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A.M. Hilfanova[1], D.V. Zabara[2], O.V. Lysytsya[3], A.V. Volkova[3]

Hematopoietic stem cell transplantation in patient with DOCK8 deficiency: Ukrainian experience

[1]European Medical School, International European University, Kyiv, Ukraine
[2]SI «Institute of Pediatrics, Obstetrics and Gynecology named after academician O.M. Lukyanova of the NAMS of Ukraine», Kyiv
[3]National Pediatric Specialized Hospital «OKHMATDYT», Kyiv, Ukraine

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Dedicator of Cytokinesis 8 (DOCK8) deficiency is a combined immunodeficiency that exemplifies the broad clinical features of primary immunodeficiencies (PIDs), extending beyond recurrent infections including atopy, autoimmunity, and cancer.

Purpose — to describe the natural course of hyper-IgE syndrome (HIES) disease in an 8-year-old boy and his path to diagnosis, as well as our first local history of conservative treatment for 6 months. In particular, we describe the effectiveness of omalizumab, and the application of allogeneic hematopoietic stem cell transplantation with follow-up.

Clinical case. The 8-year-old boy presented with severe eczema and an involvement of the whole surface of the body. Infectious syndrome manifested from the age of 4 months in a form of recurrent respiratory infections. Over the next few years, the child suffered from life-threatening infections with high serum IgE (>3000 IU/ml). The examination revealed a cushingoid constitution, flat-valgus feet, and dysmorphic features. Therefore, HIES was suspected.

Genetic studies have confirmed the diagnosis by detecting a pathogenic homozygous mutation in the DOCK8 gene (Deletion Exons 2–46). We decided to use a humanized monoclonal anti-IgE antibody (off-label) to control the skin syndrome rather than systemic steroids. A significant improvement in skin condition, a decrease in eosinophils, and IgE were observed. Allogeneic stem cell transplantation of hematopoietic cells (HSCT) derived from peripheral blood of an human leukocyte antigen (HLA) — identical sibling donor was performed. The donor had a pathogenic mutation identical to the recipient in the DOCK8 gene but in a heterozygous state. Our data and treatment approach may be clinically useful as a diagnostic and treatment approach to HIES.

The research was carried out in accordance with the principles of the Helsinki Declaration. The informed consent of the patient was obtained for conducting the studies

No conflict of interests was declared by the authors.

Keywords: DOCK8 deficiency, primary immunodeficiency, hyper-IgE-syndrome.

Трансплантація гемопоетичних стовбурових клітин у пацієнта з дефіцитом DOCK8: український досвід

А.М. Гільфанова[1], Д.В. Забара[2], О.В. Лисиця[3], А.В. Волкова[3]
[1]Європейська медична школа, Міжнародний європейський університет, м. Київ, Україна
[2]ДУ «Інститут педіатрії, акушерства і гінекології імені академіка О.М. Лук'янової НАМН України», м. Київ
[3]Національна дитяча спеціалізована лікарня «ОХМАТДИТ», м. Київ, Україна

Дефіцит DOCK8 (від. англ. *Dedicator of Cytokinesis 8*) молекули — це комбінований імунодефіцит із широким спектром клінічних проявів — від рецидивних інфекції, атопії до аутоімунних захворювань та онкології.

Мета — описати природний перебіг синдрому гіпер-IgE, викликаного дефіцитом DOCK8-молекули, у 8-річного хлопчика та шлях до встановлення діагнозу, а також нашу першу локальну історію консервативного лікування протягом 6 місяців.

Зокрема, описано ефективність омалізумабу та застосування алогенної трансплантації гемопоетичних стовбурових клітин із подальшим спостереженням.

Клінічний випадок. 8-річний хлопчик звернувся з тяжкою формою екземи, яка охопила всю поверхню тіла. Інфекційний синдром проявлявся з 4-місячного віку у вигляді рецидивних респіраторних інфекцій. Протягом наступних кількох років дитина перенесла небезпечні для життя інфекції з високим рівнем сироваткового IgE (>3000 МО/мл). Під час обстеження виявлено кушингоїдну конституцію, плосковальгусні стопи та дисморфічні ознаки, що дало змогу запідозрити синдром гіпер-IgE.

Генетичні дослідження підтвердили діагноз, виявивши патогенну гомозиготну мутацію в гені DOCK8 (делеція екзонів 2–46). Вирішено використовувати гуманізовані моноклональні анти-IgE-антитіла (off-label) для контролю шкірного синдрому замість системних стероїдів. Спостерігалося значне поліпшення стану шкіри, зменшення кількості еозинофілів та IgE. Проведено алогенну трансплантацію стовбурових гемопоетичних клітин, отриманих ыз периферичної крові HLA (від. англ. *human leukocyte antigen*) — ідентичного донора-сиблінга. Донор мав патогенну мутацію в гені DOCK8, ідентичну реципієнту, але в гетерозиготному стані.

Отримані нами дані та підхід до лікування можуть бути клінічно корисними як діагностичний та лікувальний підхід до синдромів гіпер-IgE.

Дослідження виконано відповідно до принципів Гельсінської декларації. На проведення досліджень отримано інформовану згоду батьків дитини.

Автори заявляють про відсутність конфліктів інтересів.

Ключові слова: дефіцит DOCK8, первинний імунодефіцит, гіпер-IgE-синдром.

Introduction

Autosomal recessive (AR) HIES is a primary immunodeficiency that originates from a mutation in the DOCK8 gene. DOCK8 deficiency impairs immune cell migration, their function and survival. It impacts both innate and adaptive immune responses. Clinically, DOCK8 deficiency is representative of allergic inflammation as well as susceptibility to infections,

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autoimmunity, and malignancy [2]. Treatment is generally unsatisfactory, with exception of HSCT, which may be curative.

The National Register of Primary Immunodeficiencies of Ukraine, which has been running since 1995, has only 2 cases of DOCK8 deficiency. The first patient is a 16-year-old male with a history of severe fungal infection and neuroblastoma who underwent allogeneic HSCT from an unrelated donor in Italy at the age of 11 [4]. Here we report a case of another patient presenting with severe eczema, atopy, and recurrent skin infections since the first months of his life. The diagnosis of the AR HIES was established at the age of 7 with a positive DOCK8 genetic test. The patient underwent hematopoietic stem cell transplantation, with a complete remission of various manifestations.

The ***purpose*** of the case report — to describe the natural course of the HIES in an 8-year-old boy and his path to diagnosis, as well as our first local history of conservative treatment for 6 months, in particular the effectiveness of omalizumab, and the application of allogeneic HSCT with follow-up.

Case presentation

A 8-year-old boy presented with severe eczema and a total involvement of the body surface (Fig. 1). He was born from a third normal pregnancy from non-consanguineous marriage and has two healthy siblings. The patient suffered from the birth: swelling of eyelids was noted in the first two weeks of his life which was later accompanied by atopic dermatitis and complicated by a bacterial-fungal infection. He had been receiving systemic glucocorticoids for a long time to treat eczema. The infectious syndrome manifested from the age of 4 months in a form of recurrent respiratory infections. In the first year of his life it was represented by oral candidiasis and diarrhea (5 months), pneumonia (7 months), aphthous stomatitis, bilateral acute otitis media (9 months) and acute toxic hepatitis (10 months). Over the next few years, the child suffered from life-threatening infections: sepsis, Kaposi eczema, intestinal bleeding (4 years), staphylococcal sepsis (5 years), severe bilateral pneumonia, and reactive polyarthritis (6 years). Allergic symptoms other than eczema manifested as well, such as multiple sensitizations to food allergens (cow's milk protein, gluten of cereals, casein, etc.) and seasonal allergic rhinitis with high serum IgE (>3000 IU/ml). The boy received transfusions of plasma, erythrocyte mass, and intravenous immunoglobulin (IVIg). BCG vaccination (the only one the patient received) didn't have complications.

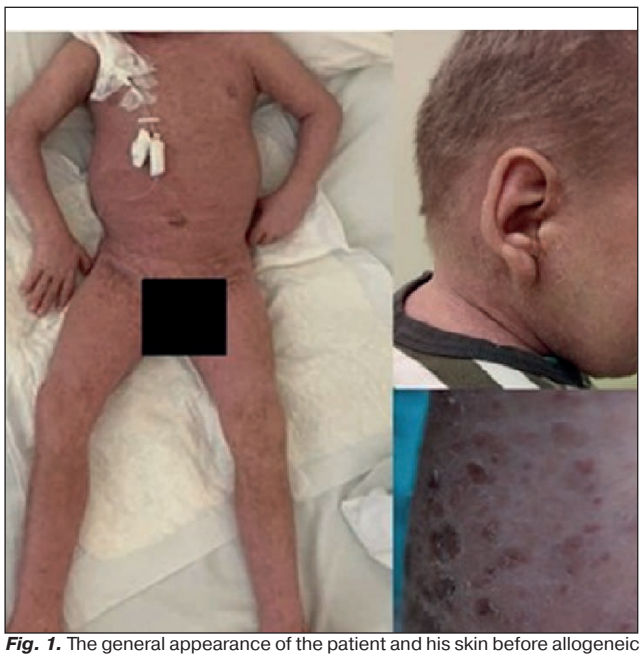

Fig. 1. The general appearance of the patient and his skin before allogeneic hematopoietic stem cell transplantation

On examination the patient has a short stature, a Cushingian constitution, flat-valgus feet and dysmorphic features: dysplastic ears, short nose, large, folded tongue, and coarse facial features. The severe eczema manifested in the form of erythema with lichenization and excoriation, intense odor, itching and damage to 100% of the body surface. On the right ear, the auto-amputation of the earlobe was revealed. It was difficult for the child to open his mouth because of the radial acid-like cracks in the perioral region. Besides, perianal warts, scarring phimosis, nail dystrophy, dry dull hair, and both rows of teeth affected by caries were revealed (Figure 1).

The general condition of the child was severe, and it affected his psycho-emotional state (frequent crying, negativity, anxiety, insomnia) and significantly impaired the quality of his ability to move, play, learn as well as the mother's life (emotional burnout, anxiety, social isolation).

Based on the described phenotype, we suspected a HIES. Our patient demonstrated traits inherent in all HIES variants — autosomal dominant (facial dysmorphism, bone fractures), and autosomal recessive variants (warts, Kaposi eczema, food allergy).

The careful follow-up examinations revealed significant changes. The anemia of chronic inflammation, thrombocytosis, lymphopenia (670 cells/μl), eosinophilia (30% or 2010 cells/μl), and increased erythrocyte sedimentation rate (42 mm/h) were noted in the hemogram. The im-

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Table 1

Results of the study of lymphocyte subpopulations by flow cytometry at the time of the initial examination of the patient

Cell population	%	Reference values, %	Cells/μl	Reference values, (cells/ μl)
Whole blood cells	–	–	5807	4700–8000
Granulocytes	77.7	–	4511	–
Monocytes	3.63	–	211	–
Lymphocytes	18.68	35–55	1085	1100–5900
T lymphocytes (CD3+)	62.4	60–76	677*	1200–2600
Activated (HLA-DR+)	36.3*	<15	246	–
NKT (CD3+CD56+)	1.2	<12	8	–
CD4+CD8+	1.2	<5	8	–
CD4-CD8-	5.3	<5	36	–
T-helpers (CD3+CD4+)	25.66	31–47	278*	650–1500
Activated (HLA-DR+)	47.81*	3–13	133.10	40–120
T-cytotoxics (CD3+CD8+)	39.47	18–35	428	370–1100
Activated (HLA-DR+)	65.77	6–29	281.61	40–270
CD4+/CD8+	0.65*		1.0–2.5	
B-lymphocytes (CD19+)	21.53	13–27	234*	270–860
-B1A (CD5+)	27.90*	<20	65.15	
Natural Killer lymphocytes (CD3-CD16+56+)	15.76	4–17	171	100–480
Immunoglobulins			Reference values	
IgA, g/L	5.16*		0.6–2.4	
IgM, g/L	0.41		0.5–2.1	
IgG, g/L	14.74		5.7–14.1	
IgE, IU/ml	16000*		–	

Note: * — data is outside the normal range.

munologic evaluation at the time showed CD4 lymphopenia, a slight decrease in B lymphocytes, activation of T lymphocytes, extremely high immunoglobulin E, and increased immunoglobulins A and G (Table 1).

Laboratory and instrumental studies revealed a delay in physical development (bone age 2.5 years), somatogenic nanism (reduced insulin-like growth factor 1(IGF-1) — 38.9 ng/ml), hypocalcemia, hypophosphatemia, hyperparathyroidism, elevated markers of osteoporosis and changes on X-ray: osteoporosis, consolidated spontaneous fracture of the elbow bone of the right hand, reduction of bone mineral density, goiter with hypothyroidism. Furthermore, pancreatic insufficiency (steatorrhea, mild steatorrhea type 3, reduction in fecal elastase), prediabetes (reduced C-peptide and insulin), and hypoalbuminemia (29.2 g/l) were noted. The microbiological analysis of the skin revealed a bacterial (*S. aureus*, *P. aeruginosa*) and fungal (*Candida albicans, Candida tropicalis*) colonization.

The genetic studies confirmed the diagnosis by detecting a pathogenic homozygous mutation in the DOCK8 gene (Deletion Exons 2–46). A monoallelic pathogenic variant in the LYST gene (c.9874G>T, p. Glu3292*) and variants with undetermined pathogenicity in the MAP3K14 (c.2615A>G, p. His872Arg) and RFX5 (c.892G>A, p. Gly298Ser) genes were also noted.

The child was treated in isolation at home and was examined by a doctor at the clinic every 2 weeks and several times a week by telephone.

The management was as follows: avoiding insolation (risk of photodermatitis and cancer), nutritional support, elimination diet, replacement therapy for pancreatic insufficiency (pancreatic enzymes) and hypothyroidism (L-thyroxine 25 mg/day), correction of the deficiency of fat-

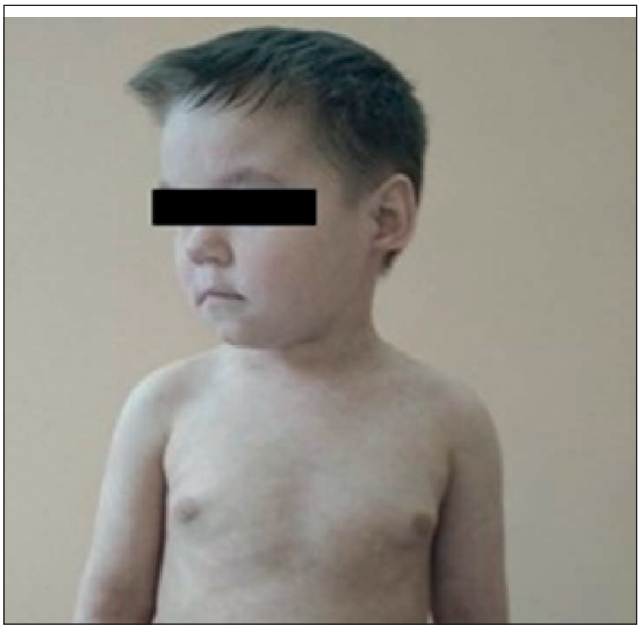

Fig. 2. The patient after allogeneic hematopoietic stem cell transplantation, day +190

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soluble vitamins A, D, E, iron, calcium, daily baths (2–3 times), skin care. Thanks to this approach, the severity of osteopenic syndrome has been reduced in 6 months. The therapy with H1-histamine receptor blockers (ketotifen, levocetirizine) had little effect. The chemoprophylaxis with antibiotics (cefuroxime, co-trimoxazole, cephalexin, ciprofloxacin) and antifungal drugs (fluconazole, itraconazole) improved skin condition but did not prevent pneumonia. IVIg 500 mg/kg was given every 4 weeks during the oral cavity sanitation.

We decided to use the humanized monoclonal anti-immunoglobulin E antibody (off-label) rather than systemic steroids to control the skin syndrome. Immediately after 5 doses (150 mg subcutaneously every 2 weeks) of Omalizumab, we observed a significant improvement in skin condition, a decrease in eosinophils, and immunoglobulin E. However, one month after stopping therapy, the skin condition worsened again.

The allogeneic HSCT derived from peripheral blood of an HLA-identical sibling donor (an older brother) was performed in August 2019 at the age of 7 years and 14 days. The donor had a pathogenic mutation identical to the recipient in the DOCK8 gene but in a heterozygous state. The prophylaxis of graft-versus-host disease (GVHD) was performed with cyclosporine and methotrexate. The platelet engraftment was recorded on day 12, erythrocytes on day 17, neutrophils on day 19. The infectious complications were manifested only in the form of candidiasis of the inguinal areas. On day 12, there was a pre-graft syndrome, and on day 24, moderate GVHD. The last infusion of intravenous immunoglobulin occurred on day 164 after transplantation, and complete discontinuation of immunosuppressive therapy on day 183.

The follow-up lasts 48 months after clinical diagnosis and 44 months after HSCT. No infectious episode or severe allergy was observed within 1 year after HSCT. The child was vaccinated against diphtheria, tetanus, pertussis, polio, pneumococcus, influenza, hepatitis B and Hib infection. 4 weeks after vaccination of 3 doses of Diphtheria, Tetanus, Pertussis (DTaP) vaccine levels of antibodies are more than 2 IU/ml to diphtheria and 4.5 IU/ml to tetanus toxoids.

One year after HSCT, the child's condition allowed him to start distance learning at school. For 17 months, there was a short-term dyspepsia syndrome and labial herpes (treated with acyclovir for 5 days). The condition of the skin and bones significantly improved, no signs of allergies were observed (Fig. 2)

We studied the prevalence of variants in the DOCK8 gene by examining 211 individuals unrelated to the proband. The prevalence of mutations was 10.14% (22/217). A large deletion (from 2 to 46 exons) was observed only in the proband, his mother, and two siblings (biological father was not examined, because true paternity was established only during HLA typing in search for related donor).

Discussion

The DOCK8 deficiency is a combined immunodeficiency, which was initially described as an AR HIES. It's common knowledge that, unlike the autosomal dominant (AD) HIES caused by loss of function mutations in STAT3, DOCK8 deficien-

Table 2

Clinical phenotype of a patient

Disease characteristics	AD-HIES	AR-HIES	Patient
Gene	STAT3	DOCK8	DOCK8
Discovered in	1966	2009	2012
Newborn rash	+++	+	swelling of the eyelids
Eczema	++++	++++	++++
Repeated abscesses of the skin	+++	++	+
Otosinopulmonary infections	++++	++++	++
Mucocutaneous candidiasis	+++	++	++
Pneumatocele	+	–	–
Facial dysmorphism	+++	–	+
Hypermobility of joints	+++	+	–
Preserved milk teeth	++++	+	–
Bone fractures	+++	+	+
Severe / recurrent viral infections (HSV, VZV, HPV, MC)	+	+++++	++++
Food allergy, asthma, anaphylaxis	+	+++	++
Autoimmunity (cytopenias, vasculitis)	–	+	–
Encephalitis, cerebral vasculitis	–	+	–
Squamous cell carcinoma and lymphoma	–	++	–

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cy lacks the osseous and connective tissue defects that are prominent within the described phenotype of AD-HIES [6]. In our case, the patient demonstrated traits inherent to all HIES variants — AD (facial dysmorphism, bone fractures, milk tooth retention), and AR variants (warts, Kaposi eczema, food allergy), (Table 2).

Given the severe skin syndrome in the child with osteoporosis, it was decided to use omalizumab before HSCT. We have relied on the experience of colleagues in the treatment of patients with severe refractory atopic dermatitis and significantly elevated serum IgE [5,7], with HIES [1], as well as our own experience of treating a female with a hyper-IgE-like syndrome due to a new monoallelic mutation in the DOCK8 gene [3]. We evaluated the good efficacy and safety of omalizumab, but due to the painful sensations of subcutaneous injections, the patient's low adherence to treatment was noted. We noted that within 2–4 weeks after its discontinuation, the skin condition, eosinophil level, and IgE were almost back to baseline.

Both Ukrainian cases have similar features: in the first case the clinical diagnosis was established at the age of 6 years, the leading manifestations at the time of diagnosis were severe persistent atopic dermatitis, manifested from the age of 1 month, an infectious syndrome represented by severe bacterial infections. Given the presence of skin mucous candidiasis from the age of 5 months and the experience of monitoring the first patient who developed severe resistant aspergillosis, we prescribed an antifungal drug for the primary prevention of aspergillosis — itraconazole at a dose of 3 mg/kg daily. With the introduction of aggressive antibiotic therapy with antistaphylococcal activity, administration of itraconazole, and intravenous immunoglobulin (IVIG) we were able to avoid the development of severe episodes of infection and the formation of chronic foci of infection. All this and the presence of a fully compatible donor enabled us to carry out the successful treatment with bone marrow transplantation 6 months after the diagnosis.

Conclusions

Severe eczema may be the earliest and most significant sign of PIDs. We have shown, that the overlap between different HIES variants is possible. Anti-IgE antibodies can help reduce eczema in patients before bone marrow transplantation without the risk of osteoporosis. Our data and therapeutic approach may be clinically useful as the diagnostic and treatment approach for HIES.

No conflict of interests was declared by the authors.

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Відомості про авторів:
Гільфанова Анна Михайлівна — к.мед.н., доц. каф. педіатрії, імунології, інфекційних та рідкісних захворювань Європейської медичної школи Міжнародного Європейського університету. Адреса: м. Київ, просп. Академіка Глушкова, 42 В. https://orcid.org/0000-0002-2541-0327.
Забара Дарія Віталіївна — к.біол.н., н.с. лабораторії імунології ДУ «ІПАГ імені академ. О.М. Лук'янової НАМН України». Адреса: м. Київ, вул. П. Майбороди, 8; тел. +38 (044) 483-62-16. https://orcid.org/0000-0003-4418-7818.
Лисиця Олександр Володимирович — зав. відділення трансплантації кісткового мозку НДСЛ «ОХМАТДИТ». Адреса: м. Київ, вул. В. Чорновола, 28/1; тел. +38 (044) 290-27-30.
Волкова Аліна Вікторівна — лікар відділення трансплантації кісткового мозку НДСЛ «ОХМАТДИТ». Адреса: м. Київ, вул. В. Чорновола, 28/1; тел. +38 (044) 290-27-30.

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