diabetes mellitus, cancer and multiple sclerosis [1].

Rickets is a childhood bone disorder in which bones soften and become prone to fractures and deformity. There was an opinion that it is a rare condition in industrialized countries, but fairly common in some developing countries [2]. Meantime, the current scientific reports give an idea that this problem is pretty common at the moment in all urbanized countries [3] both in children and adults due to different predisposing factors and life style [4].

Corresponding Author:
Tetyana Chaychenko, MD, PhD,
Professor of Department of Pediatrics No. 1 and Neonatology of Kharkiv National Medical University, Ukraine.
E-mail: tatyana.chaychenko@gmail.com

According to the recent data [5], statistics in Ukraine is as follows:

– 95% of Ukrainians are VitD deficient;

– 73% of pregnant and lactating females are VitD deficient on multivitamin supplementation.

– 88.9% allergic patients are VitD deficient;

– 53.3% asthmatic children are VitD deficient.

Definition and Diagnosis of Nutritional Rickets

Nutritional rickets (NR), a disorder of defective chondrocyte differentiation and mineralization of the growth plate and defective osteoid mineralization, is caused by vitamin D deficiency and/or low calcium intake in children [6].

Children are predisposed to rickets in case of Ca/P deficiency due to fast growth, high speed of skeleton remodeling secondary to underdevelopment of metabolic pathways. Depending on its mechanism, rickets is divided into several groups: Ca-deficient, P-deficient, Vitamin D-deficient [7].

Exogenous causes of VitD deficiency [8] are:

• Low consumption of VitD-containing food (yolk, fish, liver, milk, caviar, butter).

It is worth mentioning that consumption of natural vitamin D sources such as oil-rich fish,

fortified foods and supplements is influenced by cultural dietary practices and national policies. Plasma 25(OH)D concentrations were lower in vegetarians and vegans than in meat and fish eaters in a UK study [9].

• Low insolation time that causes problems with a conversion of 7-dehydrocholesterol to the cholecalciferol in the skin (*fig. 1*)

well be both predisposed to different form of rickets genetically and have Ca/P metabolism influenced by nutritional factors [14].

Risk groups for nutritional rickets are:

• Premature and low birth weight newborns, tweens;

• Patients with malabsorption (celiac disease, enteropathy, etc.)

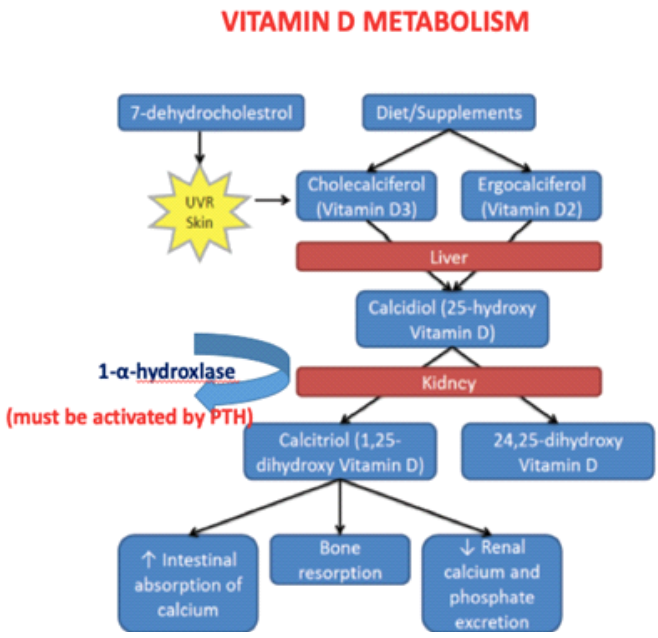


Fig. 1. Vitamin D metabolism in the human body 10 [12]

Personal characteristics, such as skin pigmentation, age, style of clothing, use of sunscreen, physical and outdoor activity and sun exposure behavior, can prevent or promote vitamin D synthesis and influence vitamin D status [10]. Interestingly that melanin efficiently absorbs UVB photons and people with increased skin melanin pigmentation (darker skin) require longer exposures to sunlight to produce the same amount of vitamin D compared with light-skinned people. Thus, relevant ethnicities are under the risk of VITD-deficiency [11].

Endogenous causes of VitD deficiency [13] are:

• Problems with intestinal calcium absorption due to malabsorption syndromes, biliary obstruction etc.);

• Impaired hydroxylation of inactive VitD 2 to active VitD3 in kidneys and liver (due to chronic diseases of the mentioned organs or genetic defects);

• Impaired balance of Ca/P absorption and excretion;

• Impaired VitD receptors function

It is worth taking into the account that some ethnicities, such as Middle East population, may

• Patients on anticonvulsants;

• Prolonged immobilization (palsy, orthopedic problems, traumas, etc.)

• Patients with a chronic liver and biliary tract diseases

• Infants on the non-adapted formula or animal milk feeding.

Classification of vitamin D status, based on serum 25OHD (VitD2) levels [6]:

– Sufficiency, >50 nmol/l;

– Insufficiency, 30-50 nmol/l;

– Deficiency, <30 nmol/l.

The diagnosis of nutritional rickets is made on the basis of history taking, physical examination and biochemical testing, and is confirmed by radiography [6].

Diagnosis of rickets should be based on the identification of characteristic manifestations of the skeletal system – signs of osteomalacia such as craniotabes (*fig. 2*), osteoid hyperplasia (*fig. 3*) and deformity of extremities (*fig. 4*).

Differential diagnosis of the rickets should be made by the comparison of laboratory findings (*tab.1*).

CASE STUDY

A girl aged 4 years and 3 months was admitted to the clinic with the only presenting complaint of low extremities deformity (*fig. 4*).

The child was born from the fourth term pregnancy (39 weeks, by caesarean section due to the scar on the uterus. Birth weight was 2360 g and length was 48 cm, which were suggestive for intrauterine growth retardation: an asymmetric variant. Apgar score was 7–8 points. She has never taken Vit D. Vaccination was done by the protocol).

According to the mother the deformity appeared at the age of 1.5 year when the child started to walk constantly. The child has never been treated.

Paternal relatives have a deformity of extremities, but have never been examined.

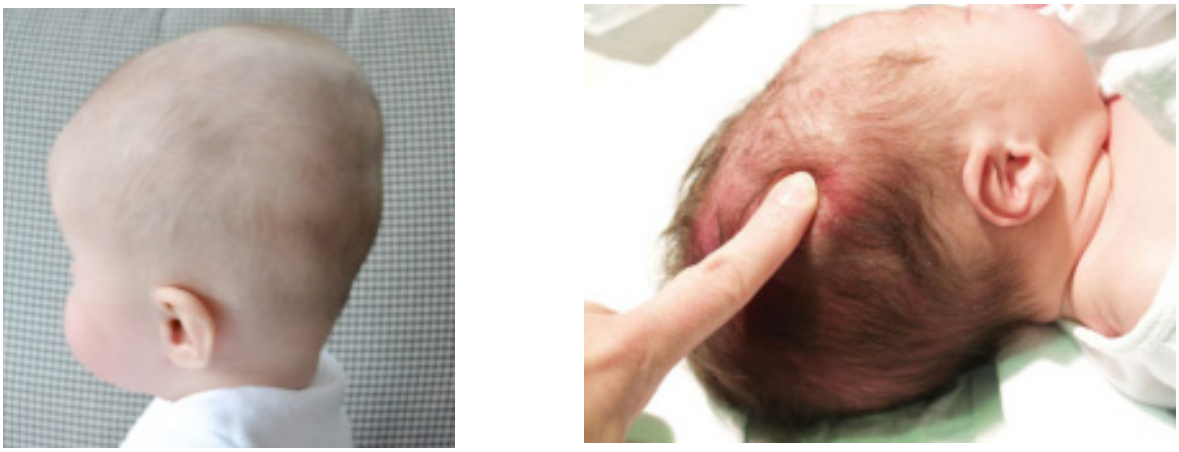


Fig. 2. Craniotabes [15]; Source: 2.bp.blogspo

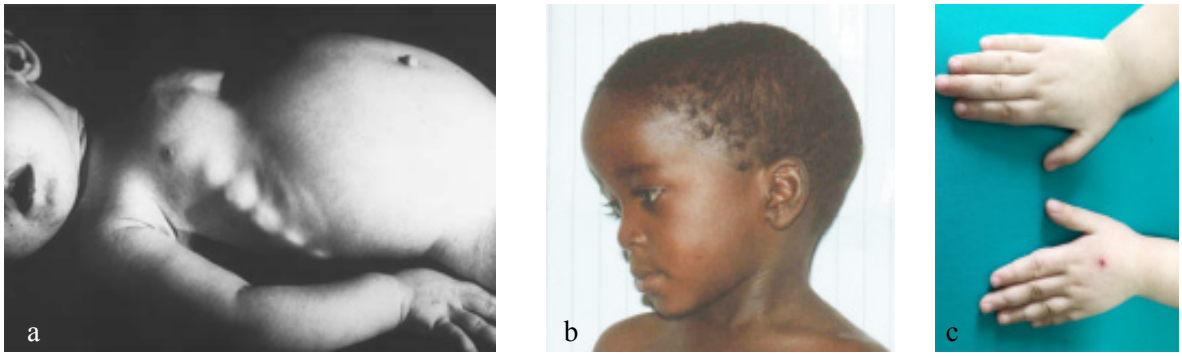


Fig. 3. Osteoid hyperplasia: a) Harrison sulcus and rosary [16]; b) Frontal bossing [17]; c) Swelling of the wrist and ankle joints

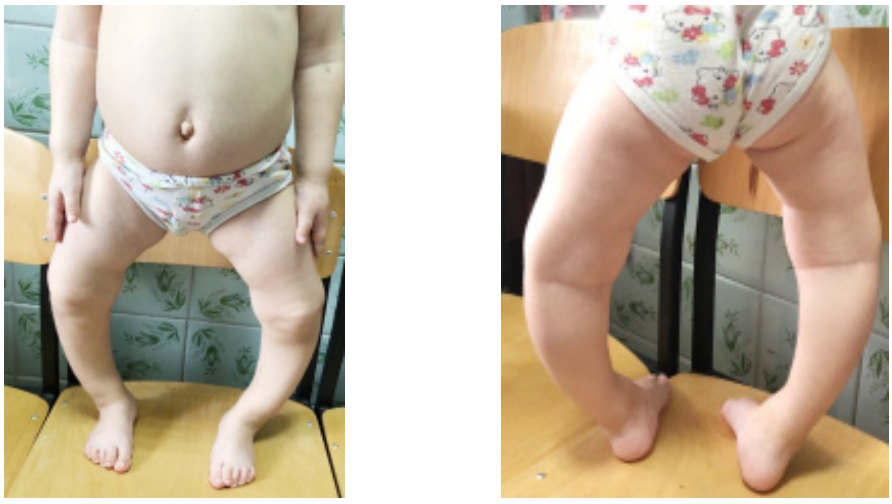


Fig. 4. Deformity of extremities

Table 1

Differential diagnosis of vitamin D and calcium related disorders [18]

Diagnosis	Ca_2	PO_4	PTH	25 OHD	1.25 – OHD
Vitamin D-deficient rickets	↓ ,N	↓	↑	↓	↓ **,N,** ↑
Vitamin D-dependent rickets – type 1 (deficiency of 1α-hydroxylation)	↓	↓	↑	N, ↓	↓
– type 2 (resistance to 1.25 – (OH) $_2$D)	↓	↓	↑	N, ↓	N ↑
X-linked hypophosphataemic rickets	N	↓	N	N	N ↓
Hypophosphataemic rickets with hypercalciuria	N	↓	N	N	↑
Tumour-induced rickets	N	↓	N	N	↓
Renal osteodystrophy	N ↓	↑	↑	N	N ↓
Primary hyperparathyroidism	↑	↓	↑	N	N ↑
Hypoparathyroidism	↓	↑	↓	N	↓ **N**
Pseudohypoparathyroidism	↓	↑	↑	N	↓ **N**
Vitamin D intoxication	↑	N	↓	↑	N ↑
Hypercalcemia in granulomatous disorders	↑	N	↓	N	↑

Physical examination:

Weight: 14 kg. Height: 85.3 cm (-3SD). Height could not be interpreted correctly due to markedly presented deformity of low extremities.

Puberty: Ax1 P1 Ma1 Me1 (Tanner 1)

Vital functions: T-36.6 C°, HR-90 bpm, RR-24 per min.

Skin and integumentary system: normal.

Lymphatic system – normal.

Bones and joints: Genu varum, rosary, swelling of the wrist and ankle joints.

Cardiovascular system – normal.

GIT: enlarged abdomen due to low muscle tone, palpation is painless, no enlargement of liver and spleen.

Stool and urination – normal.

Laboratory findings (*tab. 2*).

Results of the examination are suggestive for the appropriate both ionized and total calcium level with episodes of hypocalcemia in past history. High alkaline phosphatase level indicates that the blood calcium is a result of the massive bone resorption. Low calcium and phosphorus excretion are markers of the deficient state. PTH level is compensatory high. 25-OH VitD level is indicative for VitD-deficient state.

Diagnosis is Vitamin D Deficient rickets, active (E 55.0)

Treatment: Vitamin D supplementation 2000 IU/day together with oral Ca 500 mg/day was started. The patient is under examination in orthopedic clinic with the purpose of further

Table 2

Laboratory findings of the patient with extremities deformity

Parameter	Value	Reference range
Total calcium	2.59	2.2–2.7 mmol/l
Ionized Ca	1.26	1.16–1.32 mmol/l
P	2.32	1.29–2.26 mmol/l
Mg	1.0	0.66–1.03 mmol/l
Na	136.6	135–155 mmol/l
K	4.77	3.2–6.1 mmol/l
24-hour urine calcium excretion	0.51	2.0–4.0 mmol/day
24-hour urine magnesium excretion	0.57	4.94–119.7 mmol/day
24-hour urine phosphorus excretion	8.1	12.9–42.0 mmol/day
Parathyroid hormone	73.1	15–65 pg/ml
Alkaline phosphatase	13000	1200–6300nmol/day *l
25-OH Vitamin D	7.28	<20 ng/ml –deficit
1,25-OH Vitamin D	60.3	19.9–79.3 pg/ml

management strategy elaboration. Next scheduled visit with laboratory assessment – after 3 months of stable medication.

Treatment of rickets [6]

Dose of Vitamin D and Calcium for the Treatment of Nutritional Rickets

– For the treatment of Nutritional Rickets, the minimal recommended dose of vitamin D is 2,000 IU/day (50 μg) for a minimum of 3 months.

– Oral calcium, 500 mg/day, either as dietary intake or supplement, should be routinely used in conjunction with vitamin D in the treatment regardless of age or weight.

Appropriate Route of Administration and Duration of Therapy

– Oral treatment, which more rapidly restores 25OHD levels than intramuscular treatment.

– For daily treatment, both D2 and D3 are equally effective.

– When single large doses are used, D3 appears to be preferable compared to D2 because the former has a longer half-life.

– Vitamin D treatment is recommended for a minimum of 12 weeks, recognizing that some children may require longer treatment duration.

Prevention of rickets [6]

Dietary Calcium Intake to Prevent Rickets

• For infants 0–6 and 6–12 months of age, the adequate calcium intake is 200 and 260 mg/day, respectively.

• For children over 12 months of age, dietary calcium intake of <300 mg/day increases the risk of rickets independently of serum 25OHD levels.

• For children over 12 months of age, the panel recommends the following classification of dietary calciumintake:

– Sufficiency, >500 mg/day;

– Insufficiency, 300–500 mg/day;

– Deficiency, <300 mg/day.

Vitamin D Supplementation for the Prevention of Rickets and Osteomalacia

• 400 IU/day (10 μg) is adequate to prevent rickets and is recommended for all infants from birth to 12 months of age, independently of their mode of feeding.

• Beyond 12 months of age, all children and adults need to meet their nutritional requirement for vitamin D through diet and/or supplementation, which is at least 600 IU/day (15 μg), as recommended by the Institute of Medicine (IOM).

Target for Vitamin D Supplementation:

• In healthy children, routine 25OHD screening is not recommended, and consequently, no specific 25OHD threshold for vitamin D supplementation is targeted in this population.

Candidates for Preventative Vitamin D Supplementation beyond 12 Months of Age

In the absence of food fortification, vitamin D supplementation should be given to:

• Children with a history of symptomatic vitamin D deficiency requiring treatment.

• Children and adults at high risk of vitamin D deficiency with factors or conditions that reduce synthesis or intake of vitamin D.

Dietary Practices and Nutrient Intakes among Mothers Associated with Nutritional Rickets in Infants

• Maternal vitamin D deficiency should be avoided by ensuring that women of childbearing age meet intakes of 600 IU/day recommended by the IOM.

• Pregnant women should receive 600 IU/day of vitamin D, preferably as a combined preparation with other recommended micronutrients such as iron and folic acid.

Early Feeding, Supplementation, Complementary Feeding, and Nutrient Intake Associated with Rickets in Infants

• In addition to an intake of 400 IU/day of vitamin D, complementary foods introduced no later than 26 weeks should include sources rich in calcium.

• An intake of at least 500 mg/day of elemental calcium must be ensured during childhood and adolescence.

Association of Sunlight Exposure with Nutritional Rickets

• Because ultraviolet B (UVB) rays trigger epidermal synthesis of pre-vitamin D 3, restricted exposure to sun increases the risk of vitamin D deficiency and NR.

• Environmental factors, such as latitude, season, time of day, cloud cover, and pollution affect the availability of UVB, whereas personal factors, such as time spent outdoors, skin pigmentation, skin coverage, age, body composition, and genetics affect the dose response of UVB exposure and circulating 25OHD.

• No safe threshold of UV exposure allows for sufficient vitamin D synthesis across the population without increasing skin cancer risk.

Conclusions: NR rate tends to the incline in both low-income and industrialized countries that requires special attention of pediatricians to the classical clinical presentation with particular focus on the risk group. Proper timely prophylaxis and treatment with using appropriate dosages of VitD and Calcium are demanded so as to prevent severe bone deformity.

References:

1. Ozkan, B. J. (2010). Clin Res Pediatr Endocrinol, 2(4), 137–143.

2. Brunner, S. B.A. (2017). Everything you need to know about rickets, Medical news today, 19.12.

3. Creo, A. L., Thacher, T. D., Pettifor, J. M., Strand, M. A., Fischer, P. R. (2017). Nutritional rickets around the world: an update, Paediatrics and International Child Health, 37:2, 84–98, DOI:10.1080/20469047.2016.1248170

4. Spiro, A., Buttriss, J. L. (2014). Vitamin D: An overview of vitamin D status and intake in Europe. Nutr Bull, 39(4), 322–350. doi: 10.1111/nbu.12108

5. (2016). Materialy Pervogo mezhdunarodnogo medicinskogo foruma "Deficit vitamina D – problema nacional'nogo i global'nogo masshtaba" [Materials of the First International Medical Forum "Vitamin D deficiency – a problem of national and global scale"].

6. Munns, C.F., Shaw, N., Kiely, M., Specker, B.L., Thacher, T.D, Ozono, K.,… Hogler, W. (2016). Global Consensus Recommendations on Prevention and Management of Nutritional Rickets, J Clin Endocrinol Metab, doi: 10.1210/jc.2015–217.

7. Malcev, S.V. (2008). To the discussion of rickets, "Pediatrics", volume 87, No. 2, 120–123.

8. Pettifor, J.M. (2004). Nutritional rickets: deficiency of vitamin D, calcium, or both? Am J Clin Nutr, 80(6 Suppl), 1725S-9S. doi: 10.1093/ajcn/80.6.1725S.

9. Crowe, F.L., Steur, M., Allen, N.E. (2011). Plasma concentrations of 25-hydroxyvitamin D in meat eaters, fish eaters, vegetarians and vegans: results from the EPIC-Oxford study. Public Health Nutrition, 14, 340–346.

10. Cashman, K.D., Kiely, M. (2014). Recommended dietary intakes for vitamin D: where do they come from, what do they achieve and how can we meet them? Journal of Human Nutrition and Dietetics, doi: 10.1111/jhn.12226.

11. Holick, M.F. (2004). Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. American Journal of Clinical Nutrition, 80, 1678S–1688.

12. Holick, M.F. (1996). Vitamin D and bone health. J.Nutr, 126 (supp. l4), 1159S–1164S.

13. Majdannik, V.G. (2014). Klinicheskie rekomendacii po diagnostike, lecheniju i profilaktike vitamin d-deficitnogo rahita u detej [Clinical guidelines for the diagnosis, treatment and prevention of vitamin D – deficiency rickets in children]. Kiev, p.58.

14. Giampiero I., Baroncelli, G. I., Bereket, A., Kholy, M. El., Aud?, L., Cesur, Y., Ozkan, B., Hochberg, Z. (2008). Rickets in the Middle East: Role of Environment and Genetic Predisposition, The Journal of Clinical Endocrinology & Metabolism, Volume 93, Issue 5, 1743–1750, https://doi.org/10.1210/jc.2007–1413

15. https://gbistandart.ru/assets/f8e7163774.jpg

16. http://patologia.gabeents.com/data/Pathologic/images/banner_01.jpg

17. http://adc.bmj.com/content/89/8/781.full

18. Raine, J.E. Donaldson, M. D.C., Gregory, J. W., Savage, M. O., Hintz, R. L. (2005). Practical endocrinology and diabetes in hildren., (2nd ed). DOI: 10.1002 / 9780470994856.

Received: 17-Feb-2018
Accepted: 17-Mar-2019

INTERLEUKIN LEVELS IN PATIENTS WITH ESSENTIAL HYPERTENSION COMBINED WITH TYPE 2 DIABETES MELLITUS

Shelest B.O.

Kharkiv National Medical University, Ukraine

Abstract
The problem of combined course of hypertension of diabetes mellitus type 2 and obesity is becoming more common. This variant of comorbidity crucially increases the risk of cardiovascular complications. Inflammation is considered as an important link between the progression of hypertension and the development of adverse events. This study is devoted to the question of the relationship between the pro-inflammatory marker interleukin-6 and the increased blood pressure in patients with concomitant diabetes and obesity. The treatment of such patients with combined pathology remains the actual and difficult issue of medical practice. The article analyses the dynamics of interleukin-6 in the process of treatment with a fixed triple antihypertensive combination.
Key words: *hypertension, interleukin-6, type 2 diabetes mellitus, obesity.*

Background

Recent studies have confirmed the important role of inflammatory biomarkers in patients with arterial hypertension (AH). A constant increase in the number of articles on the role of immune disorders in the development of AH suggests crucial significance of this condition. Immune mechanisms involved in AH are recognized by many scientists, since initial changes in immune status are found in 85–87% of patients with AH. Meanwhile, a number of scientists believe that immune processes are not decisive in the formation of initial manifestations of AH, since patients with newly diagnosed disease and short disease history preserve immunity indices and sensitization of lymphocytes to the endothelium of the vessels increases only in chronical cases when complications reduce the number of immunocompetent cells and their activity.

Thus, a study of the cellular immunity state showed a change in the immune response presented by its inhibition according to the disease severity. Control of this process is carried out by a wide range of immunocompetent cells and cytokines produced by them. The cytokines are involved in virtually every link of immunity and inflammation. However, their importance in the processes of damage, protection and repair of the endothelium remains poorly understood.

The issue of interleukin participation in AH combined with type 2 diabetes mellitus (DM2) secondary to obesity is of special interest nowadays. This combination is quite common and leads to a more significant increase in the incidence of cardiovascular events. The history of cytokines began in the middle of the twentieth century with the description of the effects of cachectin [1]. Later, many natural molecules were discovered and comprehensive description of their biological effects was made [2]. The term "interleukins" was proposed at the end of the 1970s, but due to the wider impact of these substances on the human body exceeding the limits of the immune system, the term "cytokines" [2] has survived. Both terms are used today, due to its great influence. An important stage in the study of cytokines was observed in the 1980s, when murine and human interferon genes were cloned, recombinant molecules were created, fully replicating the biological properties of natural cytokines [3]. In the 1990s, after discovery of the subunit structure of cytokine receptors, the concept of "cytokine network" was formed and

Corresponding Author:
Boris Shelest, MD, PhD, Associate professor of the Department of Internal and Occupational Diseases of Kharkiv National Medical University, Ukraine. E-mail: shelestb@ua.fm

new cytokines were discovered by genetic analysis [1]. The general main properties of cytokines are pleiotropic effect, the absence of antigenic specificity, self-regulation of products and formation of cytokine network [3]. In this regard, cytokines can be isolated in an independent system of regulation of the functions of the body along with the nervous and hormonal ones. Within the immune system, they interact with nonspecific protective reactions and specific immunity, acting in both directions [2]. At the level of the body cytokines communicate with the immune, nervous, endocrine and other systems, including the regulation of protective reactions. Cytokines are the most universal regulatory system, since they realize their biological activity at the distant, after secretion by cell-producers, and in intercellular contact [4]. They affect virtually all cells involved in the development of inflammatory process, after being synthesized in the inflammation cell. There is a direct correlation with the content of IL-6 and the level of arterial pressure in patients with AH.

AH is usually associated with DM2 due to mutual pathogenesis promoted by inflammation. This kind of combination results in a higher risk of morbidity and mortality because of increased chances of cardiovascular events and renal disease [5]. A lot of studies evaluated changes in oxidative stress and inflammatory processes with time in hypertensive patients with DM2 [6,7]. The issue of impact exerted by inflammatory biomarkers on hypertension progression with and without presence of diabetes mellitus is not fully ascertained. Since AH is the most valuable among modifiable risk factor for cardiovascular complications of diabetes, a decrease in blood pressure is crucially important in improving the clinical outcomes [8]. And the problem of the treatment of patients with concomitant diseases including AH with DM2 with obesity is one of the most challenging problem of contemporary medicine.

2 Purposes, subjects and methods:

2.1 Purpose – to assess the efficacy of fixed combined antihypertensive therapy on IL-6 levels in patients with a combined course of AH and DM2.

2.2 Subjects & Methods

The study involved 61 patients, including 29 men and 32 women aged 51 to 74 (58.1 ± 6.75) years (main group). The diagnosis of essential hypertension was made at systolic blood pressure (SBP) of ≥ 140 mmHg, and/or diastolic blood pressure (DBP) equal or over 90 mmHg according to the criteria of the European (2013) and Ukrainian (2012) guidelines, all patients had stage 2 of AH, 11 patients (5 males, 6 females) had stage 1 of AH (SBP:140–160 mm Hg), and the rest (50 patients, 24 males, 26 females) had stage 2 of AH (SBP over 160 mm Hg). DM2 was established according to the IDF criteria (2015). The average HbA1c level was 7.73±1.19%. 14% were smokers. The exclusion criteria were insulin dependent diabetes mellitus, valvular heart defects, connective tissue diseases, liver disease, cancer, remodeling of the heart and vessels, injuries, acute inflammatory process, chronic heart failure exceeding the second stage. The control group consisted of 30 age- and sex-matched persons with hypertension without the signs of DM2 and obesity. All the patients underwent ECG, EchoCG, ultrasound investigation of abdominal organs (by indications), radiography of the chest organs, clinical laboratory studies, basic biochemical blood plasma assay. Enzyme-linked immunosorbent assay was used for quantitative determination of IL-6.

All of the participants signed an informed consent and were entirely aware of the aims and methods of the study. The study was conducted according to the provisions of Helsinki Declaration of the World Medical Association and the statute of the Ukrainian Association of Bioethics and GCP regulations.

The antihypertensive therapy included a fixed combination of 4 mg perindopril, 1.25 mg indapamide and 5 mg amlodipine. The control check-up of patients was carried out after 3 weeks and 6 months. Measurement of office blood pressure was carried out in the morning before administering medication after a 5-minute rest (three times with calculating the mean). The target office BP level was considered <140/90 mm Hg. The values are presented in the form of mean and standard deviations for quantitative values (M±m). Statistical analysis of the results was performed using Statistica 12.0 software. The differences were identified using t-test and Pearson correlation coefficient (PCC).

Conflict of interests. There is no conflict of interests.

3 Results and discussion

Clinical examination of the patients from the main group enrolled in the study at admission showed the following parameters: heart rate 81.9±4.51 bpm, left ventricular ejection fraction 53.9±5.34%, total cholesterol: 6.11±1.55 mmol/l, high-density lipoprotein cholesterol 0.89±0.09 mmol/l, triglycerides 2.53±0.19 mmol/l, plasma

creatinine 63.7±3.43 micromol/l, fasting glucose 5.1±0.3 mmol/l.

Prior to treatment systolic blood pressure (SBP) was elevated by 21% and diastolic by 16% as compared to the control group. In 3 weeks of treatment by fixed combination (*Chart 1*), SBP decreased by 22.02% (168.1±10.3 mmHg to 131.5±8.1 mm Hg, p<0.05), DBP by 16.33% (98.1±7.3 mmHg to 82.5 ±5.1 mmHg). The target levels of blood pressure were identified in 41 (67%) patients while 20 (33%) patients did not reach them over the period of 3 weeks. In the group of AH combined with DM2, the content of interleukin-6 was 9.59±2.17 pg/ml (*Chart 1*). The level of IL-6 was over 8.0 pg/ml in all the main group patients.

Comparison of the initial IL-6 levels in patients with AH and DM2 and control group revealed its significant increase in the examined patients (p<0.01). The level of Il-6 decreased to 6.11± 1.98 pg/ml (by 36.3%, p<0.05) 3 weeks after the fixed combination treatment, as presented in *Chart 1*. Assessment of correlation of blood pressure level with Il-6 content in all the examined patients showed that the correlation coefficient established the value of the correlation coefficient equal to r=0.53 (p<0.05), and ΔDBP: r=0.48 (p <0.05). Another treatment regimen, including 8 mg perindopril, 2.5 mg indapamide and 5 mg amlodipine was administered only to 2 patients after 3 weeks due to insignificant efficacy of the treatment.

Follow-up examination was performed 3 months after the start of treatment. SBP was 129.8 ± 8.9 mmHg, which was 23.21% less than the initial level (p <0.01). DBP at that moment was equal to 79.3 ± 8.1 mmHg, which was 19.4% less than the initial level (p <0.05). And all the patients were found to have the target levels of blood pressure. The results showed diminished level of Il-6, namely 4.57±1.42 pg/ml, which was 52.63% less than before the treatment (p<0.05). The magnitude of correlation between the initial concentration of IL-6 and ?SBP after 3 months was r=0.55 (p <0.05), ?DBP - r= 0.43 (p <0.05).

A significant number of studies have been conducted to study the role of cytokines in the formation and nature of hypertension. It has been proved that interleukins, proteins responsible for intercellular communication produced by activated

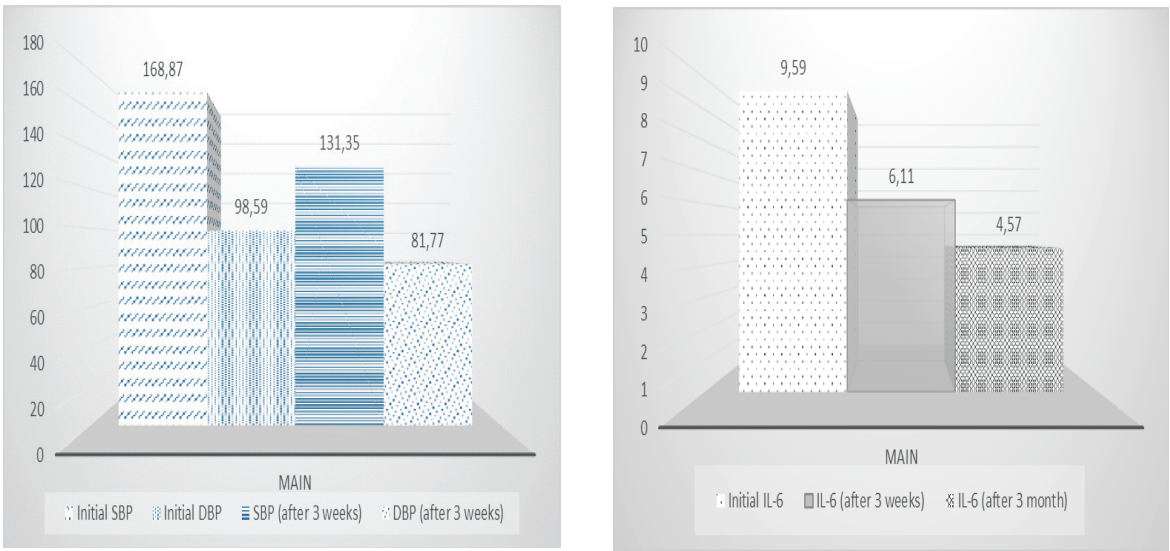


Chart 1. Interleukin-6 and blood pressure levels in the main and control groups and their changes with time secondary to treatment

between the level of SBP and Il-6 concentration was r=0.51 (p <0.05), between the level of DBP and concentration of IL-6 r=0.43 (p<0.05). It is important to emphasize a significant decrease in blood pressure both with fast goal achievement evidences for high efficacy of suggested treatment scheme for patients with comorbid pathology.

Assessment of the relationship between the initial concentration of IL-6 and ? SBP in 3 weeks after beginning of treatment in the main group

immune cells, play an important role in the coordination of immunological responses in hypertension. The most typical effect is the induction of proliferation. With a wide range of biological properties, they represent a powerful communicative system that initiates and regulates inflammatory processes of all organs and systems [9]. Interleukins have their own serial numbers that do not belong to one subgroup of cytokines and they are united by the common functions.

The name "interleukin" is given to the mediator in accordance with the criteria developed by the nomenclature review committee of the International Union of Immunological Societies: molecular cloning and expression of the gene of the studied factor; the presence of a unique nucleotide and an amino acid sequence; receiving neutralizing monoclonal antibodies; production by cells of the immune system, the presence of an important biologic function in the regulation of the immune response. Patients with AH combined with DM2 have impaired immune status, including changes in the cytokine profile of the body [10]. Much attention to interleukin 6 is due to the fact that this proinflammatory cytokine triggers the secretion of other cytokines and is one of the mediators of the acute phase of the process [11]. Increased coagulation and oxidative stress lead to the elevation of inflammatory cytokines such as interleukin-6, monocyte chemoattractant protein 1, along with a decrease in insulin-like growth factor I in hypertensive patients with DM2. High IL-6 levels are linked with obesity and insulin resistance and have been manifested in various complications in DM2 patients [12].

It has been shown [13] that inflammation, along with oxidative stress, is a significant pathogenic chain in the progression of AH and DM2, especially with high blood pressure levels. Pouvreau C. et al. estimated that such inflammatory indices as interleukin-1β and interleukin-10 significantly differed from normotensive patients and patients with hypertension ($p<0.03$) and from the hypertensive compared to AH combined with DM2 patients ($p<0.05$). Assessing hypertension progression Pouvreau C. et al. also determined significant changes in the levels of inflammatory markers: insulin growth factor-1, monocyte chemoattractant protein 1 and ($p<0.05$). Thus, these patients with comorbidity require more intensive treatment regimen, especially in hypertensive patients with high blood pressure.

Investigation of Pouvreau C. et al. [13] showed that clinical combination of AH with DM2 and obesity requires special management of patients, which aims to reduce the increased risk of further morbidity and mortality. In addition, this study showed that patients with concomitant diabetes mellitus were treated by antihypertensive drugs much more intensively, which made it possible to significantly reduce both oxidative stress and the severity of inflammation, and it was similar to our study in the aspect of treating such patients. The significant difference between the control group and hypertensive patients with DM2 therefore indicates the potential use of these markers in clinical practice during examination of hypertensive patients with DM2.

Lukic et al. [14] revealed that obesity and type 2 diabetes mellitus (DM2) are associated with an increased risk of hypertension development, although the processes and chains contributing to hypertension in diabetes are not completely obvious. Lukic et al. analyzed the interdependence of insulin resistance (IR) levels, plasma insulin levels, and pro-inflammatory cytokines (IL-6 and TNF-α), which, were previously proven to be risk factors for hypertension in patients with type 2 diabetes who have increased body weight. Lukic et al. found that the IR index was significantly lower, and insulin levels were statistically elevated in the group of concomitant disorders: hypertension with DM2 and obesity. In addition, the group with concomitant disorders had statistically the highest IL-6 values, and the researchers found no significant difference in TNF-α levels. Our results correspond to the findings of Lukic et al. and the both studies ascertain that hypertension development depended on an increase in IR in patients with DM2 and obesity. This IR elevation was associated with an increase in the proinflammatory cytokine IL-6. The results of Lukic et al. suggest that interventions in reducing IR may be helpful in decreasing the risk of hypertension in patients with type 2 diabetes mellitus.

Conclusions

IL-6 concentration was significantly increased in patients with arterial hypertension and diabetes mellitus, compared with the control group. The level of IL-6 in patients with arterial hypertension and diabetes mellitus had a direct correlation connection with arterial pressure, to a greater extent with systolic and to a smaller one with diastolic. The treatment by fixed combination successfully decreased the IL-6 level in patients with combined arterial hypertension and diabetes mellitus unidirectional with a decrease in blood pressure. Moreover, the proposed therapeutic scheme allowed us to achieve target levels of blood pressure in 3-month period. Our study had some limitations, mainly due to a quite limited number of patients.

The further prospects are related to the deeper investigation of the nature of the relationship among the inflammatory indices in patients with various types of arterial hypertension comorbidity.

References

1. Shtygasheva O.V., Ageeva E.S., Iptyshev V.M. (2011). Rol' immunoreguljatornyh citokinov v patogeneze hronicheskogo gastrita i jazvennoj bolezni, poisk prediktorov zabolevanij [The role of immunoregulatory cytokines in the pathogenesis of chronic gastritis and peptic ulcer disease, the search for predictors of diseases]. Sibirskij medicinskij zhurnal, 1, 88–90.

2. Ketlinskiy, S.A., Simbirtsev A.S. (2008). Citokiny. [Cytokines]. SPB: "Foliant", p. 408.

3. Galova E.A. (2008). Znachenie citokinov v patogeneze hronicheskogo gastroduodenita u detej doshkol'nogo vozrasta [Cytokines' significance in the pathogenesis of chronic gastroduodenitis in preschool children]. Citokiny i vospalenie. 7, (1), 48–51.

4. Zheleznjakova G.F. (2009). Citokiny kak prediktory techenija i ishoda infekcii [Cytokines as predictors of infection's course and outcomes]. Citokiny i vospalenie, 8, (1), 10–17.

5. Yan Q., Sun D., Li X., Chen G., Zheng Q., Li L., Gu C., Feng B. (2016). Association of blood glucose level and hypertension in Elderly Chinese Subjects: a community based study. BMC Endocr Disord, 16(1), 40.

6. Cheung B.M., Li C. (2012). Diabetes and hypertension: is there a common metabolic pathway? Curr Atheroscler Rep, 14(2), 160–6.

7. Al-Shukaili A., Al-Ghafri S., Al-Marhoobi S., Al-Abri S., Al-Lawati J., Al-Maskari M. (2013). Analysis of inflammatory mediators in type 2 diabetes patients. Int J Endocrinol, 2013, 976810.

8. de Boer I.H., Bangalore S., Benetos A. (2017) Diabetes and Hypertension: A Position Statement by the American Diabetes Association. Diabetes Care, 40, 1273.

9. Svetlova M.S., Vezikova N.N., Romashina V.V. (2009). Ocenka soderzhanija s-rb, interlejkina-1 i -6 i receptornogo antagonista interlejkina-1 v krovi bol'nyh rannim osteoartrozom kolennyh sustavov [Assessment of the C-RP, interleukin-1 and interleukin-6 and receptor antagonist interleukin-1 levels in patients with early osteoarthritis of the knee joints]. Terapevticheskij arhiv, 6, 52–56.

10. Godbout J.P., Glaser R. (2006). Stress-Induced Immune Dysregulation: Implications for wound Healing, Infections Disease and Cancer. J. Neuroimmune Pharmacol, 1, (4), 421–427.

11. Gadek-Michalska A., Bugajski A.J., Bugajski J. (2008). Prostaglandins and IL-1β in the hypothalamic-pituitary-adrenal response to systemic phenylephrine under basal. J. Physiol. Pharmacol, 59, (3), 563–575.

12. Butkowski E.G., Brix L.M., Al-Aubaidy H.A., Kiat H., Jelinek H.J. (2016). Diabetes, oxidative stress and cardiovascular risk. J Med Clin Sci, 5(1), 17–23.

13. Pouvreau C., Dayre A., Butkowski, E.G., de Jong B., Jelinek, H. F. (2018). Inflammation and oxidative stress markers in diabetes and hypertension. Journal of inflammation research, 11, 61–68.

14.Lukic L., Lalic N.M., Rajkovic N., Jotic A., Lalic K., Milicic T., Seferovic J. P., Macesic, M., Gajovic J. S. (2014). Hypertension in obese type 2 diabetes patients is associated with increases in insulin resistance and IL-6 cytokine levels: potential targets for an efficient preventive intervention. International journal of environmental research and public health, 11(4), 3586–98.

Received: 14-02-2019
Accepted: 19-03-2019

GENETIC DETERMINANTS OF OSTEOPOROTIC RISK IN CALCIUM-DEPENDENT DISEASES – CHRONIC PANCREATITIS AND HYPERTENSIVE DISEASE

Viun T.I., Pasieshvili L.M.

Kharkiv National Medical University, Ukraine

Abstract

Objectives: to determine the genetic determinants of osteoporotic risk in the comorbidity of calcium-dependent diseases - chronic pancreatitis and hypertensive desease. Subjects and methods: two groups of patients were formed for the study – the main one – 70 patients with chronic pancreatitis and hypertensive disease; and the comparison group – 40 persons with isolated course of chronic pancreatitis. The polymorphism of VDR, LCT and FDPS genes as well as the comparison of pathological alleles of these genes was investigated with the definition of the possible influence of these indices on the course of the disease and formation of complications. Results show that patients with a combined course of CP and HD have an increased risk of osteoporosis, which is expressed by an increase in the number of fractures compared with healthy people. As the genetic determinants of the development of osteopenic syndrome in these patients, there is the presence of the allele of the VR gene, the VDR gene and the SS allele of the FDPS gene. The presence of the LC allele of the LCT gene has no independent predictive value, but in combination with the identified variants of the genes, VDR and FDPS promote an increase in osteoporosis risk.

Key words: *chronic pancreatitis, hypertonic disease, osteoporosis, VDR gene polymorphism, LCT gene polymorphism, FDPS gene polymorphism.*

Introduction

At present, diseases of the joints, bones and the spine are often considered to be complications arising from the comorbidity of many diseases of the internal organs. So, it has been proven that the presence of overweight and obesity contributes to the formation of osteoarthritis, especially of knee joints, which is the result of not only mechanical pressure on the joint, but also the effects of hormones-like substances (e.g. apelin-13) produced by fatty tissue [6]. In addition, it has been shown that the development of obesity over the 2nd stage is a prognostic disadvantage for the development of osteoporotic changes [7]. Similar changes in joints and bone tissue occur in patients with diabetes mellitus, which is associated not only with the effect of adipocytes hormone-like substances but also with the malfunction of microcirculation and all types of exchange [18].

It is proved that changes in bone tissue, namely imbalance in the parameters of calcium metabolism, are indicative for patients with coronary artery disease. At the same time, calcium coming out of bones precipitates on vessels, thus triggering not only the development of osteopenic states, but also atherosclerosis [4].

These data were the basis for the formation of a group of diseases, the course of which is accompanied by changes in the indices of bone marrow markers: either due to increased losses of calcium matrix, or lack of its components for the proper formation of bones, that is, contribute to the damage to both joints and their derivatives, as well as bones themselves. These diseases were called calcium-dependent, and their course was associated with the formation of secondary osteoporosis [9, 14]. These diseases include disorders of the esophagus, cardiovascular and endocrine systems, etc.

Corresponding Author:
Tetiana Viun, MD, PhD student Department of General Practice – Family Medicine of Kharkiv National Medical University, Ukraine.
E-mail: viun.tatiana@gmail.com

The World Health Organization has officially identified OP as one of the ten most important chronic diseases of humanity, as it is very widespread, has a clear definition, diagnostic methods, and sufficient opportunities for prevention and treatment. OP is a systemic disease of the skeleton from the group of metabolic bone diseases, characterized by a decrease in bone mass and a violation of bone marrow microarchitectonics, which leads to a reduction in bone strength and, consequently, to an increased risk of fractures [5, 13]. Bone tissue plays a major role in calcium homeostasis regulation [11].

Development of chronic gastrointestinal diseases undoubtedly has a negative impact on calcium metabolism. Thus, the emergence of maldigestion syndromes and malabsorption in many diseases of the digestive tract leads to impairment of the absorption of mineral and organic substances, contributes to the formation of hypocalcemia and, ultimately, a decrease in mineral density of bone tissue [12, 19]. Chronic pancreatitis is one of the diseases negatively affecting bone metabolism [15]. The long course of the disease, its recurrent nature, accompanied by a disturbance in the absorption of many macro- and micronutrients, promotes the formation of a pathological process, that is, secondary osteoporosis [3].

Hypertensive disease is another common disorder that makes a significant contribution to the development of OP [8]. Systemic vascular lesion with the formation of endothelial dysfunction, one of the mechanisms of which is the interaction of pro- and anti-inflammatory immune mechanisms, cell membrane disruption as current changes in the composition of fatty acids, and the imbalance of the POL-AOS processes, the effect of diseases on the macro-elemental composition of the body and vitamin balance should be considered as a common pathogenic link between CP and HD [2]. In this case, it can be assumed that the common pathogenic links can increase and contribute to the development of complications, not only due to their combination, but also provoked by each nosological form. The combination of HD and CP potentiates two directions of calcium loss: with HD due to changes in the redistribution of potassium-sodium-calcium mechanism between cell and extracellular space, which requires an additional "presence" of calcium. At the same time, CP is characterized by an impairment of its absorption, as a result of inadequate digestion of food and diarrhea, and in this case, vitamin imbalance – lack of vitamin D as a result of intake and absorption [2, 14]. That is, comorbidity of HD and CP triggers aggravating preconditions that operate in different directions, but lead to the same result, calcium metabolism disruption [1, 3].

Several researchers have determined that the development of diseases and their complications may be the result of the presence of candidate genes and their adverse polymorphism may provoke changes in pathogenic trends in the course of diseases. That is, a combination of diseases can occur not only accidentally in a particular patient, but is a result of a coincidence of a number of circumstances, among which the leading role belongs to genetic aberrations. Among the many genes involved in the regulation of bone metabolism, the special role belongs to the gene of receptors of vitamin D (VDR), lactase gene (LCT) and farnesyl diphosphates synthase gene (FDPS) [5, 10, 16, 17].

That is, participation of these genes can be considered as a leading factor in the formation of secondary osteoporosis.

2 Purposes, subjects and methods:

2.1 Purpose – to determine genetic determinants of osteoporosis at comorbidity of calcium-dependent diseases – chronic pancreatitis and hypertensive disease.

2.2 Subjects & Methods

The study involved 110 patients with CP and in 70 cases CP was accompanied by HD (main group). The comparison group included 40 patients with isolated course of CP. There were more women (73 persons – 66.4%) than men. The age of the patients ranged from 29 to 43 years and on average in groups it was 33.2±2.1 (main) and 32.9±3.1 (comparison). The control group included 78 practically healthy persons of the same age and gender, which allowed us to compare the findings.

Verification of the diagnosis of HD, the determination of the stage and degree of the disease was carried out in accordance with the recommendations of the European Society of Hypertension (ESH) for the management of arterial hypertension (2009) and the recommendations of the Working Group on Arterial Hypertension of the Ukrainian Association of Cardiologists (2012).

The diagnosis of CP was determined on the basis of patient's presentation, history taking, clinical, laboratory and instrumental findings, referring to the Order of the Ministry of Health of Ukraine No. 271 dated 13.06.2005, updated on 10 September 2014 by Order No. 638.

The state of excretory function of PG was assessed by the level of pancreatic elastase-1 in serum of patients. The evaluation was carried out by the immune enzyme method using the commercial test systems of ScheBo (Germany), according to the enclosed instructions for the immune enzyme analyzer Labline-90 (Australia). Structural state of PG was determined during ultrasound.

Measurement of blood pressure (BP) was performed according to the Unified clinical protocol of medical aid for arterial hypertension, approved by the Order of the Ministry of Health of Ukraine as of 24.05.2012 No.384. Determination of vitamin D receptor gene polymorphism, LCT gene 13910 C/T marker polymorphism and farnesyl diphosphates synthase polymorphism (FDPS c.IVS1 T-99G) was performed using the sets of "Litehh" (Russia) by the polymerase chain reaction method for real-time amplification using fluorescent labels on the Rotor-Gene ™ 6000 six-channel analyzer ("Corbett Research", Australia).

The analysis of the frequency and nature of absorbtionally-verified violations of SFSBT (structural and functional state of bone tissue) was performed according to the X-ray examination by dual-energy X-ray absorptiometry (DEXA).

The obtained data were processed by analysis of the tables using Statistica software package. The statistical significance of the results was evaluated using the χ-square Pearson criterion.

Conflict of interests. There is no conflict of interests.

3. Results and discussion

All patients with HD had stage II and level 2 of arterial hypertensive disease: mean systolic blood pressure in the group was 164±6.3 mmHg and diastolic 98.4±3.1 mmHg, which was confirmed by the characteristic changes in the ECG and the detection of violations in the target organs.

The majority of patients in the main group and in the pancreatic elastase-1 group had a moderate degree of excretion of pancreatic insufficiency (43–61.4% and 25–62.5%, respectively). A slight degree of violation of enzymes synthesis was observed in 38.6% and 37.5% of patients, respectively. Patients with severe form of excretory insufficiency were not involved. Ultrasound examination and clinical presentation confirmed chronic pancreatitis: inflammation and inflammatory tissues were determined in the gland.

The analysis of the frequency and nature of disorders of the structural and functional state of bone tissue SFSBT verified by absorption method and according to DEXA data showed that 33 persons (30%) of 110 patients with CP had changes in bone mineral density (BMD). In this case, in the main group, signs of osteoporosis were confirmed in 11 cases (15.7%), and osteopenia in 12 cases (17.1%). In the comparison group, these figures were 10% and 15% respectively (*table*).

Frequency and nature of disorders of the structural and functional state of bone tissue in patients with CP combined with HD and isolated CP verified by absorption method

Patients with CP combined with HD and isolated CP			Structural-functional state of bone tissue according to DEXA					
			Osteopenia		Osteoporosis		Without impairments	
Number of patients	abs.	%	abs.	%	abs.	%	abs.	%
Main group	70	100	12	17,1	11	15,7	47	67.2
Comparison group	40	100	6	15	4	10	30	75

The analysis of the frequency and nature of SFSBT impairment verified by absorption method showed that in patients with the combined course CP and HD, these violations were observed in a greater number of patients than in the comparison group (23 (32,9%) versus 10 (25%) patients, respectively); however, there were no differences in the statistical significance.

At the same time, the analysis of the history data showed that both in the main group of individuals and in the comparison group, patients had previous limb fractures 29 (41.4%) and 4 (10%), respectively. However, these statistical data do not always coincide with SFSBT factors, namely, the impairment of the structural and functional status of bone tissue in the main group in the densitometric study was observed less often – 23 versus 29. This discrepancy had no statistical significance and was most likely due to the peculiarities of the group being examined – young people with a mobile lifestyle and, consequently, possible traumatic situations.

Thus, we can conclude that concomitant hypertension in patients with CP complicates the course of OP.

In determining the polymorphism of the receptor gene of vitamin D, a statistically significant dependence on the distribution of gene alleles from the group of patients was revealed ($\chi 2 = 30.08$, df = 4, $p < 0.01$). Thus, according to the results of genetic testing, control patients were divided into three groups. Thus, the first Group 1 included 17 patients (24.3%) who were carriers of the bb genotype; Group 2 – carriers of the Bb genotype – 34 (48.6%) and Group 3 – carriers of the BB-genotype – 19 persons (27.1%). In the group of patients with isolated CP, genotype bb was in 22.5% of patients (9 cases); BB – 35% (14) and Bb – 42.5% (17 cases). When combined with CP and HD, the distribution was as follows: 15.7% (11 cases), 51.4% (36 cases) and 32.9% (23 cases), respectively. Thus, the overwhelming majority of patients with CP, combined with HD (58.6%), had an abnormal BB allele, which was 1.7 times more frequent than in the comparison group and 2.2 times in relation to the control group.

The frequency distribution of genotypes and alleles of the LCT gene in the control group corresponded to the following: T/T genotype was found in 19.2% (n = 15), C/T genotype in 32.1% (n = 25) and C/C genotype in 48.7% (n = 38). In the comparison group, T/T genotype was found in 17.5% of patients (n = 7); the genotype of the C/T gene of LCT was observed in 27.5% of the subjects (n = 11) and C/C genotype was 55% (n = 22). Assessment of the distribution of genotypes and alleles in the main group of patients showed T/T genotype in 11 patients (15.7%), C/T genotype in 20 (28,6%) and C/C genotype in 39 patients with a combination of CP and HD, which was 55.7%. Thus, changes in the polymorphism of C/C genotype of the LCT gene in patients with chronic CP and in combination with CP and HD did not have any significant differences with regard to control.

The statistically significant nature depended on the genotypes of the polymorphic FDPS gene ($\chi 2 = 23.58$, df = 2, $p < 0.01$). In the control group, the carriers of SS genotype were represented by 2 individuals (2.6%), there were 24 carriers of AS genotype (30.8%), and AA genotype was found in 52 patients (66.6%). In the comparison group (CP patients), SS genotype was found in 22.5% of cases (9 people), AS in 37.5% (15) and AA in 40.0% (16) In patients with combined CP and HD, the FDPS gene polymorphism was found in 30.0% (21 cases), 22.9% (16) and 47.1% (33), respectively.

Thus, comparison with control in patients of both groups showed an "increase" in the frequency of SS genotype: 2.6 ± 1.8% in control; 22.5±6.6% and 30.0±5.5% for CP and its combination with HD, respectively, with the decrease in the frequency of AA genotype (66.7±5.3%, 40.0±7.7%, 471±6.0%, respectively).

Comparison of the pathological alleles of all three genes for the general sample of patients (188 cases) was the largest number of cases of the combination of pathological alleles of the VDR gene, the CT gene of the LCT and CC of the FDPS gene – 38.9%, this value is statistically significant (Pearson Chi- square, $\chi 2 = 9.06011$, df = 4, $p = 0.05$). The data is presented in *fig. 1*.

In the distribution of the frequencies of the VDR, LCT and FDSP genes in patients with isolated CP (n = 40), the highest number of cases was the combination of pathological alleles of the VB gene of the VDR gene, the CC of the LCT gene and the AC of the FDPS gene of 40.4%.

In connection with a significant increase in the dimension of the tables in the consistent analysis of the three genes, the results should be considered as a hypothesis describing the tendency of the phenomenon under study (*fig. 2*).

The results of the comparison of pathological alleles in the CP group combined with HD (n = 70) also have the status of a hypothesis concerning the trend of a compatible distribution. The combination of pathological alleles of the VDR gene of the VDR gene, the CC of the LCT gene and the CC of the FDPS gene was 40.7% (*fig. 3*).

Thus, we can state that as a result of a small sample, most data do not have statistically significant results, and the resulting distributions can only be considered as a tendency. With a consistent analysis of the three genes, the tendency of the pathological alleles B of the VDR gene and the allele C of the gene LCT and FDPS

Conclusions

Patients with CP and HD are patients with an increased risk of osteoporosis, manifested by an increase in the number of fractures (without a clear association with changes in BMD) as compared to healthy subjects. As the genetic determinants of the development of osteopenic syndrome in these patients, there is the presence of the allele of the BB gene of the VDR gene

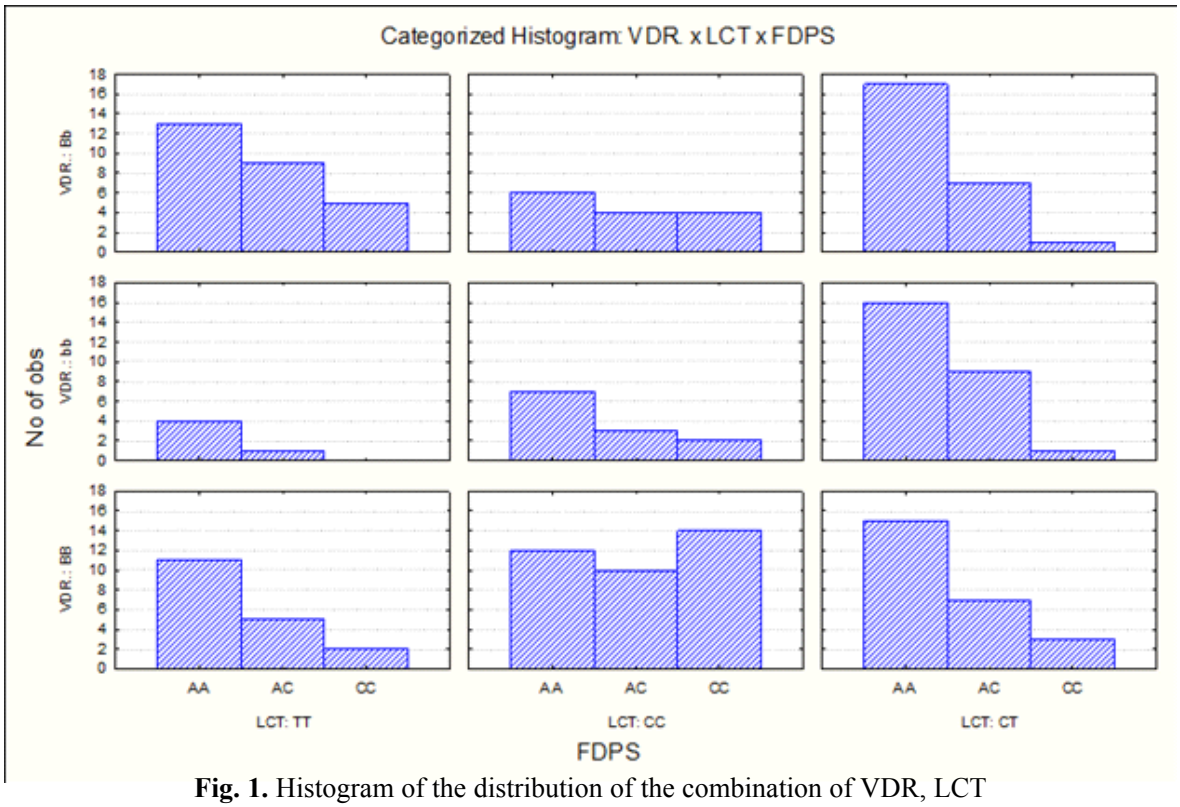


Fig. 1. Histogram of the distribution of the combination of VDR, LCT and FDSP genes in the total sample of patients

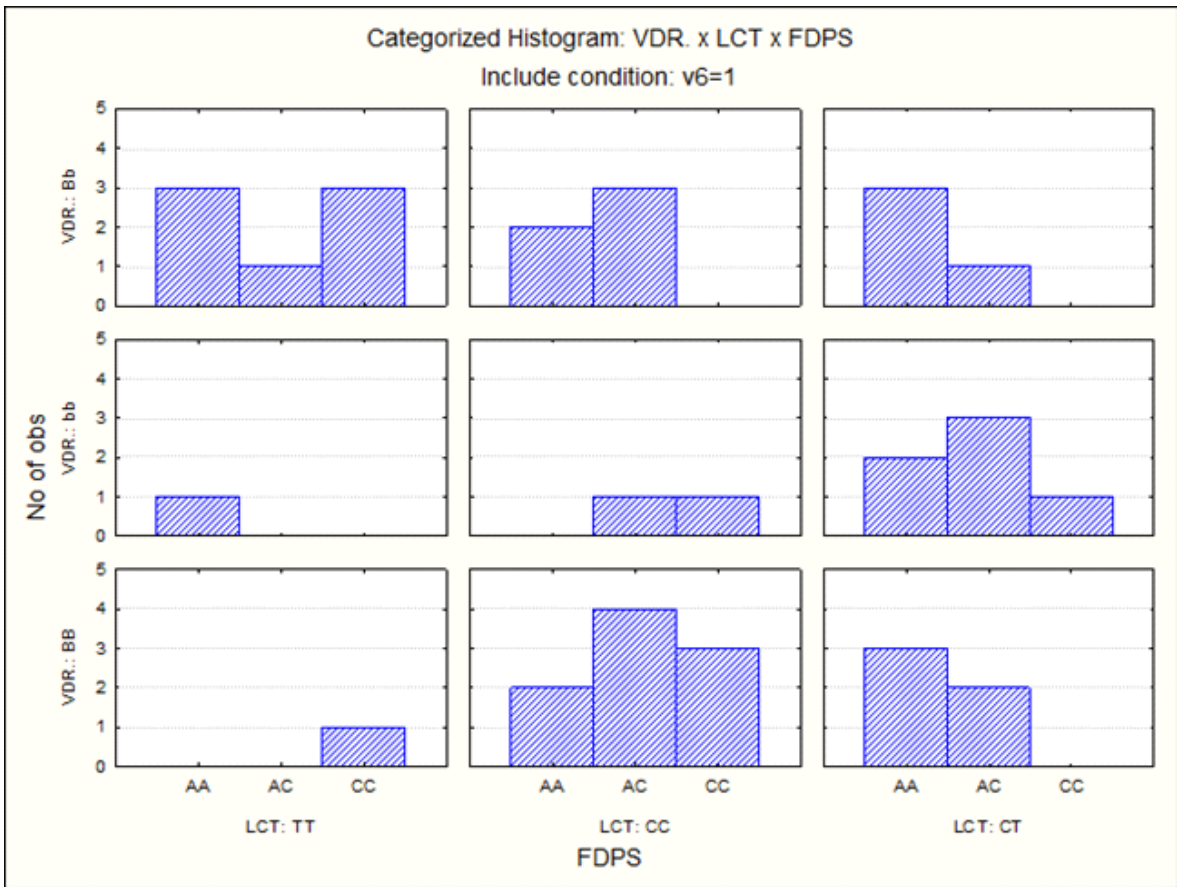


Fig. 2. Distribution histogram of the combination of VDR, LCT and FDSP genes in patients with isolated CP

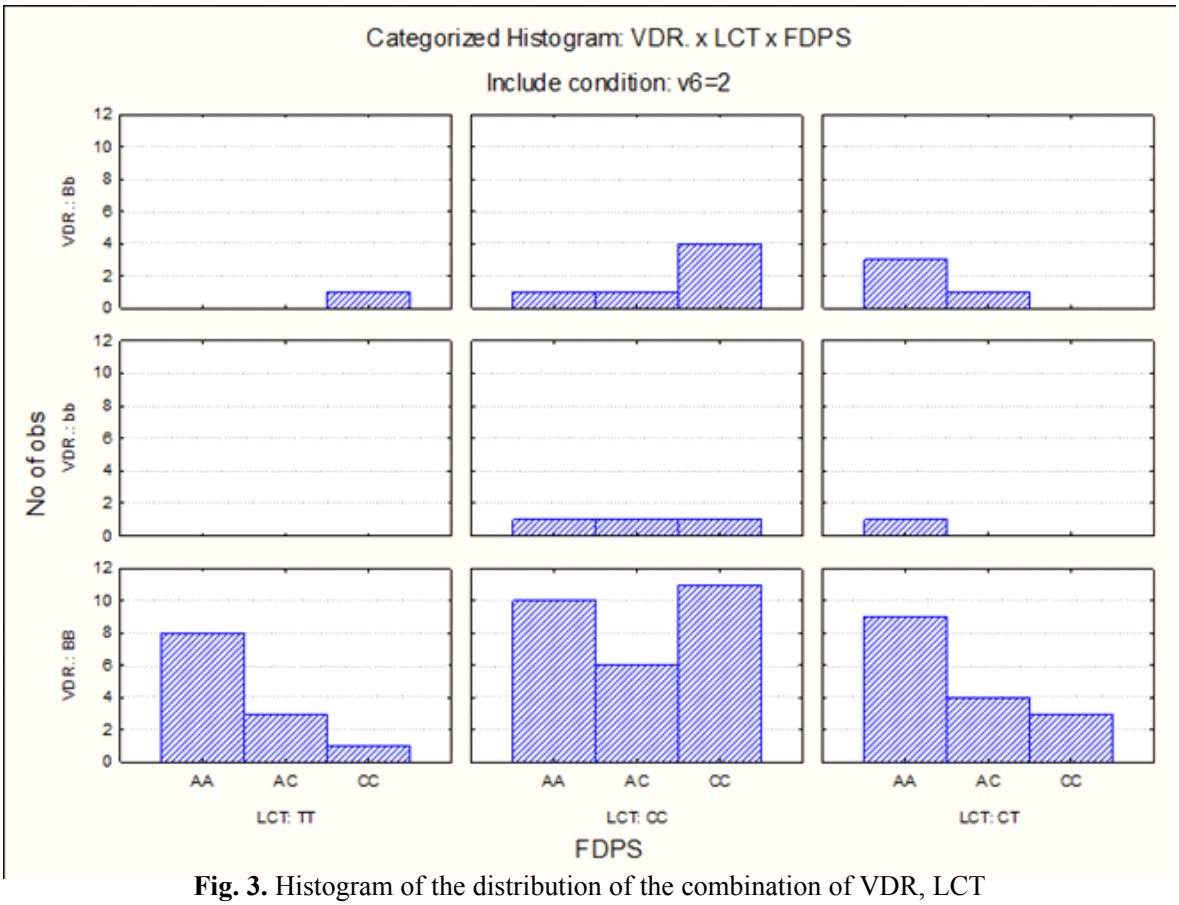


Fig. 3. Histogram of the distribution of the combination of VDR, LCT and FDSP genes in patients with CP accompanied by HD

and the CC allele of the FDPS gene. The presence of the CC allele of the gene LCT has no independent predictive value, but in combination with the identified variants of the genes, VDR and FDPS trigger an increase in the risk of osteoporosis.

Prospects for further research are related to the substantiation of genetic research for early diagnosis and prevention of the risk of osteopenic states in people with comorbidity of chronic pancreatitis and arterial hypertension.

References

1. Babinets L.S., Kvasnyska O.S., Mignenko L.M., Pinkevich O.Ya. (2011). Osteodeficiency and the effect of concomitant pathology on its depth in chronic pancreatitis. Bukovinsky medical bulletin, V15, № 2(58), 183–185

2. Viun T. I. (2018). Mechanisms of implementation of osteopenic states in patients with the combined course of chronic pancreatitis and hypertension. Vestnik club of pancreatologists, № 4 (41), 36–41.

3. Viun T.I., Pasieshvili L.M. (2018). Priorities of the diagnostic search of osteopenic conditions in patients with chronic pancreatitis and hypertension. Ukrainian Recognition of scientific and practical specialties. Suchasna Gastroenterologiya, № 3(101), 14–20.

4. Ivanova K.V. (2018). Dynamics of indicators of remodulation, resorption of bone tissue and lipid profile of blood in patients with coronary heart disease depending on the body mass index. Modern medicine: trends and prospects of development: a collection of materials of international scientific-Practical Medical Conference (Republic of Poland, Rzeszow, July 9, 2018), 91–94.

5. Krylov M.Y., Nikitinskaya O.A., Samarkina E.Y., Demin N.V., Toroptsova N.V. (2016). Farnesyl diphosphate synthase (fdrs) and geranylgeranyl diphosphate synthase (ggsp1) gene polymorphisms and efficiency of therapy with bisphosphonates in russian women with postmenopausal osteoporosis: a pilot study. Rheumatology Science and Practice, 54(1), 49–52. doi.org/10.14412/1995-4484-2016-49-52

6. Tereshkin K.I. (2015). Role of determination of genetic markers and apelin levels in patients with osteoarthritis on the background of obesity in clinical practice. Materials of NPK with international

participation "Chronic non-communicable diseases: measures of prevention and control of complications", Kharkiv, 210–211.

7. Tereshkin K.I., Pasieshvili L.M. (2016). Prognostic and diagnostic value of apelin during osteoarthrosis in patients with obesity. Problems of Endocrine Pathology, Issue 2, 70–75.

8. Bang D., Xu J., Keenan R., Pike V., Lehmann R., Tenner C., Crittenden D., Pillinger M., Krasnokutsky S. (2016) Cardiovascular Disease Prevalence in Patients with Osteoarthritis, Gout, or Both. Bulletinofthe Hospital Joint Disease, 74, 113–8.

9. Duggan S.N., O'Sullivan M., Hamilton S., Feehan S.M., Ridgway P.F., Conlon K.C. (2012). Patients with chronic pancreatitis are at increased risk for osteoporosis. Pancreas., 41(7), 1119–24. doi: 10.1097/MPA.0b013e31824abb4d

10. Haussler M.R., Whitfield G.K., Kaneko I., Haussler C.A., Hsieh D., Hsieh J.C., Jurutka P.W. (2013). Molecular mechanisms of vitamin D action. Calcif Tissue Int., 92(2), 77–98. doi: 10.1007/s00223-012-9619-0

11. Hoes J. N. (2015) Management of osteoporosis in rheumatoid arthritis patients. Expert Opin. Pharmacother,16(4), 559–571.

12. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium (2011). Ross A. C., Taylor C. L., Yaktine A. L. et al. Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): National Academies Press (US). Available from: http://www.ncbi.nlm.nih.gov/books/NBK56070.

13. International Society for Clinical Densitometry, The. Official positions 2015 ISCD combined: official positions of the international society for clinical densitometry. Available at: www.ISCD.org. June 2015.

14. Kendir C., van den Akker M., Vos R. (2017). Cardiovascular disease patients have increased risk for comorbidity: A cross-sectional study in the Netherlands. Eur. J. Gen. Pract. № 23, 1–6.

15. Manohar M., Verma A.K., Venkateshaiah S.U. (2017) Pathogenetic mechanisms of pancreatitis. World J. Gastrointest. Pharmacol, Vol. 8, № 1, 10–25.

16. Marozik P., Mosse I., Alekna V., Rudenko E. (2013). Association Between polymorphisms of VDR, COL1A1 and LCT genes and Bone Mineral Density in Belarusian women with severe postmenopausal osteoporosis. Medicina (Kaunas),177–183.

17. Olmos J.M., Zarrabeitia M.T., Hernandez J.L. (2012) Common allelic variants of the farnesyl diphosphate syntase gene influence the response of osteoporotic women to bisphosphonates. Pharmacohenom J., 12, 227–32. doi: 10.1038/tpj.2010.88

18. Riancho J.A. (2018) Epigenetics of Osteoporosis: Critical Analysis of Epigenetic Epidemiology Studies. Curr. Genom. V.6, 405–410.

19. Viun T., Pasieshvili L. (2018). Pathogenetic links of the combined course of chronic pancreatitis and hypertensive disease and their role in the formation of complications. Georgian medical news, № 10(283), 81–84.

Received: 17-Jan-2019
Accepted: 11-Mar-2019

VARIATIVITY OF CLINICAL-PSYCHOPATHOLOGICAL CONTENT OF DISORDERS RELATED TO ALCOHOL CONSUMPTION IN PERSONS WITH DIFFERENT PSYCHOLOGIC TRAUMATIC EXPERIENCES AND LEVELS OF PSYCHOSOCIAL STRESS

Gaponov K.D.

Kharkiv Medical Academy of Postgraduate Education, Ukraine

Abstract

The article presents the results of a comprehensive survey of 312 men suffering from alcohol dependence: 107 combatants, 89 forcibly displaced persons and 116 civilians in the city of Kharkiv and Kharkiv region. The study has shown that the clinical diversity and severity of disorders associated with alcohol consumption (the style of alcohol consumption, the ability to control the attraction to consume, tolerance, the structure of the withdrawal state, etc.), and their psychopathological arrangement (depression, anxiety, interpersonal sensitivity, hostility, phobic anxiety, somatization, paranoia) are associated with the severity of psychosocial stress that the patients experience. The factor of the presence of psychotraumatic experience, not associated with a distinct response to a stressful event, does not significantly affect the variability of psychopathological symptoms of individuals with alcohol dependence. The revealed patterns should be taken into account when developing treatment and rehabilitation and preventive measures for persons suffering from alcohol dependence.

Key words: *psychosocial stress, psychotraumatic experience, psychopathological manifestations, disorders related to the alcohol consumption.*

Introduction

According to the results of a collaborative study of the global incidence of alcohol-related diseases in 195 countries of the world for the years from 1990 to 2016, published in the journal Lancet (2018), Ukraine ranks 2nd in the world in terms of the number of years lost due to disability or premature death due to the alcohol consumption (DALY). Also, Ukraine ranks 2nd in the world in the number of years that Ukrainians live with alcoholism (YLD); according to the rate of death due to alcohol, Ukraine ranks 9th in the world, and the number of deaths associated with alcohol consumption is 1.3% of their total number [1]. The above suggests low effectiveness of the existing system for providing medication.

The current state of the prevalence of alcohol dependence and the provision of medication to the population in the country is a reflection of socio-political processes taking place in Ukraine. First of all, it relates to the factors associated with the effect of suppressive stressors, such as political and economic instability and hostilities in the East of Ukraine [2–4].

The relationship between the presence of stress and the alcohol consumption is confirmed by a large number of studies with a significant evidence base and is recognized by all scientific schools and directions: the results of epidemiological, genetic, biochemical, neurophysiological, clinical researches convincingly testify to its presence [5, 6].

Meanwhile, in spite of the obvious need, the accumulation of this knowledge has not yet led to an understanding of how to use new knowledge to affect the reduction of harm from alcohol and the effectiveness of alcohol dependence treatment

Corresponding Author:
Kostiantyn Gaponov, MD, PhD, Chief Doctor of the Regional Clinical Hospital "Regional Narcological Dispensary", of the of the Narcology Department at the Kharkiv Medical Academy of Postgraduate Education of the Ministry of Health of Ukraine, Ukraine.
E-mail: kostiantyn1807@gmail.com

in people experiencing significant stress. Taking into account the systemic interaction of the two mentioned phenomena, approaches to treatment of alcohol dependence with comorbid post-stress conditions should be based on biopsychosocial principles, and existing therapeutic and rehabilitation strategies should be substantially modified taking into account the vector of stress on the formation and the course of alcohol dependence.

2 Purposes, subjects and methods:

2.1 Purpose – to analyze the peculiarities of the correlation between the variability of manifestations and the psychopathological arrangement of alcohol dependence, with the presence of psychotraumatic experience and the severity of psychosocial stress, to understand the ways of modification of existing therapeutic and rehabilitation strategies, taking into account the aggravating effect of stress on the formation and the course of alcohol dependence.

The hypothesis of the work was the statement that the factor of the presence of psychotraumatic experience itself not associated with a distinct response to a stressful event does not significantly affect the indices of the severity of alcohol-related disorders, which significantly influences the choice of therapeutic strategies for individual contingents of patients with alcohol dependence.

2.2 Subjects & Methods

The study was carried out on the basis of the Municipal Non-Commercial Enterprise of Kharkiv Regional Council "Regional Narcological Dispensary" during 2014–2018, where upon condition of informed consent, being committed to the principle of bio-ethics and deontology, 312 men with alcohol dependence were examined: 107 combatants who had the experience of engaging in military actions on the East of Ukraine as participants in the Anti-Terrorist Operation and Operation of the Joint Forces; 89 forcibly displaced persons from temporarily occupied districts of Donetsk and Lugansk region; and 116 residents of the city of Kharkiv and Kharkiv region who were not combatants or forcibly displaced persons.

The study included the use of clinical, clinical-psychopathological and psycho-diagnostic methods. Alcohol dependence was diagnosed by clinico-psychopathological method that was supplemented, in addition to a clinical structured interview according to the diagnostic criteria of ICD-10, by psychodiagnostic studies using the AUDIT test (for identifying disorders associated with alcohol abuse and determining the degree of danger of its use) [7] and scales SADQ-C [8]. Measurement of the severity of psychosocial stress was carried out on the scale by L. Rider [9] and the scale of psychological stress by Lemyr-Tessier-Fillion in edition of N. E. Vodopyanova (PSM-25) [10]. In addition to the severity of psychosocial stress, the severity and structure of post-traumatic stress was also assessed by means of the scale of the impact of the traumatic event by M. Horowitz in edition of N.V. Tarabrina [11]. The evaluation of the specificity of psychopathological symptoms was performed using the Symptom Check List-90-Revised-SCL-90-R expressiveness questionnaire in edition of N.V. Tarabrina [11]. The statistical-mathematical analysis included the formation of descriptive statistics and the analysis of discrepancies using non-parametric methods: the Mann-Whitney test and Fischer's exact criterion.

Conflict of interests. There is no conflict of interests.

3 Results and discussion

According to the criterion of the severity of the psychosocial stress (according to L. Rider's scale), the patients were divided into the following three groups: with a low level – 35 persons (the indicator on a scale is up to 0.99 points), with a moderate level – 84 persons (the indicator is from 1.00 to 1.99 points), and with a high level – 193 persons (the indicator is more than 2.00 points).

Relatively low level of psychosocial stress was determined in 2 (1.9%) combatants (group C1), 9 (10.1%) displaced persons (group DP1) and 24 (20.7%) locals (group L1) (average indicator in the group is 0.62±0.21 points). Moderate level of stress was detected in 29 (27.1%) combatants (group C2), 22 (24.7%) displaced persons (group DP2) and 33 (28.4%) locals (group L2) (average indicator is 1.39±0.30 points). Severe stress level was detected in 76 (71.0%) combatants (group C3), 58 (65.2%) displaced persons (group DP2) and 59 (50.9%) urban residents (group L3) (average indicator is 2.47±0.38 points). Differences in the comparison of the average severity of psychosocial stress in these groups were statistically significant ($p<0.01$).

The average indices of the severity of psychosocial stress among people of different social groups were the following: among the combatants – 2.24±0.63 points; displaced people – 2.03±0.72 points; local residents – 1.68±0.78 points (differences were statistically significant when comparing groups of combatants and locals, displaced persons and locals, $p<0.01$).

A similar tendency was found regarding the vulnerability to psychological stress (method PSM-25): the average severity of the combatants was 151.62±25.82 points, of the displaced persons – 143.56±31.20 points, of the locals – 131.09± 36.04 points (differences in the comparison of combatants and displaced persons $p>0.05$, combatants and locals $p<0.01$, displaced persons and locals $p<0.01$). The average indicator in the group of individuals with a low level of response to psychosocial stress was 72.46±9.37 points, with a moderate level of response was 123.30± 19.97 points, and with a severe level was 162.25 ±9.43 points (differences statistically significant in comparison all groups among themselves, $p<0.01$). The study of the impact assessment of the traumatic event on the mental state of the respondents has proven the following. On the one hand, it is absolutely anticipated that the average severity of the impact of the psychotraumatic experience was higher among the combatants (52.83±22.12 points) than that of the displaced persons (47.67±22.02 points), and in the latter – higher than in the local residents (40.06± 17.75 points) (differences are significant when comparing the numbers of combatants and / or displaced persons with locals – combatants vs. locals $p<0.01$; displaced persons vs. locals $p<0.05$; differences between combatants and displaced persons are not reliable $p>0.05$). Meanwhile, the average severity of post-traumatic responses in individuals with a low level of psychosocial stress was 23.23±0.65 points (upper limit of the low severity range), moderate – 28.61±3.86 (lower limit of the range of moderate severity), severe – 58.69 ±18.28 points (range of high severity), while the differences were statistically significant in the comparison of all groups among themselves ($p<0.01$). Thus, we can see that among the representatives of different contingents, including the presence of psychotraumatic experience "by default" (combatants and / or displaced persons), despite the traumatic events experienced, there are a significant number of people with low or insignificant severity of pathological post-traumatic stress. The intensity of the pathological effect of the traumatic event is due to the expressiveness of the stress response to it, which is associated with the severity of the tested psychosocial stress.

The severity of clinical manifestations of alcohol dependence also turned out to be heterogeneous among the surveyed people, but was associated with the level of psychosocial stress: in people with mild stress, the average rate on AUDIT scale was 15.17±2.32 points, with a moderate response to stress – 21.53±1, 99 points, severe – 31.51±6.35 points (differences are statistically significant when comparing all groups among themselves $p<0.01$). The average severity of alcohol dependence among combatants was 30.43±7.31 points, displaced persons – 28.60 ± 7.78 points, and locals – 25.43±8.19 points (differences are statistically significant when comparing combatants and locals $p<0.01$, displaced persons and locals $p<0.01$).

Differences in the severity and clinical variability of the abolition state (SADQ-C scale) for the most part did not have statistical significance between patients of different social groups (combatants – 43.48±9.17 points, displaced persons – 41.04±13.18 points, $p>0.05$; locals – 35.49±16.02 points, $p<0.01$), however, there were significant differences in the severity of psychosocial stress (*table*).

According to Table 1 data, the manifestations of the severity of alcohol dependence, first of all, symptoms of the first day of withdrawal, significantly differed depending on the level of psychosocial stress: in patients with severe stress, all the symptoms were more severe, in particular, hyperhidrosis, tremor and desire to drink of varying degrees of severity during the first and second-third days of withdrawal, as compared to the symptoms, inherent in persons with lower severity of psychosocial stress. For patients with the moderate level, the most severe symptoms were symptoms of hyperhidrosis, tremor, as well as the desire to drink in the first day of withdrawal. In individuals with mild psychosocial stress, there were single affective symptoms and manifestations of tolerance.

Further analysis of the clinical content of alcohol-related disorders had a significant difference, depending on the level of psychosocial stress experienced by the patients (*fig. 1*).

In patients with a low level of psychosocial stress, the clinical-psychopathological picture of alcohol dependence predominated ($p<0.01$): one-day excesses (48.6%) or pseudo dipsomania (42.9%); situational primary attraction to alcohol, arising periodically, was more often provoked by external factors (100%); a strong desire or an insuperable desire to consume alcohol that was manifested by a secondary attraction that arose after any dose of alcohol, with a partial loss of quantitative control (60.0%) or a symptom of a critical dose (40.0%); the absence of pathological time course of clinical manifestations of intoxication (97.1%).

Clinical variability of the structure of withdrawal state in people with different levels of psychosocial stress (on the scale of SADQ-C)

No.	Manifestations of severity of alcohol dependence on the scale of SADQ-C	Level of psychosocial stress			Level of statistical significance of differences		
		low	moderate	severe	p 1-2	p 1-3	p 2-3
Manifestations of the first day of withdrawal syndrome, M ± m							
1	Some hyperhidrosis	0.09±0.28	2.14±0.73	3.37±0.58	<0.01	<0.01	<0.01
2	Hands tremor	0.14±0.36	2.38±0.77	2.97±0.82	<0.01	<0.01	<0.01
3	Body tremor	0.14±0.36	1.40±0.49	2.33±0.95	<0.01	<0.01	<0.01
4	Intense hyperhidrosis	0.17±0.38	1.63±0.62	2.26±0.95	<0.01	<0.01	<0.01
5	Fear	0.17±0.38	1.50±0.59	2.23±0.84	<0.01	<0.01	<0.01
6	Fear of meeting people	0.17±0.45	1.56±0.52	2.04±0.78	<0.01	<0.01	<0.01
7	The face of despair	0.40±0.55	1.98±0.79	2.07±0.94	<0.01	<0.01	>0.05
8	Fright	0.43±0.56	1.62±0.74	1.80±0.85	<0.01	<0.01	>0.05
9	Desire to drink	0.51±0.82	1.56±0.72	1.48±0.72	<0.01	<0.01	>0.05
10	Strong desire to drink	0.80±0.90	1.58±0.84	1.54±0.79	<0.01	<0.01	>0.05
11	Need to drink for tremor removal	0.54±0.78	1.43±0.66	1.64±0.86	<0.01	<0.01	>0.05
12	Very strong desire to drink	0.31±0.68	1.69±0.90	1.91±1.13	<0.01	<0.01	>0.05
Daily tolerance, M ± m							
13	Tolerance of more than 250 ml of vodka	0.49±0.66	1.58±0.93	1.98±1.09	<0.01	<0.01	<0.01
14	Tolerance of more than 500 ml of vodka	0.34±0.59	1.44±0.97	2.28±1.17	<0.01	<0.01	<0.01
15	Tolerance of more than 1 l of vodka	0.40±0.50	1.70±0.92	2.04±1.09	<0.01	<0.01	<0.05
16	Tolerance of more than 2 l of vodka	0.06±0.24	1.86±1.05	1.90±1.08	<0.01	<0.01	>0.05
Manifestations of the second-third day of withdrawal syndrome, M ± m							
17	Salivation	0.80±0.83	1.89±1.15	2.51±1.09	<0.01	<0.01	<0.01
18	Hands tremor	0.83±0.98	2.23±1.32	3.40±1.04	<0.01	<0.01	<0.01
19	Body tremor	0.97±0.66	2.23±0.72	3.11±0.94	<0.01	<0.01	<0.01
20	Very strong desire to drink	1.37±1.52	3.49±0.94	3.77±0.56	<0.01	<0.01	<0.01

A characteristic feature of the clinical image of alcohol dependence, inherent in this category of patients, was the absence of a clinically defined syndrome of withdrawal and awareness of the harmful effects of alcohol dependence.

In patients with the moderate stress level, the primary attraction to alcohol developed independently of the provocative effect of external factors (44.0%), or was of the nature of the internal unconscious need (26.2%); consumption was carried out in the form of pseudo dipsomania (35.7%) or permanent consumption secondary to high tolerance (36.9%); characterized by an impairment of the capacity of quantitative control with partial (38.1%) or total loss (59.5%), as well as restriction of the repertoire of alcohol consumption, loss of the importance of such factors as place, time and environment during its consumption; manifestations of somatic harm (complications in the cardiovascular system – 52.4%, intestinal system – 34.5%); non-severe withdrawal state; the primary amount partially recognized and formally did not deny the presence of harmful effects of alcohol abuse ($p<0.01$).

Persons with the high level of stress were found to have the following ($p<0.01$): constant alcohol consumption secondary to high (42.5%) or low (36.8%) tolerance; spontaneous, without struggle of motives (47.7%), or compulsive primary pathological attraction to alcohol (36.8%); loss of a quantitative (53.9%) or situational (43.0%) control in a state of intoxication with a change in its form: a change in the form of intoxication with a depressive and anxiety component was characteristic for 15.5% of patients, previously unusual aggression in the combination with motor activity in a state of intoxication was found in 13.0% of patients (psychopathic behavior was manifested by explosiveness, predisposition to non-motivated aggression, and asocial actions), intoxication with features of polymorphic symptoms of the

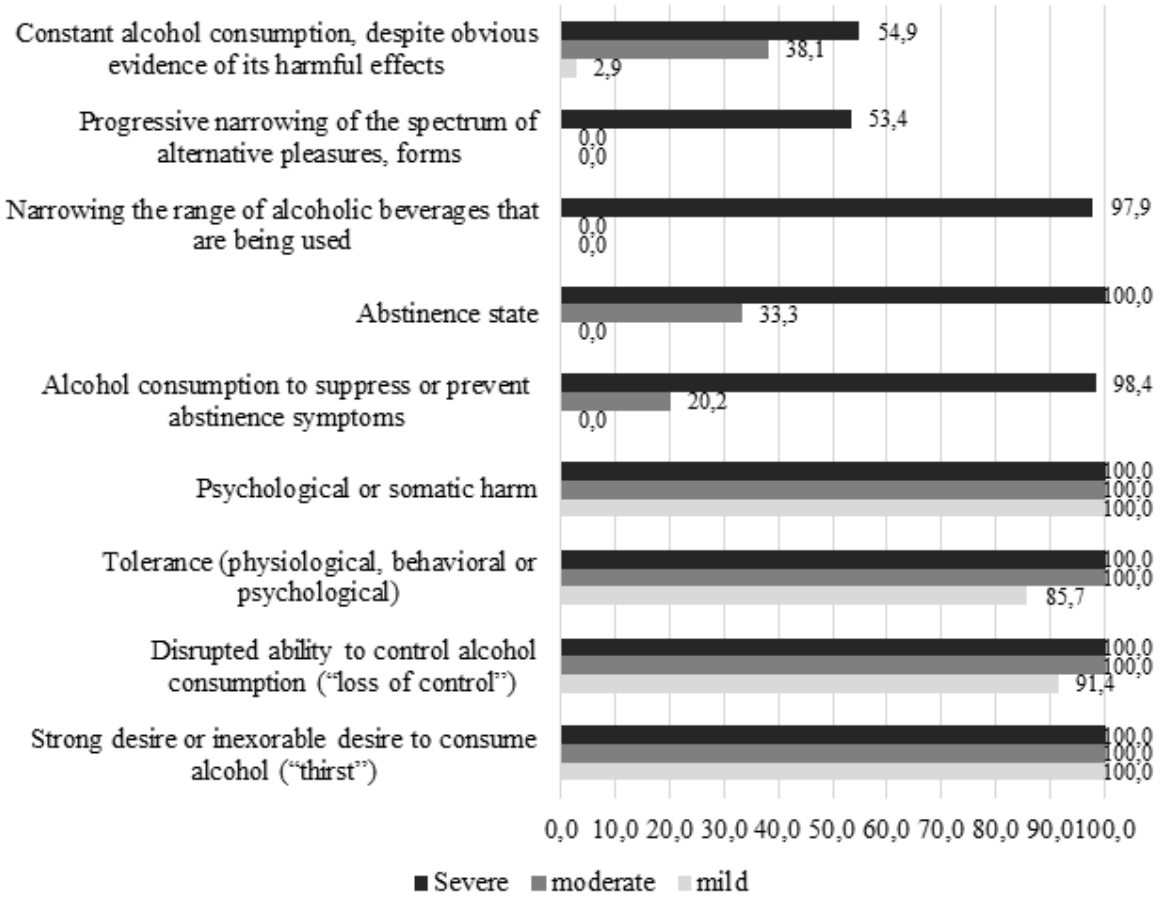


Fig. 1. Clinical specificity of disorders associated with alcohol consumption in people with different levels of psychosocial stress

dysphoric-explosive component was observed in 8.3% of the patients.

Furthermore, this category of examined patients was found to have: severe withdrawal syndrome with a compulsive-vital pathological attraction in its structure; a progressive loss of alternative interests in favor of the alcohol consumption and a longer time to buy and consume it; alcohol anosognosia and continuation of alcohol consumption, despite its obvious harmful somatic, psychological (affective and cognitive) consequences: the combination of affective flattening and indifference to the environment and severe somatic and vegetative manifestations.

The specificity of comorbid psychopathological arrangement was also determined by the level of stress experienced by the patients: an increase in the severity of psychopathological symptoms as increased severity of psychosocial stress was recorded.

Thus, among the combatants (groups C1, C2, C3 in *fig. 2*), the differences noted were most severe for depression, obsessive-compulsive symptoms, and somewhat less for somatization, interpersonal sensitivity and psychosis. The General Symptomatic Index (GSI) was increasing with an increase in the severity of psychosocial stress: in the C1 group it was 0.45±0.07 points, in the C2 group it was 0.57 ± 0.21 points, in the C3 group it was 0.71 ± 0.26 points. The Positive Symptomatic Index (PSI) was the highest in the C3 group (30.00 ± 8.52 points), slightly less in the C2 group (27.50 ± 2.12 points), and the lowest – in the C1 group (26.48 ± 7.19 points). Significant ($p<0.05$) discrepancies between the groups were found for the Positive Distress Symptomatic Index (PDSI), with a tendency to increase the severity of distress as the severity of psychosocial stress increased: in the C1 group, the rate was 1.40 ± 0.10 points, in the C2 group – 1.90 ± 0.27 points, in the C3 group – 2.11 ± 0.28 points.

The forcibly displayed persons (groups DP1, DP2, DP3) maintained the same general tendencies to increase the indices of the severity of psychopathological symptoms combined with the increase in the severity of psychosocial stress (*Fig. 3*): displaced persons with alcohol dependence, with a low degree of psychosocial stress, were

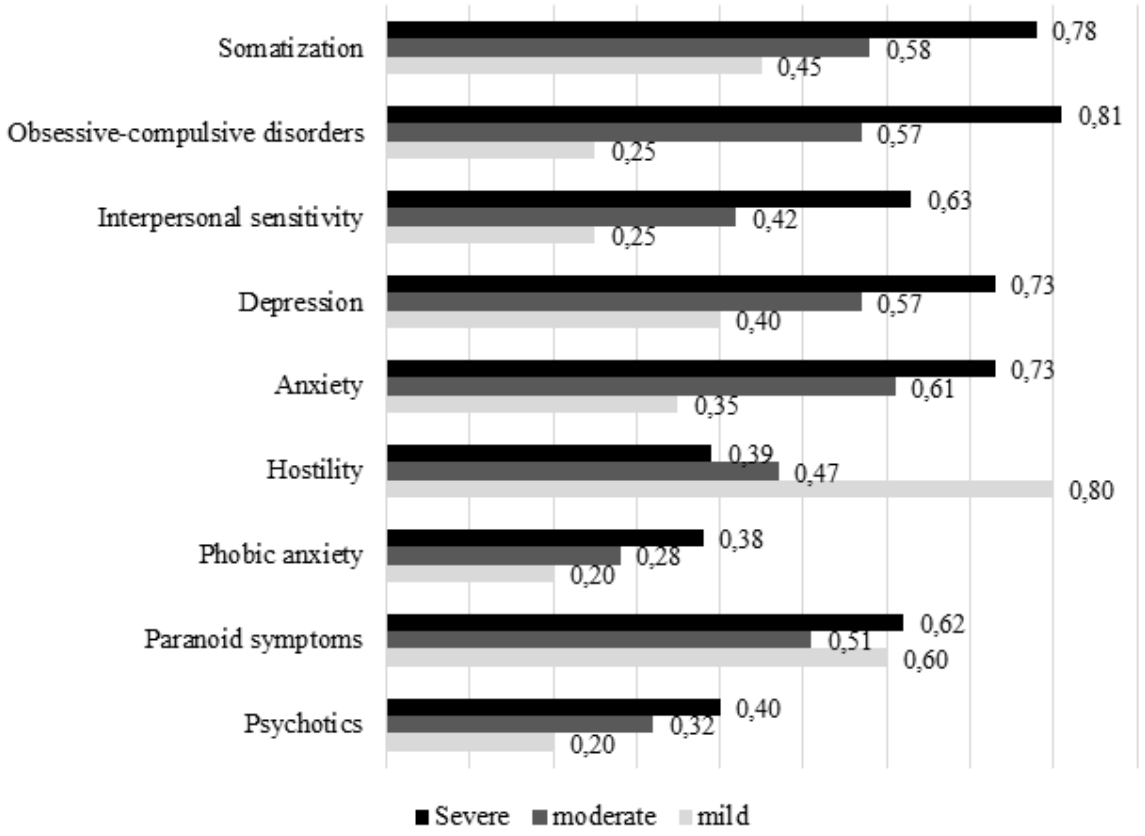


Fig. 2. Indices of the severity of psychopathological symptoms among combatants with alcohol dependence and different degrees of psychosocial stress

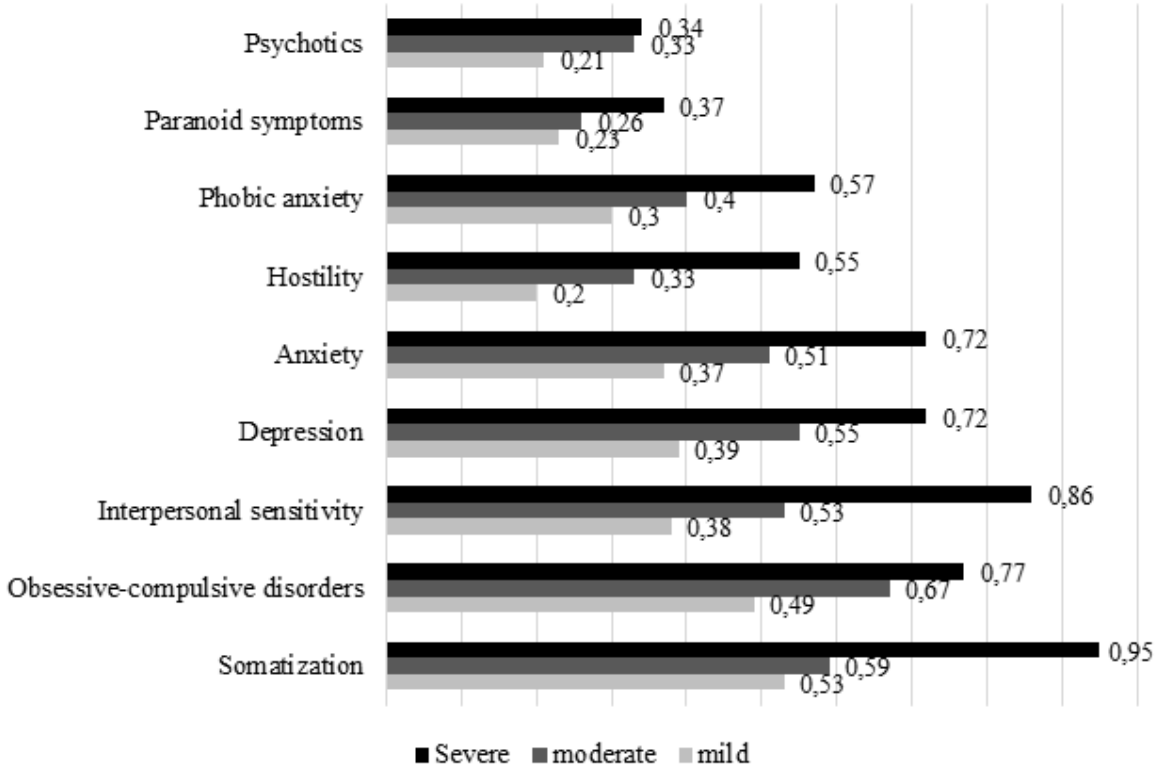


Fig. 3. Indices of the severity of psychopathological symptoms among forcibly displaced persons with alcohol dependence and different degrees of psychosocial stress

characterized by the lowest quantitative indices, with the highest degree of psychosocial stress - the highest rates, and indices in the group with a moderate degree of psychosocial stress occupied an intermediate position. Most clearly these differences were expressed for depression, somewhat less for interpersonal sensitivity, paranoid symptomatology and psychoticism. The General Symptomatic Index (GSI) among displaced persons was significantly increasing ($p<0.05$) with an increase in the severity of psychosocial stress: in the DP1 group it was 0.40 ±0.12 points, in the DP2 group it was 0.57 ± 0.12 points, in the DP3 group – 0,76 ± 0,28 points. The Positive Symptomatic Index (PSI) significantly differed in the groups DP1 (23.22± 5.70 points) and DP2 (28.77±4.47 points), and not significantly differed in the groups P2 and P3 (31.26±8.40 points). Significant ($p<0.05$) discrepancies between the groups were found for the PDSI index, while the severity of the distress was increasing with the increase in the severity of psychosocial stress: in the DP1 group it was 1.59 ± 0.15 points, in the DP2 group – 1.78±0.20 points, in the DP3 group – 2.14±0.25 points.

The highest degree of the regularities regarding the increase in the severity of psychopathological symptoms combined with the increase in the severity of psychosocial stress were expressed in the group of local residents (groups L1, L2, L3 in *fig. 4*): virtually all psychopathological symptoms revealed statistically significant differences in the indices between the groups with mild, moderate and severe psychosocial stress. The integral indices in this group showed a clear tendency to increase with the increase in the severity of psychosocial stress. Thus, the General Symptomatic Index (GSI) in the L1 group was 0.30 ± 0.08 points, in the L2 group - 0.50 ± 0.16 points, in the L3 group - 0.67 ± 0.21 points. The Positive Symptomatic Index (PSI) was 16.92 ± 3.28 points, 22.52 ± 5.36 points, and 27.19 ± 6.69 points, respectively. The PDSI index was1.60 ± 0.16 points, 1.97 ± 0.23 points and 2.17 ± 0.24 points, respectively.

In our opinion, this may be due to significantly higher severity of psychosocial stress in groups of combatants and displaced persons, and the more complex nature of the response to stress in these groups, which has

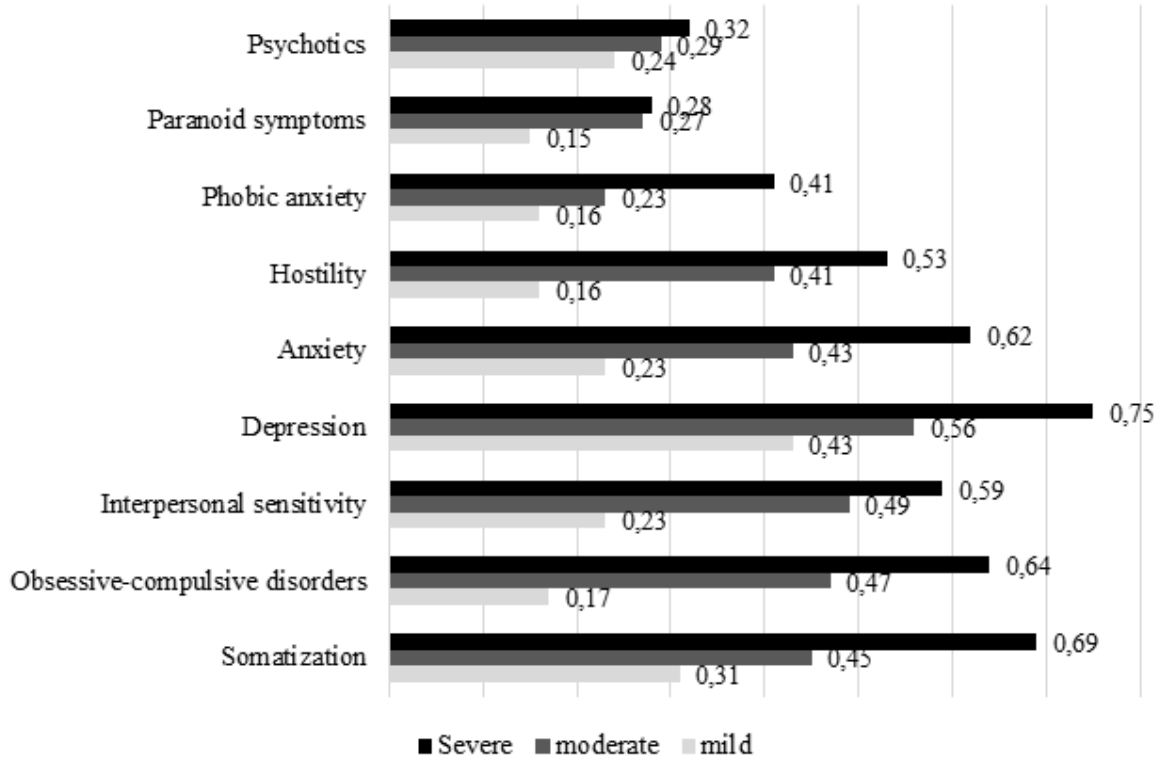


Fig. 4. Indices of the severity of psychopathological symptoms among local residents with alcohol dependence and different degrees of psychosocial stress

led to more complicated patterns, especially in the group of combatants.

Conclusions

Thus, the study has shown that the clinical diversity and severity of alcohol-related disorders and their psychopathological arrangement are associated with the severity of psychosocial stress experienced by patients.

The factor of availability of psychotraumatic experience itself not associated with a distinct response to a stressful event does not significantly affect the variability of the psychopathological symptoms of persons with alcohol dependence, which significantly influences the choice of therapeutic strategies for the individual contingents of these patients.

References

1. Degenhardt L, Charlson F, Ferrari A, Santomauro D, Erskine H, Mantilla-Herrara A, … Vos T. (2018). The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Psychiatry. Nov 1. pii: S2215–0366(18)30337-7. doi: 10.1016/S2215–0366(18)30337-7.

2. Maruta N.O., Kalens`ka G.Yu., Yavdak I.O., Malyuta L.V. (2018) Rozlady` psy`xichnogo zdorov'ya u vnutrishn`o peremishheny`x osib (Disorders of Mental Health in Internally Displaced Persons). Ukrayins`ky`j visny`k psy`xonevrologiyi. T. 26, vy`p. 2 (95). S. 68–71.

3. Deny`senko M.M., Laky`ns`ky`j R.V., Shestopalova L.F., Lins`ky`j I.V. (2017) Osnovni klinichni varianty` poststresovy`x rozladiv u kombatantiv (The main clinical variants of post-stress disorder in combatants) Ukrayins`ky`j visny`k psy`xonevrologiyi. T. 25, vy`p. 2 (91). S. 40–44.

4. Markova M. V., Gaponov K. D. (2016). Post-stressed disorders in servicemen who took part in the fighting: prevalence and expected consequences. WPA Congress of Epidemiology and Public Health 2016, 29.03 – 01.04.2016. Book of Abstracts. – Munich, Institute of Psychiatric Phenomics and Genomics, 2016. P. 30–31.

5. Gaponov K.D. (2016) Alkogol`na zalezhnist` v umovax social`nogo stresu: epidemiologichni, klinichni i likuval`ni aspekty` (Alcohol dependence in conditions of social stress: epidemiological, clinical and medical aspects). Ukrayins`ky`j visny`k psy`xonevrologiyi. Tom 24, vy`p. 4 (89). S. 54–60.

6. Gaponov K.D. (2018). Alkogol`na zalezhnist` i social`ny`j stres: bioximichni, nejrofiziologichni i psy`xosocial`ni mexanizmy` vzayemovply`vu (Alcohol dependence and social stress: biochemical, neurophysiological and psychosocial mechanisms of mutual influence). Ukrayins`ky`j visny`k psy`xonevrologiyi. T. 26, vy`p. 1 (94). S. 104–109.

7. Babor Th. F., Higgins-Biddle J. C., Saunders J. B., Monteiro M. G. (2001). AUDIT. Alcohol Use Disorders Identification Test. WHO/MSD/MSB/01.6a Original: English Distribution: General. 28 p.

8. Stockwell T., Sithavan T., McGrath D. (1994). The measurement of alcohol dependence and impaired control in community samples. Addiction.. Vol. 89. P. 167–174.

9. Gaponov K.D., Sosin I.K., Goncharova O.Yu., Markova M.V. (2018). Sposib diagnosty`ky` klinichnoyi specy`fiky` i prognozu perebigu alkogol`noyi zalezhnosti u osib z rizny`m psy`xotravmaty`chny`m dosvidom i rivnem psy`xosocial`nogo stresu (A method of diagnostics of clinical specificity and prognosis of the course of alcohol dependence in people with different psychotraumatic experiences and levels of psychosocial stress). Informacijny`j ly`st MOZ Ukrayiny` # 249–2018. 4 s.

10. Vodop`yanova N.E. (2009). Psy`xody`agnosty`ka stressa (Psychodiagnosis of stress). SPb.: Py`ter. 336 s.

11. Tarabry`na N.V. (2001). Prakty`kum po psy`xology`y` posttravmaty`cheskogo stressa (Practicum on the psychology of post-traumatic stress). SPb: Py`ter. 272 s.

Received: 18-Jan-2019
Accepted: 18-Mar-2019

AGE FEATURES OF BONE TISSUE DENSITY IN THE POSTERIOR AND INFERIOR WALLS OF THE FRONTAL SINUS

Gargin V.V., Lupyr A.V., Alekseeva V.V.,Yurevych N.O.

Kharkiv National Medical University, Ukraine

Chronic rhinosinusitis is a significant social, medical and economical problem. Elderly patients are unique among all groups of patients. The purpose of our study was to determine physiological variability of frontal sinus in the posterior and inferior walls and to compare it with variability in purulent-polypous rhinosinusitis. Subjects and methods: The study involved SCT examination of 40 male patients: 10 tomograms of patients aged 30–40 and 10 of patients aged 75–85. The tomograms of patients without ENT diseases were used for the control group. The study group included tomograms of patients aged 30–40 and 75–85 with chronic rhinosinusitis. Results. An average bone density of the posterior and inferior walls of the frontal sinuses was calculated. The bone density of the group aged 30–40 was 191.5±11.6 Hu in the inferior wall, 176.6±21 Hu in the posterior and 169.1±16.8 Hu and 164±21 Hu in the group aged 75–85 according to the above order. The study showed pronounced changes in the bone density in purulent-polypous frontal sinusitis. In the group aged 30–40 it was as follows: 120.1±8.3 Hu, 162.1±24 Hu in the inferior wall and 101.4±6.95 Hu, 127.4.8±15.4 Hu in the posterior wall. Conclusions: It can be assumed that the decrease in the bone density is associated with age. And it is more severe in case of chronic frontal sinusitis.

Key words: *Frontal sinus, CT, elderly, bone density.*

Introduction

Chronic rhinosinusitis represents a significant social, medical and economic problem [1]. According to some reports, the incidence of this disease can be equal to diabetes and heart diseases [12] and accounts for 10.9% of the urban population in Europe and 12.5% of the United States population [5]. The course of chronic rhinosinusitis has distinct age-specific features, which also affect the methods of further treatment [7]. Elderly patients occupy a special place among all groups of patients. The incidence of complications of rhinosinusitis at this age is much greater than in younger patients, although clinical presentation of inflammatory diseases affecting the perineal sinuses is less severe due to changes in the immune status, hormonal age changes, concomitant diseases, changes in behavior, namely predisposition to depressive states. The most severe intracranial and intraorbital complications are associated with frontal sinusitis [13]. Bone alteration is, in particular, one of the most significant links in the development of chronic rhinosinusitis in general and chronic frontal infections and is associated with demineralization, disappearance of trabecula, cortical destruction and focal sclerosis. These changes may correlate with the severity of the disease [2]. There are ways to predict the probability of complications by bone thickness according to the Global Osteitis Scoring Scale (GOSS) by Georgalas and others, which is based on bone thickness measurement, but this indicator does not always reflect the degree of destruction. [3].

2. Purposes, subjects and methods:

2.1 Purpose – to determine the physiological age variability of the posterior and inferior walls of the frontal sinus and to compare it with those in chronic purulent-polypous frontal sinusitis.

Corresponding Author:
Tetyana Chaychenko, MD, PhD,
Professor of Department of Pediatrics 1 and Neonatology of Kharkiv National Medical University, Ukraine.
E-mail: tatyana.chaychenko@gmail.com

2.2 Subjects & Methods

The study was carried out within the framework of the planned comprehensive research carried out at Kharkiv National Medical University on the topic "Morphological features of organs and systems of the human body at the stage of ontogenesis", state registration number 0144U004149.

Spiral computed tomography (SCT) is one of the most informative non-invasive intravital method for examination of paranasal sinuses [8]. The study involved 40 male patients (to exclude the impact of factors occurring during menopause, women were excluded from this study). The study implied evaluation of SCT findings of 10 patients aged 30–40 years and 10 patients aged 75–85 years who underwent this examination in connection with a disorder not related to ENT organs (a tomography was performed to determine the presence of an unconfirmed stroke). The study also included 20 patients with chronic purulent-polypous frontal sinusitis, who underwent examination in accordance with the order of the Ministry of Health of Ukraine No. 181 as of 24 March 2009 "On approval of medical treatment protocols in the field of otorhinolaryngology". Ten of these patients were aged 30–40 years and ten were aged 75–85 years. The Hounsfield scale [6] showed that the density of the posterior wall was potentially dangerous for the development of intracranial complications [4], and the inferior wall of the frontal sinus was dangerous for the development of intraorbital complications [9]. The obtained digital data were statistically processed using the Student-Fisher method, the mean value for each variation series (X), the mean-square deviation, and the mean error (m) were determined. Statistical processing was performed on a personal computer using Microsoft Office Excel 2010 (US). Statistically significant results were considered $p < 0.05$.

Conflict of interests. There is no conflict of interests.

3 Results and discussion

The results of calculations are presented in *tables 1–4*.

Physiological mean density of the posterior wall of the frontal sinus was calculated as follows: in the group of people aged 30–40 it was 191.5.1 ±11.6 Hu, and in the group aged 75–85 – 169.1± 16.8 Hu in the inferior wall and 176.6.1±21 Hu and 164±21 Hu, respectively, in the region of the posterior wall (*table 1, 3*). The inferior wall density was 165±18.8 Hu and 137.6±14.4 Hu in accordance with the above order. The study showed that the density of bone tissue significantly ($p<0.05$) decreased with age.

In chronic purulent-polypous sinusitis, the density was 120.1±8.3 Hu and 101.4±8.3 Hu in the inferior wall and 162.1±24 Hu and 127.4± 15.4 Hu in the posterior wall in accordance with the above order.

Calculation and comparison of densitometric indices of different groups under investigation showed that the density of bone tissue significantly depended on age ($p < 0.05$). It decreased with age both in physiological conditions $p = 0.00035$ and $p = 0.0016$ in the region of the inferior and posterior walls, respectively, and in conditions of chronic purulent-polypous maxillary sinusitis $p = 0.002$ and $p = 0.0016$ according to the specified order.

Physiological density of the inferior and posterior walls of the frontal sinus in was calculated two different age groups. The density of the posterior wall was found to be greater in the group of people aged 75–85. Moreover, physiological density decreased not only with age, but also in chronic inflammation. However, at young age, these changes were more pronounced, by 26% as opposed to the age group of 75–85 years, where it decreased by only 9%. Such a more severe response is likely to be due to the increased tension of the immune response to the inflammatory process and the uniqueness of the immune response to the pathological process in the elderly [10].

Thus, age has a significant meaning not only in the course of chronic rhinosinusitis, but also in the physiological density of bone tissue in general and frontal sinus in particular. Older people undergo rearrangements in the structure and

Table 1

Physiological density of bone tissue of the inferior wall of the frontal sinus

Age (years)	1	2	3	4	5	6	7	8	9	10	x	M
30–40	195	183	195	178	197	215	172	194	186	200	191,5	11,6
75–85	142	173	179	157	198	182	154	182	175	149	169,1	16,8

Table 2

Density of the inferior wall of the frontal sinus in chronic purulent – polypous sinusitis

Age (years)	1	2	3	4	5	6	7	8	9	10	x	M
75–85	105	93	98	89	94	108	109	107	108	103	101,4	6,95
30–40	116	113	124	128	121	139	112	117	115	116	120,1	8,3

Table 3

Physiological density of the bone tissue of the posterior wall of the frontal sinus

Age (years)	1	2	3	4	5	6	7	8	9	10	x	M
30–40	190	140	210	165	168	196	178	167	152	200	176,6	21
75–85	168	154	216	141	173	155	157	151	151	174	164	21

Table 4

Density of the posterior wall of the frontal sinus in chronic purulent – polypous sinusitis

Age (years)	1	2	3	4	5	6	7	8	9	10	x	M
30–40	172	165	159	178	163	140	154	135	178	177	162,1	24
75–85	135	158	93	138	145	107	118	137	154	89	127,4	15,4

microarchitectural structure of the bones due to the shortage of steroid hormones in this age category [11], which has been repeatedly proven for the femur in elderly. Our study allows us to assume the correctness of this statement for bone tissue.

Thus, elderly patients should be treated with extreme caution, since the density of bone tissue of the frontal sinus is physiologically lower, although its reduction under the action of purulent-polypous process is less severe than in the group of younger patients. It has been shown that the inferior wall density in patients aged 75–85 is reduced more than that of the posterior wall, suggesting higher probability of intraorbital than intracranial complications in this group of patients.

Conclusions. Thus, the following conclusions can be drawn from the research:

1. Physiological density of the posterior wall is more than that of the inferior in people aged 75–85.

2. The density of the inferior and posterior walls of the frontal sinus significantly ($p < 0.05$) varies with age.

3. The density of both inferior and posterior walls, equally decreases with age by 9.9% and 6.4% respectively.

4. Under the influence of pathological process, the posterior wall density is more stable in the group of people aged 75–85 and is reduced only by 9%, whereas in patients aged 30–40 by 26%.

References:

1. Adouly T, Adnane C, Khallouk A, et al. (2017). Moroccan adaptation and validation of the rhinosinusitis quality-oflife survey. Eur Arch Otorhinolaryngology, 274(3):1507–1513.

2. Carr T.F.(2016). Complications of sinusitis. Am J Rhinol Allergy, Vol. 30 (4). – P. 241–245.

3. Dong Y,Zhou B, Niu YT, Wang ZC (2011). [CT evaluation of bone remodeling in rabbit models with rhinosinusitis]. [Article in Chinese]. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi., 46(10):848–53.

4. Freeman JL, Winston KR. (2015). Breach of Posterior Wall of Frontal Sinus: Management with Preservation of the Sinus. World Neurosurg,.83(6):1080-9. doi: 10.1016/j. Dec 18..12.023. wneu.2014.

5. Halawi AM, Smith SS, Chandra RK. (2013). Chronic rhinosinusitis: epidemiology and cost. Allergy Asthma Proc, 34(4):328–334

6. Hofer M. CT Teaching Manual - A Systematic Approach to CT Reading, 2nd Ed.P. 20.

7. Renteria AE, Mfuna Endam L, Desrosiers M.Do (2017). Aging Factors Influence the Clinical Presentation and Management of Chronic Rhinosinusitis? Otolaryngol Head Neck Surg., 156(4):598–605. doi: 10.1177/0194599817691258.

8. Schaafs LA, Pfeil J, K?hlitz T, Hamm B, Niehues SM. (2018). Low-dose computed tomography of the paranasal sinuses: performance of two different iterative reconstruction algorithms Radiat Prot Dosimetry., Aug 25. doi: 10.1093/rpd/ncy153].

9. Shumway CL., Wade M. (2018). Anatomy Head and Neck, Orbit Bones StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Sep 25.

10. Stanojcic M, Chen P, Xiu F, Jeschke MG. (2016). Impaired Immune Response in Elderly Burn Patients: New Insights Into the Immune-senescence Phenotype. Ann Surg., 264(1):195-202. doi: 10.1097/SLA.0000000000001408].

11. Torremade-Barreda J, Rodriguez-Tolra J, Roman-Romera I, Padro-Miquel A, Rius-Moreno J, Franco-Miranda E. (2013). [Testosterone-deficiency as a risk factor for hip fracture in eldery men]. [Article in Spanish] Actas Urol Esp., 37(3):142-6. doi: 10.1016/j.acuro.2012.06.009. Epub 2012 Dec 13.

12. Kucuksezer UC., Ozdemir C., Akdis M., Akdis CA. (2018). Chronic rhinosinusitis: pathogenesis, therapy options, and more. Expert Opinion on Pharmacotherapy. 2018 Nov;19(16):1805–1815. doi: 10.1080/14656566.2018.1527904. Epub 2018 Oct 20.

13. Volkov AG, Stagnieva IV. (2012). Ostryj i hronicheskij frontit: tekushhee sostojanie problemy [Acute and chronic frontitis: the current view of the problemi]. Vestn Otorinolaringol., (6):98–102.

Received: 23-Jan-2019
Accepted: 17-Mar-2019