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A case report of Omenn syndrome in siblings

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Summary

The article describes a case of Omenn syndrome in neonatal period. Omenn syndrome was diagnosed in two of three children of the same parents. Both of children had skin erythroderma since birth and eosynophilia in blood tests. The course of the disease in both cases was fatal. Condition has inborn character and autosomal recessive pattern of inheritance. Around third month of life first symptoms of the disease appear: chronic diarrhea, failure to thrive, severe infections, hepatosplenomegaly, erythroderma, loss of hair. Marrow bone transplantation or cord blood stem cell transplantation is the only treatment. Diagnosis of Omenn syndrome is difficult because of incomplete clinical picture of the disease in newborn period, rarity of disease and skin changes similar to those in ichtiosis, histiocytosis, other SCID or atopic eczema.

It is particularly important to be vigilant in case of skin changes such as severe erythroderma and skin desquamation accompanied by abnormalities in blood tests. Such patients should be referred to hematological centers. Vaccination with attenuated vaccines should be postponed. Detailed laboratory tests in Omenn syndrome reveal low level of IgG, IgA, IgM and elevated level of IgE, absence of B-cell clones and abnormal amount of T-cell clones. Families burden with severe combined immunodeficiency disease (SCID) require genetic counseling. Families affected by Omenn syndrome or RAG-dependent SCID could benefit from prenatal diagnosis by detection of RAG genes mutations of fetal samples by direct sequencing.

Key words

Severe Combined Immunodeficiency; infant

Case report

A girl parents was born vaginally in 39th week of gestation with birth weight 3420g. Newborn girl was rated at 10 points on the Apgar score.

Adaptation of respiratory and circulatory systems proceeded correctly. From early beginning erytrodermia and desquamation of the skin was observed. The most intense lesions were on the scalp, neck, chest and limbs. Lesions were not painful (Fig. 1, 2). Ultrasound examination do not reveal additional congenital defects.

During pregnancy mother had twice oral herpes simplex infection and a cold in third trimester.

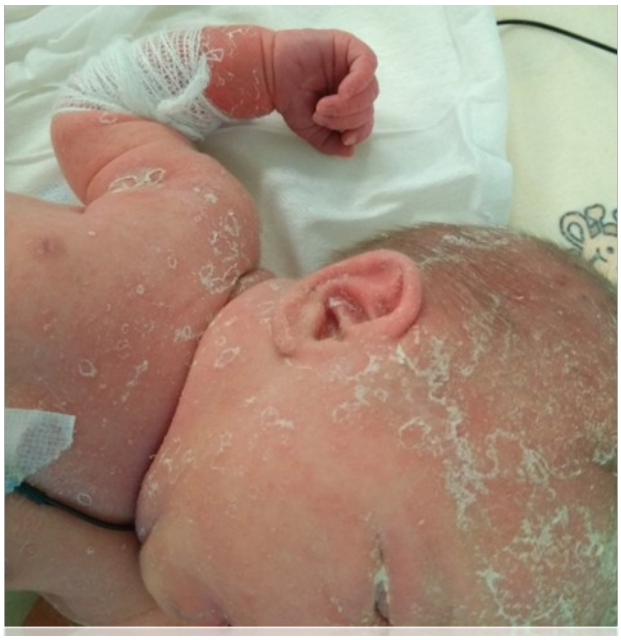

Fig. 1. Baby girl born in 39th week of gestation at 1st day of life with mild erytrodermia and desquamation of the skin. The most intense lesions were on the scalp, neck, chest and limbs.

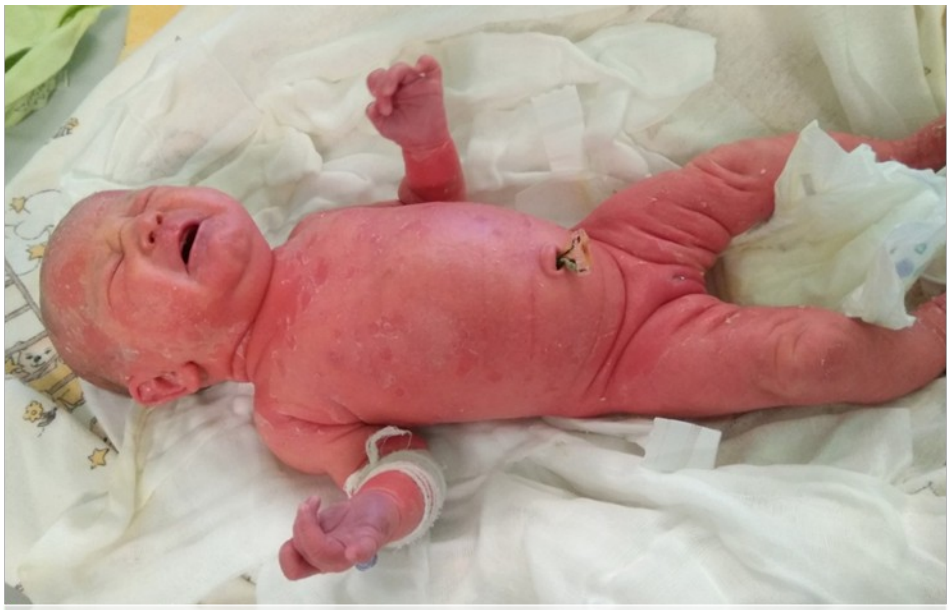

Fig. 2. Baby girl at 3 day of life, the erytodermia is more intense.

Tabl.1 Blood tests of three children. Incorrect test results are marked in red.

Blood test	Boy (1)	Boy (2)	Girl (3)	Normal values
RBC	5.64	5.22	5.47	3.6-4.7 (M/uL)
HB	19.2	18.8	18.3	12.0-14.5 (g/dL)
HCT	51.0	54.5	50.2	37.0-41.0 (%)
MCH	34.0	36.0	33.5	24.0-31.0 (pg)
MCHC	37.6	34.5	36.5	31.0-37.0 (g/dl)
MCV	90.4	104.4	91.8	98.0-114.0 (fl)
WBC	14.97	45.0	13.93	4.0-10.0 (K/uL)
NEU	7.88	15.10	7.60	2.8-6.8 (K/uL)
LYM	4.56	10.59	1.24	0.8-4.3 (K/uL)
BASO	0.18	0.66	0.13	0.0-0.2 (K/uL)
EOS	0.97	14.14	3.40	0.0-0.5 (K/uL)
MONO	1.38	4.80	1.56	0.2-0.8 (K/uL)
% NEU	52.6	33.2	54.6	
% LYM	30.5	23.4	8.9	
% MONO	9.20	10.7	11.20	
% EOS	6.50	31.20	24.40	
% BASO	1.20	1.50	0.90	
PLT	262	37	271	120-400 (K/uL)

During hospitalization the girl was consulted several times by dermatologist.

Skin specimens for bacterial and fungal culture showed growth of Escherichia coli ESBL (-Mother's vaginal culture also reveal growth of Escherichia coli ESBL(-). Blood test revealed eosynophilia and monocytosis (Table 1). The child was treated with antibiotic until bacterial or fungal infection was excluded as the cause of skin changes.

At 9th day of life the girl was discharged from the Neonatal Department with recommendation of further dermatological diagnosis towards congenital dermatosis. Her general condition was good, superficial desquamation was still visible on the skin. (Fig. 3).

Vaccination against tuberculosis was postponed, till completing the dermatological diagnostics.

At age of one month the girl was hospitalized because of severe respiratory infection. At that age infant girl presented severe desquamation of the whole surface of the skin, lack of hair and eyebrows (Fig. 4). Additionally she had hepatosplenomegaly. Eosynophilia and lymphopenia were maintained in the blood smear test. Lymphocyte phenotyping confirmed extremely low level of lymphocytes B. She was diagnosed with Ommen syndrome and qualified for bone marrow transplantation (BMT). The girl died at the age of 3 months, expecting BMT.

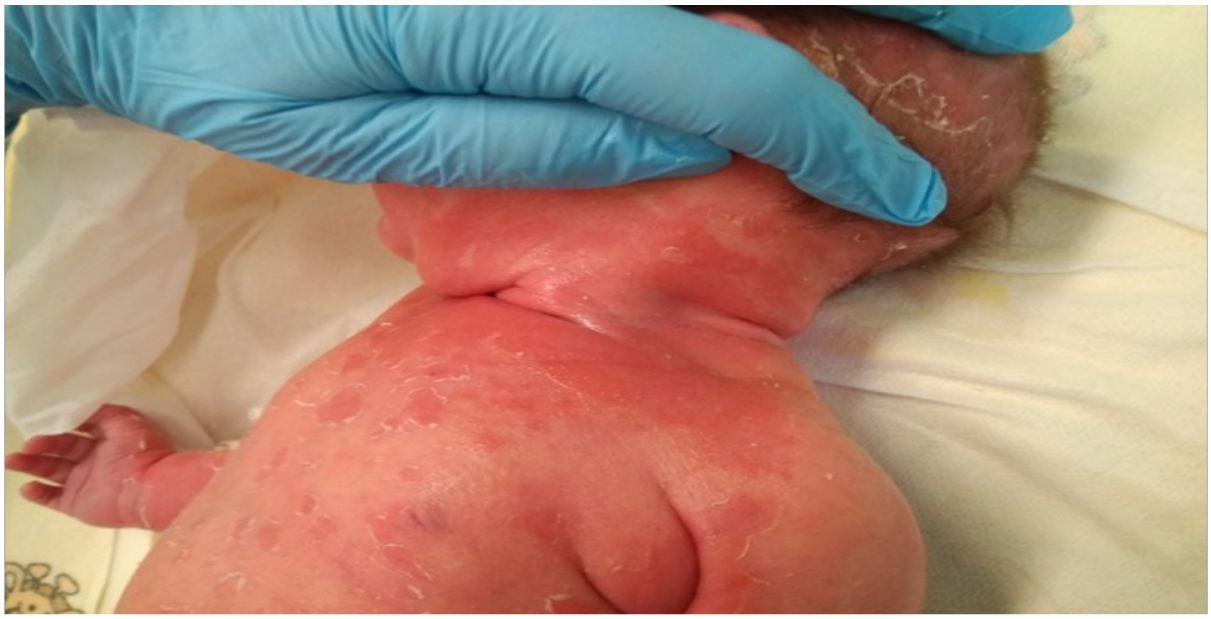

Fig. 3. Baby girl at first week of life. The lesions on the neck and chest.

Fig. 4. Baby girl at age of 3 months with severe desquamation on the whole surface of the skin, lack of hair and eyebrows (photo thanks to mother's courtessy)

The first child of these parents was a boy born healthy without any congenital defects or skin diseases.

The second child of the featured parents was born prematurely in 31st weeks of gestation with birth weight 2420g. He required resuscitation and assisted ventilation. Preterm boy was rated at 2-2-2-3 points on the Apgar score.

Physical examination showed erythema with extensive skin defects, maceration of the epidermis and bleeding erosions, mainly in bends. Skin lesions were diagnosed as ichtiosis. (Fig. 5). Blood test showed leukocytosis, thrombocytopenia and eosinophilia. (Table 1). He was diagnosed as a congenital sepsis and died in third day of life because of multiorgan failure.

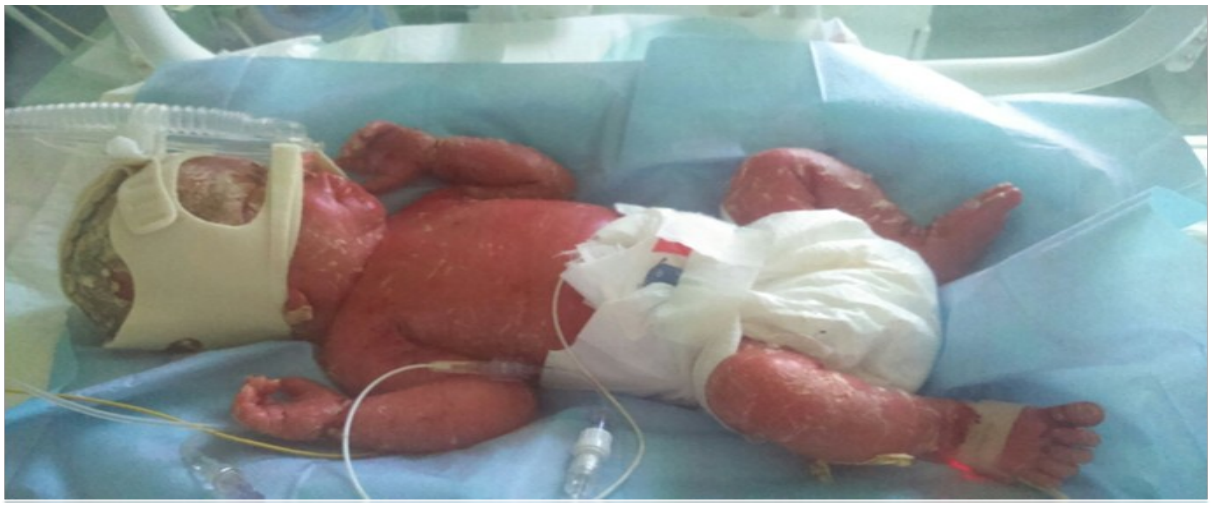

Fig. 5. Baby boy born prematurely at 31 weeks gestation with with extensive skin maceration of the epidermis and bleeding erosions.

Disscusion

Omenn syndrome is a rare severe combined immunodeficiency disease (SCID). The occurrence of Omenn Syndrome is unknown. Omenn syndrome is inherited in autosomal recessive pattern, therefore the disease may affect both boys and girls. Healthy parents are carriers of mutation. There is 25% risk with each pregnancy of having a child affected by the disorder[1,3] (Fig. 1).

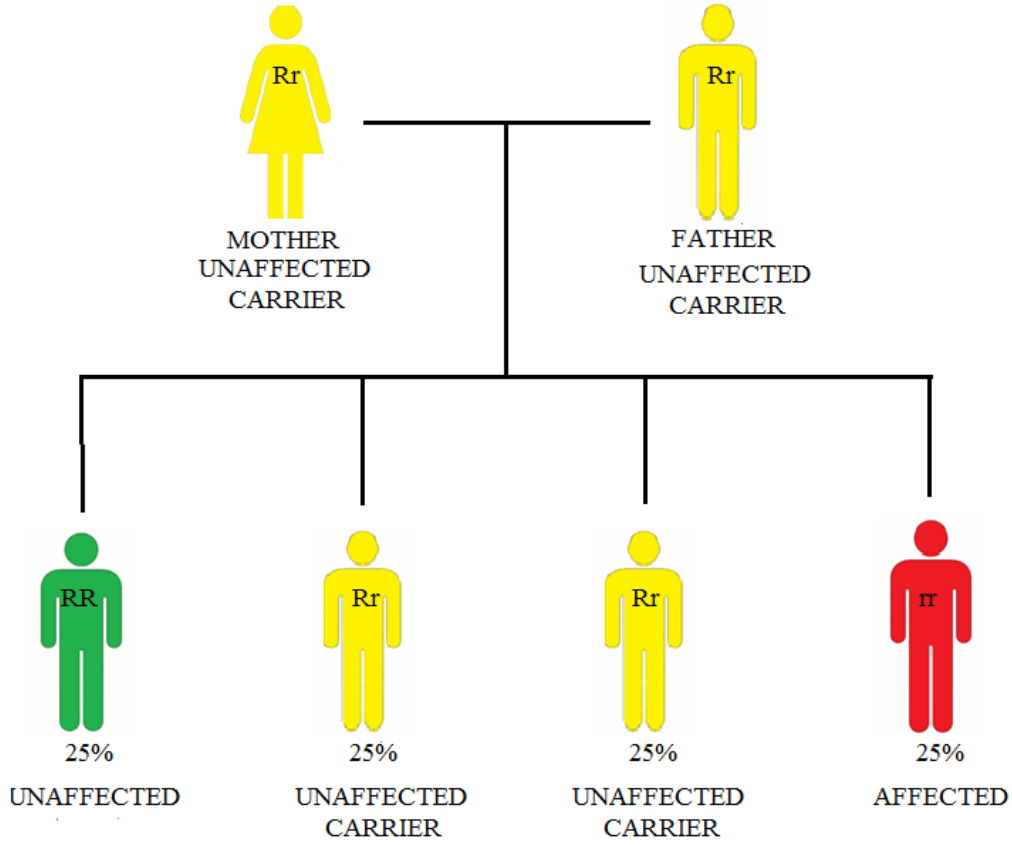

Fig. 1 Omenn syndrome- inheritance diagram, autosomal recessive pattern of inheritance (own elaboration)

According to The United States Immunodeficiency Network (USIDNET), an organisation specialized in scientific researches relating immunodeficiency diseases, there is 344 cases of SCID, and 8 of Omenn Syndrome in US[4]. Almost all cases of Omenn Syndrome concern Caucasian Race[4].

Data published in Orphanet Report 2019 depicted 25 cases of Omenn Syndrome worldwide[5].

Summarizing, occurrence of two cases of Omenn syndrome in one family is extremely rare.

Omenn Syndrome is caused by mutations in genes responsable for proper function of immune system. The most common mutations concern the RAG1 and RAG2 genes[1,6].

RAG1 and RAG2 genes encode proteins that are situated on lymphocytes surface. Those proteins take part in recognizing foreign pathogens. Both proper/adequate amount and a variety of surface proteins guarantee proper function of human immune system[6].

Mutations in RAG 1 and RAG2 genes result in reduction of surface proteins on lymphocytes B and lymphocytes T therefore diminish their ability of recognizing foreign pathogens. A patient became prone to infections. Moreover mutations in RAG1 and RAG2 genes result in

limited diversity of surface proteins resulting in T-cells autoimmune reaction toward own tissue[6].

The natural course of the Omenn syndrome

The article presents a rare picture of Omenn syndrome in neonatal period. Despite inborn character of condition first symptoms of disease usually reveal later, however typically before third month of life[1,2].

Children are born in good condition and regularly gain on weight. The only aberrancy is generalized exfoliative erythroderma, considered as a hallmark of Omenn Syndrome[3,4].

After initial well-being, when maternal storage of immunoglobulins decrease, appears chronic diarrhea and failure to thrive. Children became prone to infections, which might be life-threatening. Meantime autoimmunological reaction develops resulting in hepatosplenomegaly, limphadenopathy, erythroderma and hair loss[3,4].

If perinatal risk factors of infection are present a newborn might develop serious infection since first days of life, as it concerned prematurely born boy.

Tab. 3. Table presents set of signs and symptoms that may occur in Omenn Syndrome according to The United States Immunodeficiency Network 4.

99%-80%	79%-30%	29%-5%
Abnormality of lymphocytes	Aplasia/Hypoplasia of the eyebrow	Anemia
Hair loss	Desquamation of skin soon after birth	Hypothyroidism
Chronic diarrhea	Dry skin	Nephrotic syndrome
Erythroderma	Edema	Autoimmunity
Failure to thrive	Eosynophilia	Tyroiditis
Hepatomegaly	Fever	Sepsis
Lymphadenopathy	Leukocytosis	
Severe combined immunodeficiency	Pneumonia	
	Pruritus	
	Splenomegaly	

Diagnosis is difficult because of incomplete clinical picture of disease in newborn period, rarity of disease and skin changes similar to those in ichtiosis, histiocytosis, other SCID or

atopic eczema. Omenn syndrome should always be taken into consideration in differential diagnosis of those disorders.

Distinctive feature of Omen Syndrome is eosynophilia in peripheral blood[1,3,4]. Typically eosynophilia might be a result of allergic reaction or parasitic infection, however these causes are not it is typical in neonatal period. White blood count are usually normal. Leukocytosis indicates early onset sepsis.

Taking into consideration blood abnormalities and similarities of skin changes in both children: the girl and the boy, it is highly probable that second child, born prematurely, also suffered from Omenn Syndrome (Fig. 2).

Further diagnosis of Omenn syndrome include detailed laboratory tests that reveal abnormal amount of T-cell clones in blood, absence of B-cells, low level of IgG, IgA, IgM and elevated level of IgE[1]. Omenn syndrome is fatal. The only treatment is marrow bone transplantation or cord blood stem cell transplantation[1,2].

Severe combined immunodeficiency diseases are contraindications to vaccination with attenuated vaccines for example tuberculosis and MMR vaccine[1].

In conclusion, immunodeficiency syndromes may manifest in the neonatal period. It is particularly important to be vigilant in case of skin changes such as severe erythroderma and skin desquamation combined with abnormalities in blood tests. Such patients should be urgently referred to hematological centers. In the presence of severe skin lesion, vaccination with live virus vaccines should be postponed.
Family burden with severe combined immunodeficiency disease (SCID) require genetic counseling. Families affected by Omenn syndrome or RAG-dependent SCID could benefit from prenatal diagnosis by detection of *RAG* genes mutations of fetal samples by direct sequencing[7].

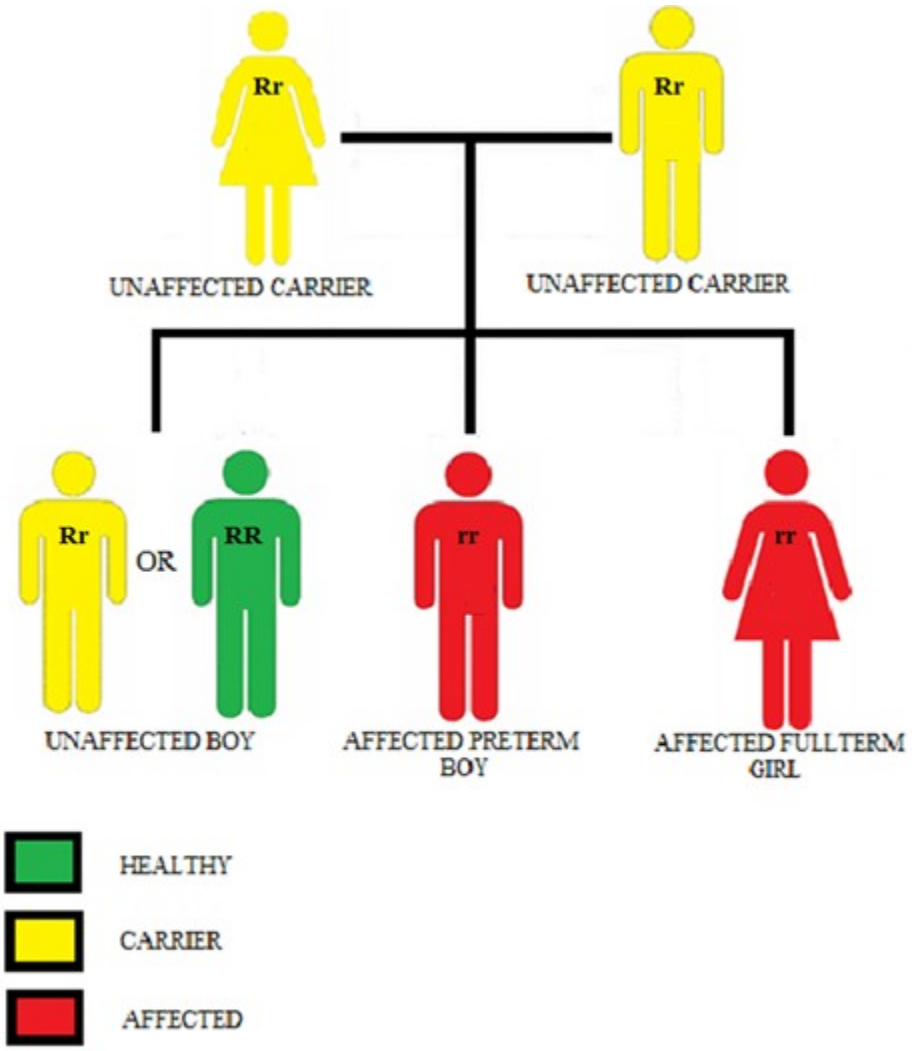

Fig. 2 Pedigree of the family with Omenn syndrome (own elaboration)

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