THIAMINE RESPONSIVE MEGALOBLASTIC ANEMIA (ROGERS SYNDROME) IN A THREE-YEAR-OLD CHILD

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Thiamine responsive megaloblastic anemia (TRMA), or Rogers syndrome, is a rare autosomal recessive disease characterized by the development of megaloblastic anemia, diabetes mellitus, and progressive sensorineural hearing loss. In some cases, the syndrome causes ophthalmological disorders (retinitis pigmentosa, optic nerve atrophy, maculopathy, nystagmus), heart diseases (paroxysmal atrial fibrillation, supraventricular tachycardia, congenital heart defects, intracardiac conduction disorders) and neurological disorders (epilepsy, cerebrovascular accidents). TRMA develops due to a mutation in the *SLC19A2* gene, which encodes ThTr-1 (thiamine transporter protein) expressed in hematopoietic stem cells, pancreatic beta cells, and inner ear cells. The article presents a clinical case of TRMA in a three-year-old child, with the onset in the first year of life, manifesting as anemia and diabetes mellitus. Thiamine therapy ensured a pronounced positive dynamics: the patient's peripheral blood parameters normalized. The clinical description and the literature review herein aim to raise awareness of doctors of all specialties about this syndrome. An atypical clinical picture and lack of knowledge about TRMA often delay the diagnosis and start of therapy.

Keywords: thiamine-responsive megaloblastic anemia, Rogers syndrome, bone marrow, ring sideroblasts, diabetes, sensorineural deafness, gene *SLC19A2*

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ТИАМИН-ЗАВИСИМАЯ МЕГАЛОБЛАСТНАЯ АНЕМИЯ (СИНДРОМ РОДЖЕРСА) У РЕБЕНКА ТРЕХ ЛЕТ

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Тиамин-зависимая мегалобластная анемия (ТЗМА), или синдром Роджерса, — редкое аутосомно-рецессивное заболевание, характеризующееся развитием мегалобластной анемии, сахарным диабетом и прогрессирующей нейросенсорной тугоухостью. У части пациентов выявляют офтальмологические нарушения (пигментную ретинопатию, атрофию зрительного нерва, макулопатию, нистагм), поражение сердца (пароксизмальную мерцательную аритмию, наджелудочковую тахикардию, врожденные пороки сердца, нарушения внутрисердечной проводимости) и неврологические нарушения (эпилепсию, нарушение мозгового кровообращения). ТЗМА развивается вследствие мутации в гене *SLC19A2*, кодирующем белок-переносчик тиамина ThTr-1, который экспрессируется в гемопоэтических стволовых клетках, бета-клетках поджелудочной железы и клетках внутреннего уха. В статье представлен клинический случай ТЗМА у ребенка трех лет, с дебютом заболевания на первом году жизни в виде анемии и сахарного диабета. На фоне проводимой терапии тиамином у пациента достигнута выраженная положительная динамика в виде нормализации показателей периферического анализа крови. Описание собственного клинического наблюдения, а также представление обзора литературы направлено на повышение осведомленности врачей всех специальностей о данном синдроме. Атипичная клиническая картина и отсутствие знаний о ТЗМА часто являются причиной задержки постановки диагноза и начала терапии.

Ключевые слова: тиамин-зависимая мегалобластная анемия, синдром Роджерса, костный мозг, кольцевые сидеробласты, сахарный диабет, нейросенсорная глухота, ген *SLC19A2*

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Thiamine responsive megaloblastic anemia (TRMA, OMIM 249270), or Rogers syndrome, is an extremely rare autosomal recessive disease with a characteristic medical triad: megaloblastic anemia, progressive sensorineural hearing loss, and diabetes mellitus. Some patients are diagnosed with congenital heart defects, optic atrophy, and cerebrovascular disorders [1–3]. Hematological manifestations include ring sideroblasts in bone marrow; leukopenia and thrombocytopenia may be moderately pronounced or lacking, and pancytopenia is rarely detected [4, 5]. TRMA develops as a result of changes in the *SLC19A2* gene that encodes thiamine transporter 1 (ThTr-1). The *SLC19A2* gene is expressed mainly in hematopoietic stem cells, pancreatic beta cells, and inner ear cells [6]. In other organs, thiamine is brought to cells by ThTr-2 transporter protein, which remains functionally active [7].

There is no reliable information about prevalence of TRMA. There have been described 183 patients from 138 families. The majority of cases (62%) were registered in the families where spouses are closely related to each other (37.7% in the Middle East, 21.9% in South Asia, and 17% in the Mediterranean countries), with the debut during infancy and adolescence [8]. The disease was first described by L.E. Rogers et al in 1969; the patient was an 11-year-old girl with bilateral sensorineural hearing loss, diabetes mellitus, and recurrent megaloblastic

Table 1. Interpretation of the patient's hemogram

Indicators	08.02.2024	Unit of measurement	Normal value
Leukocytes	9.12	10^9/l	6.05–9.85
Erythrocytes	2.55	10^{12}/l	4.2–4.6
Hemoglobin	74	g/l	115–138
Hematocrit	20.8	%	31–40
Average erythrocyte volume	81.6	fL	75–100
Average hemoglobin content in an erythrocyte	29	Pg	25–33
Average hemoglobin concentration in an erythrocyte	356	g/l	322–368
Relative red cell distribution width	15.4	%	11–16
Platelets	103	10^9/l	204–356

anemia. It was assumed that anemia stems from disruptions of metabolism of vitamin B1, a hypothesis later confirmed when the condition was alleviated by oral administration of thiamine [9].

Case description

A three-year-old boy, first pregnancy, first vaginal birth at 38–39 weeks, birth weight — 3280 g, height — 51 cm. The Apgar score was 7/8 points. Boy's ethnicity — ingush. His parents are not closely related to each other. Case history: at the age of 10 months, CBC revealed a drop in hemoglobin count to 85 g/l; the patient received iron preparations for two months, to no effect. Further on, the boy periodically needed transfusions of packed red cells. At the age of one year, he was diagnosed with diabetes mellitus (hyperglycemia — up to 31 mmol/l, glycated hemoglobin — 9.1%). Prescriptions: insulin therapy in the basic bolus mode (aspart and degludec). At the age of two, parents noticed the child's problems with speech and hearing. Examination confirmed stage 4 bilateral sensorineural hearing loss. At the age of three, CBC revealed anemia (hemoglobin — 62 g/l) and thrombocytopenia (platelets — 18 thousand/ ml). The combination of conditions — diabetes mellitus, sensorineural hearing loss, anemia, thrombocytopenia — pointed to TRMA as the most likely reason thereof. On 08.02.2024, the child was admitted to the Dmitry Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology for clarification of the diagnosis and development of further therapy tactics.

Upon admission, the condition is severe per the disease, stable, no fever. Physical development typical for the age. The skin is pale, with individual petechiae on the trunk. No swelling. The tongue is clean and moist. Regular musculoskeletal system. The peripheral lymph nodes not enlarged. Cardiovascular system: heart tones clear, tachycardia up to 128–132 beats per minute. Puerile breathing in the the lungs, even over all fields, no wheezes. The abdomen soft, painless, the liver protrudes 2 cm from under the costal arch, spleen not palpable. Diuresis not factored in. Daily stool without pathological impurities.

Tables 1, 2 present the main indicators of the patient at admission to the Dmitry Rogachev National Research Medical Center. There were signs of anemia, thrombocytopenia, as well as high counts of lactate and glycosylated hemoglobin (7.78%).

The patient underwent a bone marrow puncture from two anatomical points (iliac ridges). Morphology of bone marrow (BM) aspirate was studied using light-optical microscopy (smears stained as per the Pappenheim-Kryukov method). Table 3 presents data on the BM cells differentiation and their percentage ratio.

Both punctates are rich in myelocaryocytes, polymorphic and similar in composition; both include a small amount of neutral fat, clusters of stromal elements.

The content of blast cells is 0.8% and 0.4% (Point 1 and Point 2, respectively).

Neutrophilic lineage preserved, with some cells showing signs of dyspoesis (hypogranularity, annular neutrophils). Monocytic lineage preserved, no significant morphological peculiarities. Lymphoid lineage narrowed. Erythroid lineage expanded, with features of dyspoesis (binuclearity, Howell-Jolly bodies, karyorrhexis). Erythropoiesis with megaloblastoid features in most cells (Fig. 1). Hemoglobinization delayed in basophilic forms. Megakaryocytic lineage expanded, represented by megakaryocytes at different stages of maturation. Part of the megakaryocytes with platelet release. Perls staining gives a positive reaction in 50% of erythrocaryocytes, with 45% of erythrocaryocytes classified as ring sideroblasts (Fig. 2), and 5% having the positive material in the form of a few scattered granules. The reaction was negative in 50% of erythrocaryocytes.

Instrumental studies

Electrocardiography. Normal position of cardiac electric axis. Accelerated atrial rhythm, against this background — frequent supraventricular extrasitolia (single and paired premature contractions), with the average heart rate (HR) of 149 beats/min. Complete blockade of the atrioventricular band's right leg.

Echocardiography. The study had tachyarrhythmia in the background. Both atria enlarged sharply. Left ventricle enlarged slightly, global systolic function at the lower limit of normal, may be slightly reduced. Systemic cardiac output maintained above average. Right ventricle enlarged moderately, global systolic function reduced. Secondary (possibly due to disrupted local kinetics in the left ventricular myocardium) mild mitral valve insufficiency.

Holter monitoring. Tachycardia registered through the day; all average heart rate values above normal for the patient's age. Rigid circadian rhythm profile. Recurrent supraventricular tachycardia. Frequent polytopic ventricular extrasystole. Frequent atrial extrasystole.

Table 2. Interpretation of the patient's biochemical blood assay

Indicators	08.02.24	Unit of measurement	Normal value
Glucose	4.11	mmol/l	2.6–24.9
Lactate	2.1	mmol/l	0.5–1.6
Iron	13.2	mmol/l	9–21.5

Table 3. Patient's BM aspirate examination

Cellular elements	Normal, %	Point 1, %	Point 1, %
Undifferentiated blast cells	1.6–3.4	0.8	0.4
Myeloblasts	1.6–3.0	1.2	0.8
Promyelocytes	2.3–4.0	4	3.6
Myelocytes	7.2–11.3	13.6	24
Metamyelocytes	5.5–8.5	8	7.2
Band neutrophils	14.8–22.4	18	9.2
Segmented neutrophils	9.8–20.5	18.4	20.8
Neutrophils count	40.0–66.7	62	64.8
Eosinophilic myelocytes		–	–
Eosinophilic metamyelocytes		–	–
Band eosinophils		–	–
Segmented eosinophils		2.4	2.4
Eosinophils count	3.3–6.4	2.4	2.4
Basophils	0–0.2	0.8	0.4
Promonocytes		–	–
Monocytes	0.03–3.0	3.2	2.8
Monocytes count		3.2	2.8
Lymphocytes	12.1–17.9	2.4	2.4
Plasma cells	0.03–0.3	–	–
Erythroblasts	1.0–1.9	3.2	1.6
Basophilic normoblasts	1.3–2.4	8.8	8
Polychromatophilic normoblasts	8.2–10.8	13.2	12.4
Oxyphilic normoblasts	5.9–8.8	2	4
Erythrocaryocytes count	16.4–23.9	27.2	26
Neutrophil maturation index	0.5–0.9	0.7	1.16
Hemoglobinization index	0.8–0.9	0.56	0.63
Leuko-erythroblastic ratio	3.3–4.5	2.6	2.8

Cardiologist's opinion. Atrial fibrillation, supraventricular extrasystole. Dilated cardiomyopathy (primary? arrhythmogenic myocardial dysfunction?) with a slightly decreased contractility of the left ventricle's myocardium. Second stage mitral valve insufficiency, first stage tricuspid valve insufficiency. First degree heart failure. Recommendation — antiarrhythmic therapy: amiodarone (200 mg), 100 mg orally in the morning and 50 mg orally in the evening; torasemide (5 mg) half a pill twice a day p.os.; potassium and magnesium asparaginate, one pill twice a day orally; propranolol 5 mg 3 times a day after meals.

Ophthalmologist's opinion. OU-hypermetropia/moderate myopic astigmatism. Partial atrophy of the optic nerves.

Sum total of clinical and laboratory data: megaloblastic anemia concomitant with thrombocytopenia, ring sideroblasts in BM; endocrine disorders (diabetes mellitus); sensorineural hearing loss; cardiac arrhythmia may be attributable to TRMA. Full exome sequencing recommended to confirm diagnosis. Specific thiamine therapy initiated: 150 mg/m^2/day (100 mg/day) IV (from 09.02 to 29.02). From 01.03 — thiamine 150 mg/m^2/day (100 mg/day) orally.

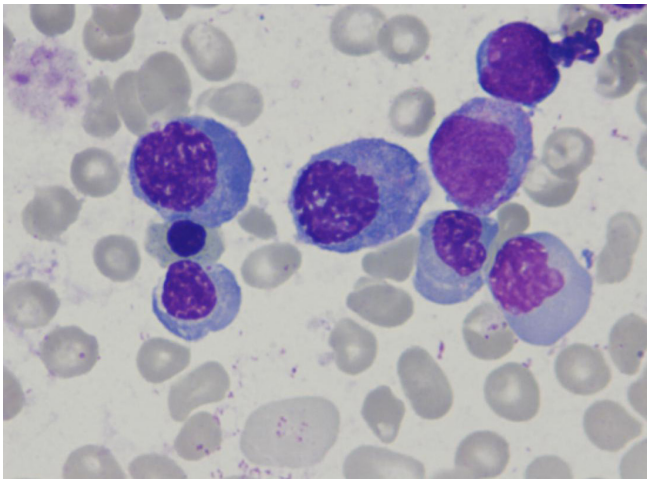

Fig. 1. Bone marrow: megaloblastic type of erythropoiesis. Pappenheim–Kryukov staining. Magnification: ×1000

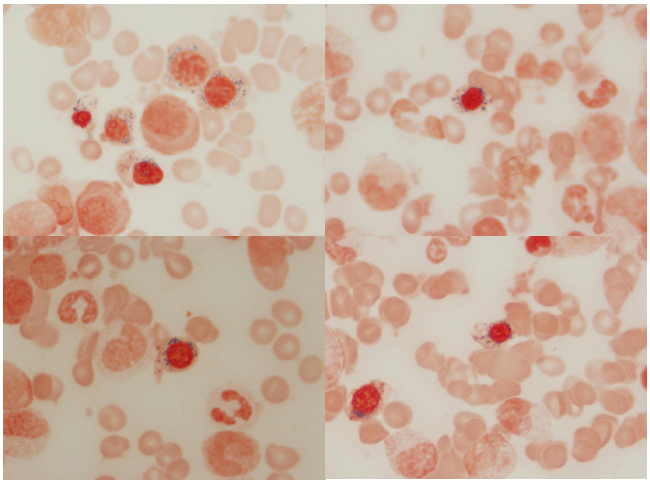

Fig. 2. Bone marrow: ring sideroblasts. Perls Prussian blue staining. Magnification: ×1000

Table 4. Interpretation of the patient's hemogram

Indicators	29.02.24	Units of measurement	Normal value
Leukocytes	10.26	10^9/l	6.05–9.85
Erythrocytes	3.88	10^{12}/l	4.2–4.6
Hemoglobin	112	g/l	115–138
Hematocrit	33.2	%	31–40
Average erythrocyte volume	85.6	fL	75–100
Average hemoglobin content in an erythrocyte	28.9	pg	25–33
Average hemoglobin concentration in an erythrocyte	337	g/l	322–368
Relative red cell distribution width	14.9	%	11–16
Platelets	343	10^9/l	204–356

The study revealed the *SLC19A2* gene to have a nucleotide replacement C.1223+1G > A in the homozygous state. Thiamine responsive megaloblastic anemia diagnosed based on the results of the studies.

Thiamine therapy yielded a pronounced positive effect: peripheral blood parameters normalized and remained stable (Table 4).

Case discussion

The article presents a rare case of TRMA in a three-year-old patient, which manifested as anemia, diabetes mellitus, and sensorineural hearing loss in the first year of life. This complex of symptoms points to TRMA as a possible disease. According to the previously published papers covering patients with TRMA, anemia was detected in 95.4% of cases, diabetes mellitus in 92.7%, hearing loss in 92.7%. Megaloblastic anemia was diagnosed in 70.8% of patients [8]. Further diagnosing efforts revealed the patient to have megaloblastic, sideroblastic anemia in BM, as well as visual impairment and cardiac arrhythmia. Thus, given the presence of the classic TRMA medical triad (megaloblastic anemia, diabetes mellitus, and sensorineural hearing loss) and the effectiveness of thiamine therapy, the clinical diagnosis is beyond doubt.

Thiamine responsive megaloblastic anemia is a very rare disease, which lowers the level of clinical alertness and complicates diagnosing. In our case, the child was diagnosed only when he reached the third year of life.

Currently, the only TRMA treatment strategy is lifelong thiamine therapy, which alleviates anemia symptoms in 97.1% of patients and allows decreasing the dose of insulin or discontinuation of its intake in in 69.9% of patients [8].

CONCLUSION

Thiamine responsive megaloblastic anemia is an extremely rare autosomal recessive disease characterized by a number of pathological conditions such as megaloblastic anemia, diabetes mellitus, loss of hearing and vision. The variety of clinical manifestations requires a multidisciplinary approach to TRMA at both the treatment and the follow-up stages. The diseases has been studied well, yet the only strategy available currently is oral administration of high doses of thiamine to address anemia. Thiamine treatment reduces the need for insulin and can delay the onset of diabetes mellitus, as well as prevent vision loss. Hearing loss in TRMA is irreversible and cannot be prevented with thiamine. Currently, genetic counseling is the most effective approach to prevention of this disease. Relatives of a TRMA patient should undergo a molecular genetic study together with their partners to determine the risk of bearing a sick child. In addition, pregnant women running a high risk of giving birth to a child with TRMA should be screened accordingly, because administration of thiamine during pregnancy can minimize or delay the appearance of symptoms of the disease.

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