THE ROLE OF HEMIC HYPOXIA IN THE DEVELOPMENT OF SENSORINEURAL HEARING LOSS IN CHILDREN ASSOCIATED WITH HEPATITIS B

Abstract

Background. There are not enough studies and evidenced researches conducted related to this topic. Therefore, we studied fetal hemoglobin in various somatic diseases in children with sensorineural hearing loss associated with hepatitis B.

Material and methods. 26 children with sensorineural hearing loss associated with hepatitis B, aged from 5 to 18 years, were examined. The comparison group consisted of 8 children with sensorineural hearing loss without concomitant somatic pathology. The control group consisted of 12 healthy children. The compulsory examination plan for patients included generally accepted laboratory and instrumental diagnostic methods: complete blood count, urine, feces, Wasserman reaction, ECG.

Results. Hb concentration in blood in patient children with sensorineural hearing loss of the associated CHB was reduced significantly by 58% compared with the healthy children. In children with CHT without CHB, the studied parameter decreased when compared with healthy children by 25%.

Key words: hypoxia; sensorineural hearing loss; hepatitis B; VEGF; PGDF; fetal hemoglobin

INTRODUCTION

Sensorineural hearing loss in children refers to diseases, the problem of diagnosis and treatment of which does not lose its relevance. The significant prevalence of sensorineural hearing loss (CHT) is due to the diversity of both endogenous and exogenous etiological factors that trigger the development of this disease [2, 4]. In the occurrence of CHT, numerous clinical observations and scientific studies have proved the role of perinatal pathology, the effects of toxic and allergic factors, and the role of viral and vascular pathology in the etiology of this disease [6, 9]. The social significance of the problem is due to the effect of hearing impairment in children on their speech development, the formation of the intellect and the personality of the child.

In modern scientific literature, it is considered established that there is hypoxia of varying severity in chronic hepatitis, which is characterized by persistent violations of the mechanisms of oxidation in the liver tissue with subsequent progression of dystrophic, fibrotic processes and the development of

decompensation of the functional state of the organ [1, 7] also with their high energy consumption.

Moreover, as has been shown in a number of studies, intralobular stellate cells of the liver are more sensitive to oxygen insufficiency compared to cells in the periportal zones and play a key role in angiogenesis with the involvement of vascular endothelial growth factor (VEGF) and platelet growth factor (PGDF) in the pathological process [12, 13, 18]. Under the influence of hypoxia, the release of HIF-1 from stellate cells is stimulated, which affects the progression of angiogenesis and fibrosis. Consequently, the delicate balance between the need of liver tissue for oxygen and its delivery can be disrupted by the pathology of this organ. Endothelial dysfunction resulting from chronic hepatitis B (CHB), causing vasodilation in the lungs, contributes to the development of hypoxemia [3]. According to the researchers, hypoxia of the hepatic parenchyma in CHB is a consequence of several mechanisms, including vascular resistance, intrahepatic shunts, intravascular thrombosis, and a venom of the venous process, a venom, and a subjugation of the venom of the procedure. and sinusoidal capillaries [14].

Due to the fact that the gas transport function of blood occupies a special place in providing adaptive and compensatory processes, in recent years, scientists have focused on studying the problem of heterogeneity of hemoglobin in various human pathological conditions [1].

Numerous studies have shown an increase in the concentration of fetal hemoglobin (HbF) in erythrocytes under various pathological conditions, which is a consequence of the adaptive reactions of the erythron to the hypoxia state [4]. It is known that HbF has an extremely high ability to bind oxygen and the increased affinity of HbF to oxygen helps the body to adapt conditions of relative hypoxia and provide the tissue with sufficient oxygen. It is believed that the increase in HbF level is a biochemical mechanism long-term adaptation to hypoxia, which is based on the phenomenon of “adaptive stabilization structures” is realized upon activation of the genetic apparatus of the cell in response to a change homeostasis [3]. Therefore, HbF is a marker of tissue hypoxia not only in newborns, but also in various adult pathologies.

Despite the considerable interest in the study of fetal hemoglobin in various somatic diseases, in the available modern literature we have not found data on its study in children with sensorineural hearing loss associated with hepatitis B.

MATERIAL AND METHODS

To solve the tasks for the period from 2016 to 2018. On the basis of the Republican Scientific and Practical Medical Center of Pediatrics, 26 children with sensorineural hearing loss associated with hepatitis B, aged from 5 to 18 years, were examined. The comparison group consisted of 8 children with sensorineural

hearing loss without concomitant somatic pathology. The control group consisted of 12 healthy children.

All patients were admitted to the hospital in the acute phase of sensorineural hearing loss associated with hepatitis. A detailed clinical diagnosis was made on the basis of the nature of complaints, anamnesis, clinical examination results, laboratory and instrumental methods of diagnosis, taking into account information from the patient's outpatient card (extracts of case histories of previous hospitalizations, data of dynamic observation of the patient in the clinic). In making the diagnosis, modern classifications of sensorineural hearing loss in children were used.

Criteria for the inclusion of patients in the study were proven viral etiology of sensorineural pathology; proven signs of HBV.

Exclusion criteria for the study were: primary pathology of the biliary system (primary sclerosing cholangitis, primary biliary cirrhosis), signs of secondary liver damage in patients with chronic diseases of the biliary tract and intestines (cholelithiasis, chronic cholecystitis, stenotic papillitis, Crohn's disease, ulcerative colitis); extrahepatic obstruction of the portal vein, associated with the consequences of surgical interventions, portal vein thrombosis, tum cholic pathology, congenital developmental abnormalities, injuries; Budd-Chiari syndrome; patients with fever associated with concomitant diseases (acute respiratory infections, pneumonia, acute intestinal infections, pyelonephritis, etc.); acute and chronic diseases of the broncho-pulmonary system;

All clinical, anamnestic and laboratory and instrumental data were entered into a detailed map developed by us. The map noted the patient's complaints, of which more often there was increased fatigue, weakness, memory and sleep disorders, dyspeptic disorders (nausea, belching, vomiting), pain and heaviness in the right hypochondrium, epigastric pain, nausea, loss of appetite. Complaints about shortness of breath and her temper, cough, pain in the heart area, the presence of heartbeat and rhythm disturbances, and changes in blood pressure were investigated in detail.

The presence of jaundice, pruritus, fever, manifestations of hemorrhagic syndrome (gingival, nasal, gastroesophageal, hemorrhoidal bleeding), arthralgia, stool disorders, flatulence, and dysphagia were taken into account. An objective examination focused on manifestations of portal hypertension and signs of disease activity for the presence of liver signs (spider veins, palmar erythema), xanthomas, Dupuytren’s contracture, lymph nodes, abdominal veins, ascites, peripheral edema, gynecomastia, and the size of the liver and spleen.

The compulsory examination plan for patients included generally accepted laboratory and instrumental diagnostic methods: complete blood count, urine,

feces, Wasserman reaction, ECG. A study was conducted in the blood of total protein and protein fractions, immunoglobulins, Circulating Immune Complexes (CIC), lipoproteins, cholesterol, bilirubin, urea, creatinine, amylase of blood and urine, determined the activity of Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST), GTP, alkaline phosphatase. The coagulogram was determined: fibrinogen content, XIII coagulation factor, fibrinolytic activity, fibrin monomers using ethanol test, fibrinogen-fibrin degradation products by the method.

For the isolation and purification of HbF, alkaline denaturation with 1.2 M NaOH, salting out with ammonium sulfate, gel filtration on a column with Sephadex G-25 (working buffer — 0.05 M phosphate buffer pH 7.4), and ion-exchange chromatography on DEAE Sephadex were used G-50 on 0.01 M Tris-chloride buffer pH 8.1. The quantitative determination of HbF was carried out by electrophoresis on an agar gel with sodium dodecyl sulfate. The HbF level in the control group was 2.26±0.02 g/l, which is Corresponds to literary data. Gender differences in the control group were absent.

Statistical analyses

Data analysis was performed using the STATISTICA v.6.0 Windows XP application package. Descriptive statistics of the trait included arithmetic average (M), minimum and maximum values, median (Me) and interquartile range [Q25-Q75]. When comparing the obtained results, the Mann-Whitney test was used due to the inconsistency of the analyzed data with the law of normal distribution. The relationship between signs was studied by the Spearman (R) correlation analysis method. Differences were considered statistically significant at $p<0.05$.

RESULTS AND DISCUSSION

As can be seen from the presented research results (table 1), the hemoglobin values of blood in the examined children with sensorineural hearing loss of the associated CHB was significantly reduced by 58% compared with the healthy children. In children with CHT without CHB, the studied parameter decreased when compared with healthy children by 25%.

Other dynamics was noted with respect to fetal hemoglobin in the blood of the examined children with combined pathology. Analysis of the results showed a significant increase in the level of fetal hemoglobin in the blood of children with CHT associated with hepatitis B on average by 1.5 times, indicating hypoxia.

Table 1.

Blood biochemical parameters in children with hepatitis B associated hearing loss

№	Indicators	Healthy children n = 12	Children sensory hearing loss combined CHB n = 26	Children sensory hearing loss without CHB n = 8
1	Hemoglobin content g/l	158,62±8,02	92,05±6,54*	119,32±8,13
2	Fetal hemoglobin (HbF) content (g/l)	2,26±0,12	3,41±0,18*	2,38±0,19
3	pO_2 of arterial blood (mm Hg)	76,05±6,11	64,82±5,43	72,43±6,32
4	pO2 arterio-venous blood difference (mm Hg)	42,35±3,12	24,89±1,57*	38,75±2,87
5	The content of desquamated endothelial blood cells (x104/l)	2,34±0,22	4,78±0,34*	3,01±0,26*
6	Endothelin 1-retention (fmol/l)	0,93±0,12	1,740±,13*	0,96±0,12
7	Von Willebrand factor (%)	76,51± 4,27	112,36± 7,11*	91,76± 6,34*
8	Activity lactate dehydrogenase (U/l)	576,12 ±11,3	1028,74± 13,85*	788,63 ±12,34
9	Aspartate aminotransferase activity (U/l)	20,61 ±1,44	69,71 ± 5.32*	32,28 ±2,52*

Note: * - significance of differences P <0.05

Hypoxia in chronic liver disease can be both local and systemic. Deficiency of oxygen entering the liver parenchyma occurs during chronic hepatitis as a result of several mechanisms that include vascular resistance, intrahepatic shunts, intravascular thrombus formation, reduction in the area of sinusoids and sinusoidal capillaries. Endothelial dysfunction (ED) plays a significant role in the development of these processes. ED is involved in the formation of portal hypertension that develops in chronic hepatitis, which leads to the formation of an extensive network of portal anastomoses, including and in the lung tissue with increased hypoxia and hypoxemia.

One of the objectives of this study was to establish the association of HbF changes with the concentration of such important markers of endothelial dysfunction as the vasoconstrictor ET-1 and the adhesive protein von Willebrand factor. As can be seen from the data of table 1, the studied markers of endothelial dysfunction were significantly increased when comparing the obtained results with the values of healthy children. Consequently, a comprehensive assessment of HbF levels, markers of endothelial dysfunction, in combination with clinical data, provides much more information about the development of tissue hypoxia and hypoxemia in sick children with combined pathology, and also allows an additional assessment of the severity of the pathological process in the liver.

It was found that in children with sensorineural hearing loss associated with hepatitis B, in 30.8% of cases there was a simultaneous increase in the concentration of HbF and a decrease in blood oxygen saturation of 64.82 ± 5.43 mm Hg. against 76.05±6.11 mm Hg, indicating moderate hypoxemia. The increase in tissue hypoxia was also indicated by the results of arterial-venous blood difference in the examined children. For a more reliable confirmation of this version, we studied the activity of lactate dehydrogenase and aspartate aminotransferase in the blood of the examined children. As can be seen from the obtained results of the research, the activity of the studied enzymes exceeded the initial indicators, respectively, by 59% and 3.3 times.

An indicator of the functional state of endotheliocytes is von Willebrand factor and endothelin-1. As can be seen from the presented research results, the level of endothelin-1 in children with the combined form of the disease was significantly higher in comparison with healthy children. The level of activity of von Willebrand factor in the blood plasma was also significantly higher than in healthy children.

Under physiological conditions, the endothelium produces a number of vasodilating and vasoconstrictive substances that support the necessary level of vascular tone. Numerous studies have shown that endothelin-1 is the most potent vasoconstrictor factor currently known. Proved that vascular endothelial is the main source of endothelin-1 in vivo.

The von Willebrand factor is a complex multidimensional adhesive glycoprotein synthesized by endothelial cells. Functionally, it is a carrier-stabilizer for procoagulant protein that circulates in the blood serum as a non-covalently bound complex and is an adhesion protein in hemostasis processes. The von Willebrand factor can bind collagen and possibly other endothelial structures and mediate platelet adhesion to the subendothelium through the binding of the glycoprotein Ib surface platelet receptor. Therefore, an increase in the level of von Willebrand factor activity is an indicator of endothelial damage.

In this study, in children with sensorineural hearing loss associated with hepatitis B, the reaction of endothelial dysfunction indicators was detected - a significant increase in endothelin-1 level and von Willebrand factor activity in the blood plasma and their interrelation with the level of oxygen partial pressure in the blood, which indicates a violation of vasoconstrictor therapy and adhesive endothelial function in this pathology. This fact is explained by the fact that with this pathology in children there are favorable conditions for the development of endothelial dysfunction, on the background of hypoxia, as well as disruption of the metabolic function of the endothelium, which can lead to an increase in the content of various biologically active substances.

In addition, an important sign of endothelial dysfunction is a change in the phenotypic activity of endotheliocytes, which results in the cells losing anticoagulant properties and enhancing the production of coagulation factors. When exposed to a damaging factor (hypoxia), leukocytes, monocytes, mononuclear phagocytes are activated, and damage and proliferation factors are produced: free radicals, interleukin-1, tumor necrosis factor a, tissue factor, trombocyte growth factor, and other biologists. active substances acting on endotheliocytes. In this situation, endotheliocytes begin to intensively secrete vasoactive and prosclerogenic substances (endothelin, etc.), the accumulation of which stimulates fibrotic changes and vascular remodeling.

Thus, an important pathogenetic role of endothelial dysfunction in children with sensorineural hearing loss associated with hepatitis B has been shown.

CONCLUSION

Firstly, dependence of the indices of partial oxygen in the blood and, to a greater extent, HbF, on the blood content of the vasoconstrictor endothelin-1, von Willebrand factor, indicates the pathogenetic significance of the leading markers of endothelial dysfunction in the development of tissue hypoxia in children with sensorineural hearing loss combined liver disease.

Secondly, combination of sensorineural hearing loss with hepatitis B in children. Pulmonary hypertension is associated with endothelial dysfunction (increased endothelin-1 concentration and von Willebrand factor activity).

Thirdly, determining level of HbF in children with CHT of combined HBV can be used to diagnose chronic tissue hypoxia and helps to clarify the severity of the pathological process, which allows to predict the progression of the disease and their complications.

References

1. Antonenko V.T., Korolev Y.N. Features of the oxygen-binding function of fetal hemoglobin: Overview // Hematology and Transfusiology. 2006:28(5): 61
2. Gappoeva E. T. Pathogenetic differences in the recovery of auditory function in the acute period of sensorineural hearing loss. Mat. VII Congress of otorhinolaryngologists of Russia. SPb.: RIA-AMI, 2006:12(4):11-12
3. Kasyanova, T.R., Levitan, B.N., Titarenko, Yu.B. Markers of endothelial dysfunction in chronic liver diseases // Kuban Scientific Medical Journal. – 2012:3(132):70–74
4. Kasyanova, T.R. The content of fetal hemoglobin in patients with viral and alcoholic cirrhosis of the liver / T.R. Kasyanova, Yu.B. Titarenko, Yu.A.Kriventsev, B.N. Levitan // Proceedings VII Nat. congress therapists. - M., 2012:6:93-94.
5. Kotova N.V. The role of non-cytokine mediators in the regulation of IgE synthesis in the norm and in atopy: abstract of dissertation // Thesis of PhD degree, Rostov-on-Don, 2001. 16p.
6. Levina Y.V., Krasyuk A.A. Transcranial electrostimulation in the treatment of neurosensory hearing loss // Proceedings of the Russian Scientific-Practical Conference "Modern Problems of Otorhinolaryngology" Moscow. – 2002: 43-44.
7. Lesik D.V., Khanferyan R.A., Andreyanova A.N. The role of histamine and histamine H3 / 4-type receptors in regulating the synthesis of IgE in atopic diseases // Kuban Scientific Medical Journal. – 2006: 3-4(84-85): 77-80.
8. Mitin, Y.V., Deeva, Y.V. Experience of Using the Betaserk Drug in Acute Neurosensory Hearing Loss // Jour otorhinolaryngology diseases. Moscow 2002:3:3-5.
9. Morozova S. V. Zaitseva, O. V. Comprehensive approach to the treatment of patients with acute sensorineural hearing loss of vascular origin // South-Russian Medical Journal. 2001:1:2.
10. Rieger N. A., Kotova N. V., Khanferyan R. A. Participation of histamine receptors in the mechanism of hyperproduction of IgE // Advances in modern natural science. Moscow. 2003:Appendix 2:64.
11. Atmaca S., Saatci M. The role of immunologic and viral factors in etiology of idiopathic sudden deafness //Mediterr J Otol - 2005 - №1 (1) - p. 31-35.
12. Autoantibodies to inner ear and endothelial antigens in Cogan. s syndrome / C. Lunardi [et al.] //Lancet - 2002 - №360 - p. 915-921.
13. Inner ear autoantibodies and their targets in patients with autoimmune inner ear diseases / M. R. Boulassel [et al.] //Arch Otolaryngol - 2001 - №121 - p. 28-34.
14. Feldmann, M., L. Steinman. Design of effective immunotherapy for human autoimmunity // Nature - 2005. - Vol. 435. - P612-619.

15. Harris JP, Sharp PA. Inner ear autoantibodies in patients with rapidly progressive sensorineural hearing loss // Laryngoscope - 1990 - №100 - p. 516-524.
16. Holstad D. L., Schachem P A., Pararella M. M. Autoimmune sensorineuralheariring loss: a human temporal bone study, Am. J. otolaryngology - 1998 - №19 - p. 33-39.
17. Garcia Berrocal J. R., Ramirez-Camacho R. Sudden sensorineural hearing loss //Ann OtolRhinolLaryngol – 2002-№111 - p. 989-997.
18. Role of viral and Mycoplasma pneumoniae infection in idiopathic sudden sensorineural hearing loss / J. R. Garcia Berrocal [et al.] //ActaOtolaryngol (Stockh) - 2000 - №120 - p. 835-839.
19. Schuknecht H. Ear pathology in autoimmune disease //AdvOtoRhinolaryngol - 1991 - №45 - p. 50-70.
20. Sensorineural hearing loss and ulcerative colitis / B. N. Kumar [et al.] // Laringology Otol. - 1997 - №111 - p277-278.
21. Sudden sensorineural hearing loss / A. L. S. Werneckl [et al.] //ArqNeuropsiquiatr - 2003 - №61(4) - p. 1018-1022.
22. Tuohy Increased Frequencies of Cochlin-Specific T Cells in Patients with Autoimmune Sensorineural Hearing Loss /Baek Moo-Jin [at al.]//The Journal of Immunology - 2006 - Vol. 177. - P4203-4210.