

Features of the immune status and immunometabolism in pediatric patients with type 3 Gaucher disease

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Особенности иммунного статуса и иммунометаболизма у педиатрических пациентов с 3-м типом болезни Гоше

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INTRODUCTION

Gaucher disease (GD) is an autosomal recessive metabolic disorder (OMIM #230800, ORPHA355) characterized by a defect in β -glucocerebrosidase (GCD), a lysosomal enzyme involved in lipid breakdown. To date, more than 700 mutations are known to cause a defect in this enzyme [1]. The incidence of GD in all ethnic group ranges from 1 in 40,000 to 1 in 60,000 [2].

Gaucher disease (GD) is classified into three types depending on the presence or absence of neurological symptoms. Type 1 (non-neuropathic) is characterized by the absence of neurological symptoms, type 2 (acute neuropathic) is characterized by severe CNS involvement from the onset of the disease, and type 3 (chronic neuropathic) is characterized by progressive CNS involvement [3].

Hematological manifestations are common features of all types of GD. Neurological symptoms in GD, including seizures, muscle weakness, ataxia, eye movement disorders, myoclonic epilepsy, and cognitive impairment, are progressive and disabling in nature [4].

As a result of insufficient catalytic activity of the enzyme, its substrate glucosylceramide (GC) and its deacylation product glucosylsphingosine accumulate. The accumulation of sphingolipids occurs mainly in cells of the reticuloendothelial system, such as splenic histiocytes, Kupffer cells in the liver, osteoclasts in bone, microglia cells in the central nervous system, and alveolar macrophages in the lungs [4].

The accumulation of substrate in macrophages causes the formation of Gaucher cells, which are characteristic of this disease. Gaucher cells are large macrophages

with a small eccentric nucleus and abundant weakly basophilic cytoplasm, which produce pro-inflammatory cytokines due to accumulated GC [2], causing the development of chronic inflammation in the visceral organs [2, 5]. GD is also characterized by excessive production of chemokines, growth factors, and complement cascade proteins (C3, C3a, C5, and C5a), which contributes to the multi-organ nature of the disease and affects the state of the immune system [6, 7].

Studies show that GCD interacts with many mitochondrial proteins: with cytosolic chaperones involved in protein folding before import into mitochondria (HSP70), with proteins of the outer mitochondrial membrane (TOM70), inner membrane (TIM23 and ATP5B), and mitochondrial matrix (HSP60 and LONP1) [8, 9]. Reduced GCD activity, which affects lysosomal function, leads to intracellular accumulation of glycolipids, disrupting normal lysosomal function and autophagy, which leads to the accumulation of alpha-synuclein. In addition, the accumulation of alpha-synuclein disrupts GTD activity, creating a self-sustaining cycle of lysosomal dysfunction, exacerbating both mitochondrial and lysosomal dysfunction [8]. Mitochondrial dysfunction manifests as a decrease in succinate dehydrogenase (SDH) activity, a key enzyme in the tricarboxylic acid cycle, which is crucial for T-cell proliferation during inflammatory responses [10]. In particular, recent studies have established the critical role of metabolism in the regulation of T regulatory cells (Tregs) through interaction with the mechanisms of transcriptional, epigenetic, and post-translational control of FOXP3 expression [11].

The main principle of GD treatment is pathogenetic, using a recombinant enzyme. Enzyme replacement therapy (ERT) is administered regularly every two weeks by intravenous drip and can significantly improve the patient's clinical and hematological parameters [12, 13]. However, in patients with type 3 GD, ERT is not effective and has no significant effect on the neurological manifestations of the disease [14].

WORK OBJECTIVE

To investigate the characteristics of immune status and CDH activity in major and minor populations of peripheral blood lymphocytes in children with type 3 Gaucher disease.

STUDY MATERIALS AND METHODS

All patients diagnosed with GD were treated at the Federal State Budgetary Institution "National

Medical Research Center for Children's Health" of the Ministry of Health of Russia between 2009 and 2024. The diagnosis of GD was made based on anamnestic and clinical laboratory data and confirmed by molecular genetic studies. To study the characteristics of immune status and SDH activity in lymphocyte populations, 22 children (13 girls and 9 boys) aged 2 to 18 years (median 8.4 years, quartiles 5.3; 11.6) with type 3 GD were examined. At the time of the examination, all patients were undergoing ERT therapy at doses ranging from 22 to 95 IU/kg: 15 patients were receiving imiglucerase, 3 patients were receiving velaglucerase alfa, 2 patients were receiving glurazym, and 2 patients were receiving taliglucerase alfa. Immune status was assessed according to the protocol described earlier [15]. The following populations were evaluated in the CD45⁺ lymphoid region: T lymphocytes (CD3⁺CD19⁻), B lymphocytes (CD3⁻CD19⁺), NK-cells (CD3⁻CD16⁺CD56⁺), NKT-cells (CD3⁺CD16⁺CD56⁺), T-helpers (CD3⁺CD4⁺), cytotoxic T lymphocytes (CD3⁺CD8⁺), Th17-lymphocytes (CD3⁺CD4⁺CD161⁺), Treg (CD4⁺CD25⁺CD127^{low}) and activated T helper cells (CD4⁺CD25⁺CD127^{high}). To identify the characteristics of immune status, the absolute and relative results of patients were analyzed as a percentage deviation from the age norm:

$$Xn = \frac{(X_{min} - X)}{0,0,1(X_{max} - X_{min})},$$

where Xn is the value of the individual indicator normalized to the age norm; X is the value of the indicator under study; X_{max} is the upper limit of the age norm; X_{min} is the lower limit of the age norm. The age norm range was taken as 100%.

An immunocytochemical method was used to detect SDH activity in major and minor lymphocyte populations [16]. The study integrates the diagnostic capabilities of lymphocyte immunophenotyping in major and minor lymphocyte populations with the capabilities of quantitative cytochemical analysis, which allows the enzyme activity to be determined in various lymphocyte populations [16]. SDH activity is assessed in conventional units. The study was conducted using CYTOMICS FC500 (Beckman Coulter, USA) and Novocyte (ACEA Biosciences, USA) flow cytometers. The comparison group consisted of 149 healthy children of comparable age.

Statistical analysis was performed using Statistica 10.0 software (StatSoft, USA). Descriptive statistics

are presented as Me ($Q_{0,25}$; $Q_{0,75}$). The Mann–Whitney nonparametric test was used to assess statistical significance, with differences considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

Sixteen patients were found to have the *L444P* mutation in a homozygous state, three patients had *L444P* in a heterozygous state, two patients had *D448H/L483P*, and one patient had *370S/D403H*.

An examination of immune status revealed that in most patients (81%), the relative and absolute number of T lymphocytes was within the age-related reference range. The populations of T-helper and cytotoxic T-cells in most patients were also within the reference values (relative counts in 40.9% and 36.4%, absolute counts in 54.5% and 54.5% of patients, respectively). The relative and absolute numbers of B lymphocytes and NK cells in most children (relative numbers in 54.5% and 54.5%, absolute numbers in 50% and 59.1%, respectively) corresponded to age-related reference ranges. The data obtained on the percentage deviation from the age norm for T-lymphocyte, T-helper, cytotoxic T-cell, and B-lymphocyte populations coincided with the results previously obtained for children with type 1 GD [15]. At the same time, in patients with type 3 GD, the NK cell content was within the age reference range, unlike patients with type 1 GD [15].

The relative and absolute Th17 content was elevated (60% and 66.7%). The relative number of Tregs was reduced in 72.7% of patients. These changes caused an increase in the Th17/Treg index, which may indicate the presence of an autoimmune component. This index has previously been shown to be informative for predicting treatment outcomes in children with autoimmune diseases [17, 18].

Using immunocytochemical analysis, a decrease in SDH activity was detected in cell populations

in children with type 3 GD compared to the comparison group. Activity indicators in patients with GD and the comparison group in the populations: T-cells (171,2 [160,7; 182,2] и 193,2 [183,6; 200,1], $p < 0,001$), T-helpers (172,4 [154,1; 199,6] and 191 [181,9; 201,3], $p = 0,007$), cytotoxic T lymphocytes (175 [158,8; 202,4] and 195,5 [184,5; 204,1], $p = 0,004$), B-cells (126,5 [119,6; 155,8] and 145,6 [136,7; 154,9], $p = 0,013$), Treg (166,8 [155,8; 199,6] and 196,3 [187; 210,7], $p = 0,0016$), Th17 (162,4 [151,6; 172,8] and 189,5 [178,4; 200,6], $p < 0,001$), activated T-helpers (178,8 [170,5; 203,4] и 197,7 [186,4; 207,6]), $p = 0,016$).

The greatest decrease in SDH activity was detected in B cells, Th17 and Tregs and amounted to 14% of the comparison group values. The obtained results of the decrease in SDH activity may indicate the need for metabolic therapy to restore Tregs anti-inflammatory function. The study has shown the effect of vitamins A, C and D₃ on the expression of the transcription factor in Tregs. In particular, vitamin A, produced by certain subsets of dendritic cells, directly and indirectly modulates the expression of FOXP3 by activating ERK and increasing methylation and acetylation of promoters in the FOXP3 locus [19]. Vitamin C can stabilize the expression of FOXP3 by demethylating the CNS2 region in Tregs [19]. Metabolites of vitamin D₃ can promote the expression of FOXP3 in T cells [19].

CONCLUSION

Children with type 3 BD are characterized by a decrease in the relative and absolute number of Tregs, and an increase in Th17 and activated T-helper cells.

SDH activity is reduced in most lymphocyte populations, with the greatest decrease observed in B cells, Tregs, and Th17.

These results support the use of metabolic therapy to correct the identified disorders.

REFERENCES

1. Feng S. et al. A review on Gaucher disease: therapeutic potential of β -glucocerebrosidase-targeted mRNA/sRNA approach. International Journal of Biological Sciences. 2024; 20 (6): 2111. <https://doi.org/10.7150/ijbs.87741>.
2. Stirnemann J.Ô., Belmatoug N., Camou F., Serratrice C., Froissart R., Caillaud C., Levade T., Astudillo L., Serratrice J., Brassier A., Rose C., Villemeur T.B.D., Berger M.G. A Review of Gaucher Disease Pathophysiology, Clinical Presentation and Treatments. International Journal of Molecular Sciences. 2017; 18 (2): 1–30. <https://doi.org/10.3390/ijms18020441>.
3. den Hollander B. et al. Clinical and preclinical insights into high-dose ambroxol therapy for Gaucher disease type 2 and 3: A comprehensive systematic review. Molecular Genetics and Metabolism. 2024: 108556. <https://doi.org/10.1016/j.ymgme.2024.108556>.

4. Chen M., Wang J. Gaucher disease: review of the literature. *Archives of pathology & laboratory medicine*. 2008; 132 (5): 851–853. <https://doi.org/10.5858/2008-132-851-GDROTL>.
5. Basistova A.A., Baranov A.A., Kaganov B.S., Bukanovich O.V. Gaucher disease in children. *Issues of modern pediatrics*. 2004; 3 (5): 47–52. (In Russ.) <https://www.elibrary.ru/item.asp?id=17802975>.
6. Szymańska K., Krasnoborska J., Samojedny S., Superson M., Szymt K., Walczak K., Wilk-Trytko K., Zarębski Ł. Gaucher's Disease — current state of knowledge and future perspectives? *Journal of Education, Health and Sport*. 2024; 64 (1): 131–148. <https://doi.org/10.12775/JEHS.2024.64.009>.
7. Pandey M.K., Grabowski G.A. Immunological cells and functions in Gaucher disease. *Critical Reviews in Oncogenesis*. 2013; 18 (3): 197–220. <https://doi.org/10.1615/CritRevOncog.2013004503>.
8. Klein A.D., Outeiro T.F. Glucocerebrosidase mutations disrupt the lysosome and now the mitochondria. *Nature Communications*. 2023; 14 (1): 13. <https://doi.org/10.1038/s41467-023-42107-7>.
9. Baden P., Perez M. J., Raji H., Bertoli F., Kalb S., Illescas M., Spanos F., Giuliano C., Calogero A. M., Oldrati M., Hebestreit H., Cappelletti G., Brockmann K., Gasser T., Schapira A.H.V., Ugalde C., Deleidi M. Glucocerebrosidase is imported into mitochondria and preserves complex I integrity and energy metabolism. *Nature Communications*. 2023; 14 (1): 1–21 <https://doi.org/10.1038/s41467-023-37454-4>.
10. Chen X., Sunkel B., Wang M., Kang S., Wang T., Gnanaprakasam J.R., Wang R. Succinate dehydrogenase/complex II is critical for metabolic and epigenetic regulation of T cell proliferation and inflammation. *Science immunology*. 2022; 7 (70): eabm8161. <https://doi.org/10.1126/sciimmunol.abm8161>.
11. Shi H., Chi H. Metabolic control of Treg cell stability, plasticity, and tissue-specific heterogeneity. *Frontiers in immunology*. 2019; 10: 2716. <https://doi.org/10.3389/fimmu.2019.02716>.
12. Shemesh E., Deroma L., Bembi B., Deegan P., Hollak C., Weinreb N.J., Cox T.M. Enzyme replacement and substrate reduction therapy for Gaucher disease. *Cochrane Database of Systematic Reviews*. 2015; 27 (3): 3–24 <https://doi.org/10.1126/sciimmunol.abm8161>.
13. Nalysnyk L., Rotella P., Simeone J.C., Hamed A., Weinreb N. Gaucher disease epidemiology and natural history: a comprehensive review of the literature. *Hematology*. 2017; 22 (2): 65–73. <https://doi.org/10.1080/10245332.2016.1240391>.
14. Zimran A., Elstein D. No justification for very high-dose enzyme therapy for patients with type III Gaucher disease. *Journal of Inherited Metabolic Disease*. 2007; 30 (6): 843–844. <https://doi.org/10.1007/S10545-007-0783-8>.
15. Kurbatova O.V., Movsisyan G.B., Konyashin M.V., Petrichuk S.V., Kuptsova D.G., Radygina T.V., Semikina E.L., Potapov A.S., Fisenko A.P. Age-related changes in the parameters of cellular immunity, the activity of intracellular lymphocyte dehydrogenases and functional activity of neutrophils in children with Gaucher disease. *Pediatric Hematology/Oncology and Immunopathology*. 2024; 23 (1): 128–138. (In Russ.) doi: 10.24287/1726-1708-2024-23-1-128-138.
16. Petrichuk S.V., Izmailova T.D., Radygina T.V. Method for measuring mitochondrial activity of lymphocytes. Patent for invention RUS 2302635 12/28/2005. (In Russ.) <https://elibrary.ru/item.asp?id=37583426>.
17. Radygina T.V., Kuptsova D.G., Kurbatova O.V., Petrichuk S.V., Semikina E.L., Fisenko A.P., Abdullaeva L.M., Bursagova B.I. Features of parameters of cellular immune depending on the activity of foci of demyelination in children with multiple sclerosis. *Medical Immunology (Russia)*. 2023; 25 (5): 1019–1026. <https://doi.org/10.15789/1563-0625-FOP-2777>. (In Russ.)
18. Kuptsova D.G., Radigina T.V., Kurbatova O.V., Materikin A.I., Epishev R.V., Opryatin L.A., Khotko A.A., Murashkin N.N., Petrichuk S.V. Content of CD4⁺T cell subpopulations in predicting the efficacy of biological therapy for psoriasis in children. *Medical Immunology (Russia)*. 2023; 25 (5): 1071–1078. <https://doi.org/10.15789/1563-0625-COC-2704>. (In Russ.)
19. Shi H., Chi H. Metabolic control of Treg cell stability, plasticity, and tissue-specific heterogeneity. *Frontiers in immunology*. 2019; 10: 2716. <https://doi.org/10.3389/fimmu.2019.02716>.

ЛИТЕРАТУРА

20. Feng S. et al. A review on Gaucher disease: therapeutic potential of β -glucocerebrosidase-targeted mRNA/saRNA approach. *International Journal of Biological Sciences*. 2024; 20 (6): 2111. <https://doi.org/10.7150/ijbs.87741>.
21. Stirnemann J.-O., Belmatoug N., Camou F., Serratrice C., Froissart R., Caillaud C., Levade T., Astudillo L., Serratrice J., Brassier A., Rose C., Villemeur T.B.D., Berger M.G. A Review of Gaucher Disease Pathophysiology, Clinical Presentation and Treatments. *International Journal of Molecular Sciences*. 2017; 18 (2): 1–30. <https://doi.org/10.3390/ijms18020441>.
22. den Hollander B., Le H.L., Swart E.L., Bikker H., Hollak C.E.M., Brands M.M. Clinical and preclinical insights into high-dose ambroxol therapy for Gaucher disease type 2 and 3: A comprehensive systematic review. *Molecular Genetics and Metabolism*. 2024; 108556. <https://doi.org/10.1016/j.ymgme.2024.108556>

23. Chen M., Wang J. Gaucher disease: review of the literature //Archives of pathology & laboratory medicine. 2008; 132 (5): 851–853. <https://doi.org/10.5858/2008-132-851-GDROTL>.
24. Басистова А.А., Баранов А.А., Каганов Б.С., Буканович О.В. Болезнь Гоше у детей. Вопросы современной педиатрии. 2004; 3 (5): 47–52. <https://www.elibrary.ru/item.asp?id=17802975>.
25. Szymańska K., Krasnoborska J., Samojedny S., Superson M., Szmyt K., Walczak K., Wilk-Trytko K., Zarębski Ł. Gaucher's Disease — current state of knowledge and future perspectives? Journal of Education, Health and Sport. 2024; 64 (1): 131–148. <https://doi.org/10.12775/JEHS.2024.64.009>.
26. Pandey M.K., Grabowski G.A. Immunological cells and functions in Gaucher disease. Critical Reviews in Oncogenesis. 2013; 18 (3): 197–220. <https://doi.org/10.1615/CritRevOncog.2013004503>.
27. Klein A.D., Outeiro T.F. Glucocerebrosidase mutations disrupt the lysosome and now the mitochondria. Nature Communications. 2023; 14 (1): 13. <https://doi.org/10.1038/s41467-023-42107-7>.
28. Baden P., Perez M.J., Raji H., Bertoli F., Kalb S., Illescas M., Spanos F., Giuliano C., Calogero A.M., Oldrati M., Hebestreit H., Cappelletti G., Brockmann K., Gasser T., Schapira A.H.V., Ugalde C., Deleidi M. Glucocerebrosidase is imported into mitochondria and preserves complex I integrity and energy metabolism. Nature Communications. 2023; 14 (1): 1–21 <https://doi.org/10.1038/s41467-023-37454-4>.
29. Succinate dehydrogenase/complex II is critical for metabolic and epigenetic regulation of T cell proliferation and inflammation. Science immunology. 2022; 7 (70). <https://doi.org/10.1126/sciimmunol.abm8161>.
30. Shi H., Chi H. Metabolic control of Treg cell stability, plasticity, and tissue-specific heterogeneity. Frontiers in immunology. 2019; 10: 2716. <https://doi.org/10.3389/fimmu.2019.02716>.
31. Shemesh E., Deroma L., Bembi B., Deegan P., Hollak C., Weinreb N.J., Cox T.M. Enzyme replacement and substrate reduction therapy for Gaucher disease. Cochrane Database of Systematic Reviews. 2015; 27 (3): 3–24 <https://doi.org/10.1126/sciimmunol.abm8161>.
32. Nalysnyk L., Rotella P., Simeone J.C., Hamed A., Weinreb N. Gaucher disease epidemiology and natural history: a comprehensive review of the literature. Hematology. 2017; 22 (2): 65–73. <https://doi.org/10.1080/10245332.2016.1240391>.
33. Zimran A., Elstein D. No justification for very high-dose enzyme therapy for patients with type III Gaucher disease. Journal of Inherited Metabolic Disease. 2007; 30 (6): 843–844. <https://doi.org/10.1007/S10545-007-0783-8>.
34. Курбатова О.В., Мовсесян Г.Б., Коняшин М.В., Петричук С.В., Купцова Д.Г., Радыгина Т.В., Семикина Е.Л., Потапов А.С., Фисенко А.П. Возрастная динамика показателей клеточного иммунитета, активность внутриклеточных дегидрогеназ лимфоцитов и функциональная активность нейтрофилов у детей с болезнью Гоше. Вопросы гематологии/онкологии и иммунопатологии в педиатрии. 2024; 23 (1): 128–138. <https://doi.org/10.24287/1726-1708-2024-23-1-128-138>.
35. Петричук С.В., Измайлова Т.Д., Радыгина Т.В. Способ измерения митохондриальной активности лимфоцитов. 2007. <https://elibrary.ru/item.asp?id=37583426>.
36. Радыгина Т.В., Купцова Д.Г., Курбатова О.В., Петричук С.В., Семикина Е.Л., Фисенко А.П., Абдуллаева Л.М., Бурсагова Б.И. Особенности показателей клеточного иммунитета в зависимости от активности очагов демиелинизации у детей с рассеянным склерозом. Медицинская иммунология. 2023; 25 (5): 1019–1026. <https://doi.org/10.15789/1563-0625-FOR-2777>.
37. Купцова Д.Г., Радыгина Т.В., Курбатова О.В., Материкин А.И., Епишев Р.В., Опрятин Л.А., Хотко А.А., Мурашкин Н.Н., Петричук С.В. Содержание субпопуляций CD4⁺Т-клеток в прогнозе эффективности биологической терапии псориаза у детей. Медицинская иммунология. 2023;25(5):1071-1078. <https://doi.org/10.15789/1563-0625-COC-2704>.
38. Shi H., Chi H. Metabolic control of Treg cell stability, plasticity, and tissue-specific heterogeneity. Frontiers in immunology. 2019; 10: 2716. <https://doi.org/10.3389/fimmu.2019.02716>.