Idiopathic CD4+ lymphocytopenia (shortly ICL – from English. “idiopathic CD4+-T lymphocytopenia”) – is the immunologic defect, which is based on CD4+-lymphocytes deficiency (<300 cells/mm³ or <20% of T-cells’ general amount), causes of which can not be determined, and which leads to serious opportunistic infections or may be asymptomatic. This is a rare immunity disorder with heterogeneous clinical manifestations and immunological profile, which can be hereditary ICL [4]. It affects 0.5 - 2% of adults [5]. ICL was first described by the Centers for Disease Control and Prevention (shortly CDC – from the English “Centers for Disease Control and Prevention”, Atlanta, USA) in 1992 in people suffering from serious opportunistic infections on the background of low CD4+-cells level, who were not found the evidence of HIV-infection or other known causes of immunodeficiency [1]. ICL is different from HIV-infection by the stable level of CD4+-cells, in contrast to the progressive decline of this subpopulation in HIV-infection.

In ICL the geographic or gender dependence is not observed. Adults make up the majority of ICL cases, although several cases were observed among children who are under the supervision of CDC. Immunodeficiency creates conditions for the formation of infectious diseases and malignancy. There are reports that show the reduced proliferation of T-cells, decreased production of cytokines, amount of circulating «naive» CD45RA+ T-cells, reduced clonal ability of precursor cells of the bone marrow, weakened chemotaxis and active apoptosis [6]. The study has also found that CD4+-lymphocytes in people with this pathology are unusually sensitive to apoptosis crossly induced by T-cell receptor due to excessive expression of ligands Fas/Fas. Two recently published articles have begun to open the curtain of genetic basis of ICL. The defects of magnesium-transporting gene (MAGT1) or activating-recombination gene (RAG1) were found in the patients [8, 9].

The hypothesis that cellular immune defect can be caused by a violation of biochemical metabolic pathways of CD3-TCR was proven in studies of Pascal Hubert in 2000. Reduced proliferation of T-cells in patients with ICL in response to stimulation of CD3-TCR was observed only in CD4+-subpopulation [5].

According to scientific publications on potential mechanisms of ICL formation, the last include, in addition to the specified ones, the production of defective cytokines (TNF and gamma-interferon), impairment of hematopoietic stem cells/cells-precursors regeneration, delayed maturation of the thymic T-lymphocytes, autoantibodies against CD4+-cells [7].

Clinical manifestation of ICL has a significant dependence on the degree of decline of CD4-cells: ICL can be detected both in patient without symptoms in accidental laboratory research, and in the very sick patients who suffer from opportunistic infections (candidiasis, cytomegalovirus, non-tuberculous mycobacterial infections, cryptococcal meningitis, persistent human papilloma virus, progressive multifocal leucoencephalopathy, Sjögren’s syndrome, etc.). Also, about 50% of
such patients have at least one skin symptom: from the infections, atopic dermatitis to basal cell carcinoma [3].

Since the level of CD4+-lymphocytes in healthy young children is much higher than the value set in adults, idiopathic CD4+-limphocytopenia in children includes the following criteria: CD4+-cells <1000/mm³ in children aged 0 to 23 months and <300/mm³ in older children or <20% of total lymphocytes’ volume in at least two separate measurements, there are no signs of infection in HIV testing (even if the mother is HIV-seropositive) and there are no signs of any immunodeficiency or treatment associated with depletion of T-cells [2].

The optimal treatment in this violation is not yet developed. Nowadays ICL treatment is symptomatic, with a focus on prevention of opportunistic infections. Such patients are recommended preventive treatment that is used in patients with HIV/AIDS with the level of CD4+-cells <200/mm³ [10]. This includes the use of transplantation of hematopoietic stem cells and IL-7 [11] or IL-2 [32-34]. Transplantation of stem cells is accompanied by own risk factors and there is no clearly documented algorithm of their use.

Prognosis depends on the severity of opportunistic infections. Patients with higher expression of HLA-DR of major histocompatibility complex on CD4+-lymphocytes and lower levels of CD8+-cells have a higher probability of mortality [11].

Considering the rarity of this syndrome we represent a case from our clinical practice: a child with diagnosis of idiopathic CD4+-limphocytopenia.

Due to the rarity of this pathology let’s consider our own clinical observation. The boy was born in the IInd full-term pregnancy, physiological birth, weighing 3200g without complications. He was breastfed up to 4 months. Allergic anamnesis is not burdened. He was vaccinated by age. Mother denies tuberculosis in the family. Family history is burdened – there is the death of male children in sibs (father’s brothers) – one aged two years had died of severe pneumonia, another one – had died at the age of eight years of severe ulcerative gastritis.

Periods of clinical syndromes and nosological forms:

In the boy from the 4th month there is an infectious syndrome as recurrent bronchial obstruction syndrome.

5th month – combined, polytopic and complicated infectious syndrome: acquired acute non-rheumatic carditis, moderate arrhythmia according to the type of sinus bradyarrhythmia; acute bilateral stagnant-bacterial pneumonia, community-acquired, uncomplicated, respiratory failure RF 0; toxic kidney.

6th month – the same combined, polytopic infectious syndrome (profiling diagnosis changes, the course of disease remains the same): cryptogenic hepatitis is found.
7th month – bronchopulmonary lesion prevails, the course remains torpid: bilateral focal pneumonia complicated by obstructive and suppurative pulmonary syndrome, prolonged duration, severity degree is III, RF I-II.

8th month – bronchopulmonary lesion prevails. For the first time (West Center of Pediatric Immunology, Lviv) such diagnosis is made idiopathic CD4+-lymphocytopenia.

9th month and 16 days – bronchopulmonary lesion prevails. Child’s condition is severe. Cough is up to 2-3 times a day with the release of vomiting with sputum up to 20 ml. There is the shortness of breath of the mixed nature; it is constant from 54 and 75 breaths per minute with the participation of auxiliary muscles, SpO2-93%. It’s poorly treated by aerosol glucocorticosteroids, some improvement is observed in the application of systemic glucocorticosteroids. There are growing signs of heart failure.

10th month – bronchopulmonary lesion prevails. Diagnosis: Idiopathic CD4+-lymphocytopenia. Is there a deficiency of alpha-1 antitrypsin? Or is there a congenital anomaly of the right lung? Polycystosis? Pneumonia is bilateral total, complicated by purulent-pulmonary syndrome (purulent endobronchitis), prolonged duration, severity degree is IV, RF II-III. Protein-energetic deficiency is of IIrd degree (BMD (body mass deficiency) – is 25%). The child’s condition is severe. There is the shortness of breath of the mixed nature, it is constant up to 76 breaths per minute with the assistance of auxiliary respiratory muscles. SiO2-88-90%. Due to the low efficiency of the received treatment, there is no need for the additional methods of examination to verify the diagnosis; the child is directed to the Children’s Specialized Hospital “OHMATDYT” in Kyiv, where it lives for 8 days. Postmortem dissection was not performed.

Dynamics of hemogram: hemoglobin levels are within 80-103 g/l, red blood cells – 3.0-4.18*10^{12}/l, periodic hypochromia of erythrocytes. In moderate leukocytosis up to 14.1*10^{9}/l, which is stated in the dynamics during the first in-patient treatment, neutrophilia is noted (absolute number – 1051 cells), especially due to stab cells. Further leukocyte count is less than 4.2*10^{9}/l and progressing absolute lymphopenia is observed up to 708. In addition, the platelet count is always low in the range of 117-150*10^{9}/l.

Dynamics of immunogram: during the 5th month – IgG 12.0 g/l, IgA 0.66 g/l, IgM 0.47 g/l; during the 6th month – IgG 1.33 g/l, IgA 1.71 g/l, IgM 0.25 g/l; during the 7th month – IgG 3.0 g/l, IgA 1.12 g/l, IgM 0.35 g/l; during the 9th month and 14 days – IgG 2.74 g/l (after intravenous immunoglobulin), IgA 2.61 g/l, IgM 1.7 g/l.

Dynamics of lymphocyte subpopulation: there is a progressive decrease of CD4\(^+\) from 8.5% up to 0.24% and respectively the decrease of IRI (immune regulating index) (CD4\(^+\)/CD8\(^+\)) up to 0.12 against the background of normal CD19\(^+\), CD3\(^+\), CD56\(^+\) it changes to the low level, depending on the precedence of viral infection syndrome genesis.
A repeated testing for various infections of different biological media by ELISA method is performed (IgG and IgM) and PCR: EBV, CMV, Tox, HCV, HBV – the result is negative.

At the age of 10 months the analysis of specific HIV-antibodies in blood serum is performed – the result is negative.

In performance of bacteriological study of biological fluids saprophytic flora is released (the child is always on the antibacterial therapy). At the age of 6 months Candida fungi were once isolated from the throat.

Data of antibiotic therapy and substitutive immunotherapy by intravenous immunoglobulin – during the 6th month: the IIIrd generation cephalosporins parenterally and macrolides orally; during the 7th month: carbapenems parenterally; during the 9th month: the IIIrd generation cephalosporins with the replacement to fluoroquinolones and immunoglobulin intravenously in the number of 700mg/kg; during the 10th month: the IIIrd generation cephalosporins in combination of biseptol and intravenous immunoglobulin in amount of 15 ml/kg.

Conclusions

1. The basis for diagnosis of idiopathic CD4⁺-lymphocytopenia has become the growing decline of CD4⁺ lymphocytes to 0.244 g/l in three tests (according to the data of flow cytometer) with the interval of 30 days against a background of progressive reduction of the absolute lymphocyte count to 708, hypogammaglobulinemia and dysimmunoglobulinemia (due to IgG reduction up to 1.33 g/l).

2. This syndrome has typical clinical and paraclinical characteristics of severe combined immunodeficiency; but at the same time it is very rare and because of the correct determination of lymphocyte subpopulation specificity, may not always be diagnosed in time.

Therefore, although ICL is a rare disease, but it should be included into the differential diagnosis of unexplained opportunistic infections and in the suspicion of T-cells’ dysfunction. A small population of patients with ICL (especially – children) has always been a limiting factor for continued scientific research and a huge obstacle to determine the etiology of this syndrome. Our clinical case report gives another patient to a few people with ICL; it may be useful in further studies.