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ATYPICAL, DRUG-RESISTANT COURSE OF COMBINED IMMUNODEFICIENCY: CASE REPORT

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Abstract

Combined immunodeficiencies (CID) are a heterogeneous group of human inborn errors of immunity with varying severity. We present a clinical case of CID (T-B+NK+), suspected by TREC assay in a 2.5-month-old child. The peculiarity of this case is the course of the disease, which, on the one hand, was characterized by a recurrent pneumonia, which was confirmed by X-ray. On the other hand, there were sudden shortness of breath, which were accompanied by cyanosis, irritation and were resistant to bronchodilator and antibacterial therapy. Appearance of venous thrombosis and progressive multiple organ failure led to the death of the child. Thrombocytosis, increased D-dimer level, and signs of hypercoagulation, positive immunoglobulin G antibodies to SARS-CoV-2 cannot rule out the role of COVID-19 in the course of the disease. Early diagnosis of combined immunodeficiencies in children can be difficult due to the atypical course, unusual symptoms of the disease, especially when they combined with other conditions. The use of newborn screening for SCID using TREC assay will allow timely detection of inborn errors of immunity with T-lymphopenia.

Keywords: *inborn errors of immunity, COVID-19, newborn screening, TREC.*

Introduction

Combined immunodeficiencies (CID) are a heterogeneous group of human inborn errors of immunity with varying severity [1-2]. Diagnosis delay and inappropriate treatment can lead to serious consequences and in some cases even to death [3-4]. Children often have no specific signs of the disease at birth, which complicates the early diagnosis of inborn errors of immunity, including CID [5-7]. Commonly, CID manifest by severe bacterial, viral and fungal infections [8-9]. In some cases, other manifestations are possible, such as early signs of allergies, malignancies or autoimmune disorders [9, 10].

Both cellular and humoral immunity is impaired in patients with CID [1]. There are different variants of CID depending on the presence or absence of T, B, and NK cells. However, CID always associated with cellular impaired immunity, which is manifested by a decrease or absence of T-cells or its dysfunction [11-12]. The establishing of T-cell lymphopenia by determining the levels of T cell receptor excision circle (TREC) in a dry blood spot formed the basis of screening for severe combined immunodeficiencies (SCID) [13-14]. Low levels of TREC can be observed in other inborn errors of immunity with T-lymphopenia [15-16], which may also be helpful in their early diagnosis.

Antibacterial and antifungal therapy is used in the case of the infectious, as well as often for the prevention of infections in the case of persistent lymphopenia.

We present a clinical case of CID (T-B+NK+) in a 2.5-month-old child with recurrent pneumonia which characterized by atypical course and was resistant to treatment. Appearance of venous thrombosis and progressive multiple organ failure led to the death of the child.

Case presentation

A girl, 2.5 months old, was referred to the hospital with complaints of shortness of breath, difficulty breathing, irritation, and intermittent coughing. The mother noted that the girl fell ill suddenly, on the day of admission. Two weeks ago, the child was treated for 10 days in the pulmonology department of the regional hospital for pneumonia and the symptoms were similar.

The anamnesis shows that the girl was born from the first full-term pregnancy, via spontaneous vaginal delivery. Formula was used for feeding due to hypogalactia.

On admission, the body temperature was 37°C, respiratory rate (RR)– 52 breaths per minute, heart rate - 128 per minute, oxygen saturation - 98%. The baby was satisfactorily fed. There were multiple stigmas of dysembryogenesis: high forehead, hypertelorism, long eyelashes, blue sclera, high arched palate, short bridle of the tongue, short neck, and wide nail bed. The patient's skin was pale. Difficulty breathing through the nose, nasal discharge was observed. The throat was hyperemic. Auxiliary muscles took part in the breathing; retraction of intercostal spaces and retraction of a sternum was observed. Dry rales were listened to in the lungs.

On admission the complete blood count (CBC) showed mild lymphopenia (1.9 10^9/l), anemia (Hb - 108 g/l), and thrombocytosis (600 10^9/l). Procalcitonin level was normal. Bilateral pneumonia was detected by X-ray examination, and diffuse mucous endobronchitis was identified with bronchoscopy.

Hypocalcemia (2.09 mmol/l) was observed in the biochemical blood analysis. Rapid antigen test for coronavirus on admission was negative. Immunoglobulin (Ig) M antibodies to SARS-CoV-2 were not detected in the child, but the test for Ig G antibodies to SARS-CoV-2 was positive (2,156; reference range up to 1.1).

Ultrasound detected thymus hypoplasia (the volume of the thymus was 9 cm^3, thymic index - 0.13% -10 centiles) and its heterogeneous structure. Echocardiography revealed an open functioning oval window of 2-3 mm, pericardial fluid on the anterior wall of 5 mm, on the posterior - 4 mm. Abdominal ultrasound was without significant deviations.

Prescribed antibacterial therapy with ceftazidime and amikacin and symptomatic therapy with bronchodilators were without a pronounced effect.

Taking into account the repeated episodes of dyspnea, which were accompanied by a violation of the child's condition and cyanosis, did not respond to bronchodilator therapy, recurrence of pneumonia, low response to antibacterial therapy, immunodeficiency was suspected. Differential

diagnosis was also performed with congenital respiratory pathology, congenital heart defects, diaphragmatic hernia, foreign body, allergy, seizures. The studies ruled out HIV infection, cystic fibrosis, allergies, and seizures. Chest computer tomography (CT) ruled out congenital pathology of the respiratory organs and diaphragmatic hernia.

A screening study to detect T- and B-lymphopenia using TREC / KREC assay showed a TREC value of 0 (twice) and a KREC value of 3.12 10^5 per 10^6 cells, indicating SCID. Subsequent immunological study confirmed the deficiency of the T-cells. The results of the immunological study are shown in table 1.

The dynamics of the CBC data are given in table 2.

The child's condition was unstable, with periodic deterioration during the treatment. Sudden shortness of breath and irritation occurred spontaneously, their intensity and frequency increased in dynamics, despite intensive care. RR during these attacks increased to 60 per minute, they were accompanied by cyanosis and a decrease in oxygen saturation to 94-96%. The attacks were resolved after the use of oxygen therapy. There was insufficient response to the drug therapy. Out of the attacks the girl's condition was satisfactory. Twice the girl was referred to the intensive care unit due to a sudden deterioration of her condition.

CBC detected increasing of lymphopenia (up to 0.7 10^9/l), and anemia. Biochemical analysis showed slightly elevated levels of liver enzymes (ALT up to 46 U/L, AST up to 90 U/L). The coagulogram (table 3) have shown a moderate decrease in prothrombin time (PT) and the international normalized ratio (INR), indicating hypercoagulation.

D-dimer on admission was normal, while after 2 weeks it increased to 2176 ng/ml (reference range up to 500 ng/ml).

One month after admission, the girl's condition suddenly deteriorated again. Attacks of shortness of breath increased in frequency and duration and were not resolved either with medication or after oxygen therapy, so the child was transferred to intensive care units (ICU). Ultrasound revealed deep vein thrombosis of the right upper extremity. The girl developed multiple organ failure, which led to her death.

Discussion

Herein we report on the first case of CID (T-B+NK+), suspected by TREC assay in Ukraine, which, unfortunately, ended in death. The peculiarity of this case is the course of the disease, which, on the one hand, was characterized by a recurrent pneumonia, which was confirmed by X-ray. On the other hand, there was sudden shortness of breath, which was accompanied by cyanosis and moderate decrease of saturation to 94-96%. The patient was treated with oxygen supplementation, but later she was resistant to oxygen therapy, as well as to bronchodilator and antibacterial therapy. Overall, taking into account dysmorphic facial features (hypertelorism, high forehead), thymic hypoplasia, hypocalcemia, T-cell deficiency, DiGeorge syndrome was suspected. Above described attacks were very similar to "tet spells" in patients with tetralogy of Fallot or other defects with a right-to-left discharge, but there was no instrumental evidence of these heart defects. Truncal heart defects are a characteristic feature of DiGeorge syndrome [12], and an increase in the frequency of attacks is observed during infectious diseases and inflammation.

It is possible that the child had another inborn error of immunity. Unfortunately, the quality and quantity of available biological material obtained from the child did not allow for in-depth genetic research by next generation sequencing (NGS). The family needs medical and genetic counseling, and the rational way is to conduct genetic testing for heterozygous carriers of pathogenic gene variants that cause immunodeficiency.

The question of the role of SARS-CoV-2 infection, both in the course of the disease and in its consequences, remains open. The girls had positive test of IgG antibodies to SARS-CoV-2. However, it is not known whether these were maternal antibodies (although there was no evidence of COVID-19 in mother during pregnancy and after delivery), or whether the child had COVID-19, which affected the course of the disease. In general, thrombocytosis, elevated D-dimer levels, and increased susceptibility to thrombosis are characteristic of SARS-CoV-2 infection [17]. Thrombocytosis, anemia, increased D-dimer level, and signs of hypercoagulation (decreased PT and INR) were observed in our patient with T-cell lymphopenia.

Usually, COVID-19 in children is characterized by a mild course, although in some cases develops acute respiratory distress syndrome, which requires a stay in ICU [18,19]. The course of the disease of moderate severity is accompanied by endothelial damage, coagulopathy and a high risk of pulmonary embolisms [18,20]. Severe course is characterized by superinfection, mainly of bacterial origin.

As for the course of coronavirus infection in patients with primary immunodeficiencies (PID), the data are contradictory. Researchers from Turkey have shown a high risk of mortality in patients with PID (23.5%), especially among patients with CID, and the presence of dyspnea on admission was an independent risk for COVID-related death [21].

A study conducted in the United Kingdom showed a higher risk of morbidity and mortality from COVID-19 in adult patients with PID compared with the general population [22]. Another study also showed a higher risk of death from COVID-19 in patients with PID, but this was more common in adult patients with comorbidity [23].

At the same time, other researchers point to a slight effect of COVID-19 on patients with PID [24, 25]. The risk of multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 is also not higher in patients with PID [26]. The researchers also note that one of the reasons for the minimal clinical impact of COVID-19 for PID patients may be a high level of awareness, strong caution, and self-isolation [24]. During the COVID-19 pandemic, caution should be focused not only in coronavirus infection in patients with PID, but also in the timely diagnosis of immunodeficiencies for preventive measures [27-30]. The implementation of SCID screening using TREC assay will allow timely detection of immunodeficiencies with T-lymphopenia.

Conclusion

Early diagnosis of combined immunodeficiencies in children can be difficult due to the atypical course, unusual symptoms of the disease, especially when they combined with other conditions. The use of newborn screening for SCID using TREC assay will allow timely detection of the disease, providing appropriate therapy and prevention, including protective measures for infections caused by SARS-CoV-2.

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Table 1. The immunological data of the patient

Parameter	Patient	Reference range
Ig A, g/l	< 0.15	0.08-0.34
Ig M, g/l	0.62	0.03-1.45
Ig G, g/l	3.7	2.3-14.1
Ig E, IU/l	2.5	< 12
CD3, %	**39.8**	55-80
CD3, 10^9/l	**0.52**	2.0-6.5
CD4, %	**20.2**	38-60
CD4, 10^9/l	**0.26**	1.4-5.0
CD8, %	19.4	15-35
CD8, 10^9/l	**0.25**	0.6-2.2
CD4/CD8	**1.04**	1.3-3.2
CD19, %	47.3	17-32
CD19, 10^9/l	0.62	0.5-2.2
NK, %	9.8	2-14
NK, 10^9/l	0.13	0.05-0.7

Table 2. CBC data of the patient

Date	RBC, 10^{12}/L	Hb, g/L	WBC 10^9/L	Platelets 10^9/L	ESR, mm/h	Leukocytes, %						
						Bands	Segm	Neutr 10^9/L	Lymph	Lymph 10^9/L	Mon	Eos
09.02	3.39	108	8.3	600	5	3	63	5.5	23	**1.9**	10	1
22.02	3.63	115	7.5	638	5	7	73	6.0	17	**1.3**	2	1
09.03	4.71	142	5.4	435	3	4	80	4.5	13	**0.7**	3	0
12.03	3.24	99	25.1	304	4	15	57	18.1	20	5.0	6	

Table 3. Coagulograms in reported patient

Date	PTT	Fibrinogen	PT	INR	Prothrombin
Reference range	24-34 sec	2.0-4.0 g/l	12.5-16.8 sec	0.98-1.16	70-120%
06.02	**36.2**	**1.93**	**12.2**	0.98	117.8
24.02		3.10	**12.4**	**0.95**	114.7
11.03	28.0	3.48	**11.9**	**0.91**	**122.7**