Ten-Year Follow-Up of a DOCK8-Deficient Child With Features of Systemic Lupus Erythematosus

abstract

Dedicator of cytokinesis 8 (DOCK8) deficiency is an innate error of adaptive immunity characterized by recurrent infections with viruses, bacteria, and fungi, typically high serum levels of immunoglobulin E, eosinophilia, and a progressive deterioration of T- and B-cell–mediated immunity. DOCK8 mutations are the second most common cause of hyper–immunoglobulin E syndromes (HIES). We report a case of DOCK8 deficiency associated with systemic lupus erythematosus (SLE). Association of SLE with HIES is very rare; to our knowledge, this is the sixth such case reported in the literature. A 10-year-old girl of consanguineous parents was followed in our clinic because of HIES since early childhood. She developed SLE with purpuric and necrotic skin lesions, diffuse arthritis, and glomerulonephritis. These autoimmune features were corroborated by the presence of antinuclear, anti-DNA, and antiphospholipid antibodies. The combination of HIES and autoimmunity makes treatment difficult, because the use of immunosuppressive drugs needed for SLE may worsen existing symptoms caused by the immunodeficiency. Our observation is the first case of association of SLE with HIES in the literature where the primary immune disease is genetically documented and labeled as DOCK8 deficiency. Pediatrics 2014;134:e1458–e1463

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KEY WORDS

DOCK8 deficiency, hyper-IgE syndrome, AR-HIES, pediatric, systemic lupus erythematosus, antiphospholipid syndrome, recurrent parotitis

ABBREVIATIONS

AD-HIES—autosomal dominant hyper–immunoglobulin E syndrome
AR-HIES—autosomal recessive hyper–immunoglobulin E syndrome
DOCK8—dedicator of cytokinesis 8
GC—germinal center
HIES—hyper–immunoglobulin E syndrome
IgE—immunoglobulin E
IgG—immunoglobulin G
SLE—systemic lupus erythematosus
UGPL—microliter antibodies anti-cardiolipin type IgG unity
UMPL—microliter antibodies anti-cardiolipin type IgM unity

Dr Jouhadi provided medical follow-up of the patient, conceptualized and designed the study, and drafted the initial manuscript; Dr Khadir took care of skin infection, eczema and suggested the diagnosis of lupus; Dr Ailal provided medical follow-up of the patient and immunological evaluation; Dr Bouayad was responsible for treating lupus and nephrotic syndrome; Dr Nadi supervised genetic extraction of DNA and the preparation of samples destined to genetic investigations; Dr Engelhardt performed the genetic investigations; Dr Grimbacher coordinated and directed this collaboration; and all authors approved the final manuscript as submitted.

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Hyper–immunoglobulin E syndromes (HIES) are a group of complex heterogeneous diseases characterized by elevated levels of serum immunoglobulin E (IgE), eczema, and immunodeficiency, responsible for severe and recurring infections. The autosomal dominant form (AD-HIES), caused by dominant negative mutations in the STAT3 gene, is additionally characterized by anomalies of the osseous and connective tissue, which do not exist in the autosomal recessive forms of HIES (AR-HIES). In the latter, we observe a high susceptibility to cutaneous viral infections, allergies, and malignancies. However, autoimmune diseases are rarely reported. Dedicator of cytokinesis 8 (DOCK8) deficiency has recently been identified as the most common cause of AR-HIES.

**CASE REPORT**

Our patient was born to consanguineous parents in 2002. At the age of 8 months, she developed a herpetic lesion of the right upper eyelid, complicated by blepharitis, a palpebral abscess, and facial cellulitis. Several months later, pyodermitis became generalized including the scalp. When the patient was 12 months old, erythematous squamous lesions and vesicular pruriginous eczema appeared behind the ears and spread over the entire body.

At the age of 33 months, the patient had a first episode of right upper lobe pneumonia. A second episode occurred 1 month later, with hospitalization for severe respiratory distress with cyanosis. Chest radiographs revealed bilateral pneumonia. Computed tomography of the chest detected segmental bronchial alveolar infection of the upper right and middle lobes and the lingula without interstitial lesions. This child had ≥5 radiologically documented pneumonias and 3 episodes of purulent otitis before the age of 6 years.

Dermatological examination revealed skin xerosis, eczema with retroauricular and nuchal furrows, macerated intertrigo covered with whitish coating in the groin fold, dripping lichenified erythematous lesions in the genital mucosa, and perianal warts. Purplish-blue ulcerated erythematous nodes were present on the knees (Fig 1) and atrophic erythematous–squamous lesions resembling discoid lupus on the cheeks (Fig 2).

Blood count showed a leukocytosis of 28,500/mm$^3$ white blood cells, of which 33% were neutrophils (9600/mm$^3$), 9% (2700/mm$^3$) were lymphocytes, 6% (1800/mm$^3$) were monocytes, and 50% were eosinophils (14 400/mm$^3$). She had 788 000/mm$^3$ platelets. Proteus rettgeri and Pseudomonas aeruginosa were isolated from ear swabs. Cultures of cutaneous lesions revealed methicillin-resistant *Staphylococcus aureus* on 4 occasions and proliferating yeasts and mycelial filaments of *Candida albicans*. Skin biopsies of the knees, inguinal fold, and retroauricular lesions showed epidermomyasis.

In this context of severe recurring infections with unusual germs, an immune deficiency disease was suspected. The first etiological assessment ruled out HIV infection. Immunoglobulins G, M, and A were high (at 16.28 g/L [normal 4.5–8 g/L], 2.44 g/L [normal 0.5–1.5 g/L], and 2.62 g/L [normal 0.4–1.22 g/L], respectively). The lymphocyte count showed a significant decrease of CD8$^+$ T cells at 271 cells/mm$^3$ (normal 800–1500 cells/mm$^3$) and a moderate decrease of CD4$^+$ and total absolute CD3$^+$ T cells at 723 cells/mm$^3$ (normal 1000–1800 cells/mm$^3$) and 1286 cells/mm$^3$ (normal 1800–3000 cells/mm$^3$), respectively. High...
serum levels of IgE at 3673 IU/mL and hypereosinophilia (40% to 50% of the leukocytes) suggested an HIES.

At 5 years old, the patient was hospitalized for an exacerbation of the eczema, purpuric lesions on the face and the neck (photosensitive zones) (Fig 3), numerous warts on both hands (Fig 4) and the peribuccal area, and nonerosive arthritis and arthralgia of the knees, elbows, and distal and proximal interphalangeal joints.

The assessment revealed anemia, with hemoglobin at 10.4 g/L, and a normal lymphocyte count at 1920 cells/mm³. Rheumatoid factor was normal at 20 IU/mL, and complement fractions C3, C4, and CH50 were normal at 1.35 g/L, 0.11 g/L, and 59 UCH50, respectively. Native DNA antibodies were present. Antinuclear antibodies were positive at 1/840 with homogenous fluorescence. The tests for anti-SSA, anti-SSB, anti-ribonucleoprotein, anti-scleroderma 70 anti-topoisomerase, anti-JO1 (autoantibodies to histidyl-tRNA synthetase localized in the nucleus and cytoplasm), and anti-centromere protein B antibodies were negative. Skin biopsy of facial lesions identified lichenoid dermatitis compatible with chronic lupus erythematosus in its lichenoid variant (Fig 5).

Autoantibodies against anti-β2-glycoprotein 1 were present (immunoglobulin G [IgG], 12 U/mL [normal <5]). Anticardiolipin autoantibodies were positive for IgG at 46 UGPL/mL (normal <10) but negative for immunoglobulin M (<10 U MPL/mL). The level of antiphospholipid autoantibodies was significant (IgG, 31 UGPL/mL [normal <15 UGPL]). Therefore, the diagnosis of SLE associated with AR-HIES and antiphospholipid syndrome was made.

At the age of 8 years, the patient was readmitted for massive proteinuria at 147 mg/kg per 24 hours, suggesting a renal complication related to SLE or renal amyloidosis. A minor salivary gland biopsy detected lymphocytic sialadenitis stage 4 according to the Chisholm and Masson’s classification, with no amyloid deposits (Fig 6). Renal biopsy revealed stage II lupus nephropathy, for which she was treated with corticosteroids for 8 months with a favorable response.

Histopathology of biopsies of enlarged lymph nodes, which were performed at the ages of 3 and 7 years to exclude lymphoma, has shown the loss of follicular architecture, reduced to lymphocyte piles with very few and small germinal centers (GCs). A marked sinusal histiocytosis was observed, with a significant deposit of plasma cells in the sinuses and interfollicular spaces (Fig 7).

At the age of 10 years, she developed her first episode of parotitis. Ultrasonography examination showed bilateral parotid hypertrophy with intraparotid lymphadenopathies. These symptoms regressed after treatment with amoxicillin.
clavulanate. Parotitis episodes recurred 3 times. The child is now 10 years old, and she is receiving hydroxychloroquine (100 mg/day), trimethoprim–sulfamethoxasole (5 mL twice a day), and topical treatments for eczema and skin infection. She has fewer acute respiratory infections but has persistent diffuse planar and tuberous warts (Fig 4). Bone marrow transplantation is being considered for this patient.

GENETICS

Homozygosity mapping with microsatellite markers D9S1858 (p-tel) and D9S917 (at 0.26 cM) revealed that the patient was homozygous at the DOCK8 locus. Therefore, we sequenced by Sanger sequencing all 48 exons of the DOCK8 gene from the patient’s genomic DNA and found a homozygous deletion of 2 nucleotides (c.3059–3060del) resulting in a frameshift at position 1020 of the DOCK8 protein and a premature termination codon 4 amino acids later: Because this mutation is a truncating mutation, no expression of a full-length DOCK8 protein is expected.

COMMENTARY

AR-HIES was identified as a separate entity in 2004 and was linked to mutations in DOCK8 in 2009. Early in the course of the disease and especially in children, the clinical distinction between the 2 forms of HIES (recessive and dominant) is difficult because of the similarity of the first symptoms, such as respiratory tract infections, eczema, and skin infection, combined with elevated levels of serum IgE and eosinophilia. Distinguishing features such as skeletal features (scoliosis, fractures) and dysmorphic characters are not evident until adolescence; for example, retained primary teeth may not be detected until the child is >8 years old.

Clinical diagnosis of AR-HIES in children is based mainly on the lack of formation of pneumatoceles during pneumonias and on the predisposition to viral skin infections. Viral skin infections most commonly seen are severe and sometimes mutilating infections with Herpes simplex, Varicella zoster, Molluscum contagiosum, and human papilloma virus, which are often diffuse and resistant to usual therapies. Some authors have reported efficiency of topical cidofovir for recalcitrant molluscum contagiosum in immunocompromised children. The facies described in AD-HIES are found in recessive forms but are less marked. Our patient did not show any ligament laxity or dental anomalies.
The pathogens isolated in our patient were methicillin-resistant *Staphylococcus aureus*, *Proteus rettgeri*, *Pseudomonas aeruginosa*, *Candida albicans*, human papilloma virus, and herpes simplex virus. In mice, mutation of *DOCK8* cripples B-cell immunologic synapses, GC formation, and long-lived antibody production. Histologically, it is uniformly characterized by a failure of GC formation.12 This aspect was found in our case. Aan de Kerk et al13 recently described an abundant plasmacytosis at sinusal and interfollicular levels and also reported an uncommon follicular hyperplasia. They proposed that the presence of GCs suggests that an intrinsic defect in B-cell development causes the observed accumulation of IgE-producing plasma cells at a post-GC level, hence contributing to the immune phenotype. The abundant histiocytosis observed in our case has never been reported in the literature, and we wonder whether it is secondary to infection or caused by the immune disregulation.

Autoimmune diseases found in our patient are SLE and antiphospholipid syndrome, as revealed by lesions suggestive of lupus at the age of 44 months. Autoimmunity is rarely described as a feature of DOCK8 deficiency, and in particular no association with SLE or antiphospholipid syndrome has been reported yet. However, before molecular diagnosis of HIES was possible, 5 cases of HIES associated with SLE were reported; 3 cases are clinically compatible with an AD-HIES phenotype14–16 and 1 case with a DOCK8 mutation.17 For the last, there was insufficient clinical data to classify the case.18

**CONCLUSIONS**

Autoimmunity and primary immune diseases could be considered sides of the same coin, reflecting different but interconnected faces of immune dysregulation. Thus, the complexity of the clinical picture of some primary immune diseases should not baffle the clinician to the point of missing the diagnosis of associated autoimmune diseases that may warrant specific treatment. Here, we report autoimmunity as part of the clinical features of a patient with HIES, related to a confirmed *DOCK8* mutation.

Allogeneic hematopoietic stem cell transplantation has been reported as curative in DOCK8-deficient patients, with rapid healing and clearance of viral and other infections. It should be considered as early as possible, given the gradual worsening of the disease.19–22 Hematopoietic stem cell transplantation has also shown dramatic positive outcomes in various autoimmune diseases, including SLE.23

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**REFERENCES**


**FIGURE 7**

Lymph node biopsy: hematoxylin–eosin stain (high magnification) showing extensive sinus histiocytosis with significant deposit of plasma cells in the sinuses and interfollicular spaces.
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