Hyper IgE syndrome associated with novel DOCK8 heterozygous mutation: a case report

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Dedicator of cytokinesis 8 (DOCK8) deficiency is an autosomal recessive combined immunodeficiency within the spectrum of hyper-IgE syndromes. The clinical case. Here we report a patient with a novel heterozygous mutation in DOCK8 gene associated with a clinical presentation of hyper-IgE syndrome (HIES).

A case report. The patient presented with severe congenital atopic dermatitis, allergic rhinitis and bronchial asthma which was developed during the third year of life. Also, the patient suffered from recurrent otitis and lymphadenopathy of the inguinal lymph nodes. The immune evaluation showed normal lymphocytes subpopulation and increased serum IgE — 32.131 IU/L. Genetic sequencing revealed a heterozygous defect c.5266A>T (p.Ile1756Phe) in the DOCK8 gene.

Conclusions. Our data and therapeutic approach may be clinically useful as the diagnostic and treatment approach for severe atopic dermatitis that does not fit the full criteria for previously reported hyper-IgE syndromes. The research was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of all participating institution. The informed consent of the child’s parents was obtained from the studies.

Key words: hyper-IgE syndrome, DOCK8, severe atopic dermatitis, omalizumab.

Гіпер-IgE синдром, пов’язаний із новою гетерозиготною мутацією DOCK8: клінічний випадок

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DOCK8 (dedicator of cytokinesis 8) дефіцит є аутосомно-рецесивним комбінованим імунодефіцитом у спектрі гіпер-IgE синдромів. У даній статті повідомляється про випадок нової гетерозиготної мутації гена DOCK8, пов’язаної з клінічним проявом гіпер-IgE синдрому (HIES), у дитини.

Клінічний випадок. Хвора мала важкий вроджений атопічний дерматит, алергічний риніт та бронхіальна астма, яка розвинулася на третій році життя. Також пацієнка страждала від рецидивного отиту та лімфаденопатії пахових лімфатичних вузлів. Оцінка стану імунної системи показала нормальну субпопуляцію лімфоцитів та підвищення IgE у сироватці крові — 32,131 МО/л. Генетичне секвенування виявило гетерозиготний дефект c.5266A>T (p.Ile1756Phe) в гені DOCK8.

Висновки. Наші дани та терапевтичний підхід можуть бути клінічно корисними як як діагностичний і терапевтичний підхід для важкого атопічного дерматиту, який не відповідає повним критеріям для синдрому гіпер-IgE, у дитини може бути корисним для клініцистів. Дослідження виконані відповідно до принципів Гельсінської Декларації. Протокол дослідження ухвалений Локальним етичним комітетом всіх учасників. Наповнення поінформованої згоди батьків дитини.

No conflict of interest was declared by the authors.

Key words: hyper-IgE syndrome, DOCK8, severe atopic dermatitis, omalizumab.

Гіпер-IgE синдром, пов’язаний із новою гетерозиготною мутацією DOCK8: клінічний слів

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Клінічний випадок. Гипер-IgE синдром, DOCK8, тяжелый атопический дерматит, омализумаб.

No conflict of interest was declared by the authors.

Key words: hyper-IgE syndrome, DOCK8, severe atopic dermatitis, omalizumab.
Introduction

Hyperimmunoglobulin E syndromes (HIESs) are rare diseases among primary immunodeficiency (PID) disorders, characterized by elevated immunoglobulin (Ig) E levels, eosinophilia and recurrent Staphylococcal infections. Bi-allelic loss-of-function mutations in the guanine-nucleotide exchange factor dedicator of cytokinesis 8 (DOCK8) cause autosomal recessive (AR)-HIES. [3] Although heterozygous carriers of mutant DOCK8 alleles appear clinically normal, there are several reports of heterozygous DOCK8 mutated gene carriers with various clinical manifestations. [1,2]

In this study we describe the case of a patient with a heterozygous mutation in the DOCK8 gene, with extremely elevated IgE levels and severe congenital atopic dermatitis, asthma and recurrent sinopulmonary infections.

Case presentation

The patient is a 5-year-old female presented with severe chronic atopic dermatitis, dysplastic ears and hypermobility of the joints, shortened right leg (by 1 cm), high palate and recurrent infections. The patient suffered from dermatitis from birth, from the age of 3 weeks; the rash has spread and intensified, accompanied by marked itching. The eczema was of recurrent nature, accompanied by widespread skin lesions (with the most severe lesions located in the joints), peeling, lichenification, itching, numerous deep excoriations and fissures, as well as superinfection with pyogenic bacteria and candida.

The exacerbations are expressed as vulvitis, enlargement and pain in the inguinal lymph nodes. From age 3.5, the false joints syndrome was noted expressed as joint pain, limitation of physical activity and morning stiffness without synovitis. In addition to the continued use of emollients and topical steroids, systemic steroids were required for control. A strict elimination diet did not improve the child’s condition.

The first episode of bronchial obstruction occurred at age 2 against the background of influenza and shortness of breath episodes; consumption subsequently occurred against the background of viral respiratory infection or provoked by cold air. From age 2, the patient suffered from constant nasal congestions; she was diagnosed with allergic rhinitis and bronchial asthma. The rhinitis was year-round in character and significantly impaired the quality of life. The basic therapy of asthma and AR with topical steroids was started at age 2 years 11 months (3 mild exacerbations of asthma at age 3–4 were noted). The allergic history is also complicated by specific sensitization to buckwheat (manifested by Quincke’s swelling), to egg whites and egg yolks, as well as to numerous foods (identified during provocative tests). The mother was allergic to bee stings and herbal medications.

The infectious syndrome is represented by recurrent skin-mucous bacterial-fungal infections (vulvitis, conjunctivitis, nasopharyngitis, adenoiditis), a left buttock abscess at age 3.5, as well as by recurrent purulent otitis and rhinosinusitis and recurrent lip sore. In particular, at age 4 an episode of bilateral purulent otitis caused by the multidrug-resistant Pseudomonas aeruginosa was observed.

The patient was found to have normal or increased IgG levels — 14.2–17.86 (5.4–14.2 g/L), slightly increased IgA levels — 2.97 (0.5–2.2 g/L), variable IgM levels — 0.15–0.96–1.87 (0.4–2.0 g/L), and increased serum IgE level (32.131 IU/L) or allergic rhinitis (with no therapy administered for 9 months) or allergic rhinitis (with no baseline therapy administered for 10 months) were noted. Short-term administration of low systemic glucocorticosteroid doses (prednisone 10 mg for 1 day, 5 mg for 2–3 more days) is required several times a month.
The research was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee (LEC) of all participating institutions. The informed consent of the child’s parents was obtained from the studies.

Discussion

Dedicator of cytokinesis 8 (DOCK8) deficiency is an autosomal recessive combined immunodeficiency within the spectrum of hyper-IgE syndromes: eczematous dermatitis, recurrent sinopulmonary infections, *Staphylococcus aureus* skin abscesses, elevations in serum IgE levels, and, sometimes, mucocutaneous candidiasis. [1]

In this case report, the patient had a heterozygous defect c.5266A>T (p.Ile1756Phe), a variant of uncertain significance in the DOCK8 gene, and had extremely elevated IgE levels, a history of atopy, recurrent sinopulmonary and skin infections. Commonly, patients with DOCK8 mutations have a combined immunodeficiency with low T cell and B cell numbers, low serum IgM levels and variable IgG antibody responses. [4] An immunological investigation revealed that our patient, despite recurrent sinopulmonary and skin infections, displayed no signs of combined immunodeficiency (e.g., lymphopenia) or low levels of serum immunoglobulins. Interestingly, the patient has hypermobility of joints (that is more usual for autosomal dominant hyper-IgE), as well as aplastic ears and high palate.

Conclusion

The c.5266A>T variant is a previously unreported mutation that is likely responsible for the findings in this patient. Although heterozygous carriers of mutant DOCK8 alleles appear clinically normal, our and previous reports suggest that extensive longitudinal studies on their phenotypes are needed to reveal if heterozygosity for DOCK8 is associated with health risks. Our data and therapeutic approach may be clinically useful as the diagnostic and treatment approach for severe atopic dermatitis that does not fit the full criteria for previously reported hyper-IgE syndromes.

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