

SHORT COMMUNICATION

***DOCK8* Mutation Syndrome: A Diagnostic Challenge for Dermatologists**Joséphine Moreau¹, Sarah Beaussant-Cohen², François Aubin^{1,3}, Pierre-Simon Rohrllich⁴ and Eve Puzeat^{1*}¹Service de Dermatologie, ²Service d'Hématologie Pédiatrique, Centre Hospitalier Universitaire Besançon, 3 Bd Fleming, FR-25030 Besançon, ³EA3181; SFR FED 4234 IBCT, Université de Franche-Comté, Besançon, and ⁴Service d'Hématologie Pédiatrique, Centre Hospitalier Universitaire, Nice, France.

*E-mail: epuzeat@chu-besancon.fr

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Primary immune deficiencies in children may be associated with early diverse cutaneous manifestations (1). Among them, hyper IgE syndrome (HIES) was recently classified into 2 different forms: a well-known autosomal dominant form of *STAT3* mutations (called Job's syndrome) and a recent autosomal recessive form associated with *DOCK8* (*dedicator of cytokinesis 8*) gene mutations (2, 3).

Although the function of Dock8 protein is unclear, severe atopic disease, repeated viral and bacterial infections and cancer predisposition are the main characteristics of *DOCK8* mutation syndrome (4, 5). We report here a new case of *DOCK8* mutation syndrome diagnosed on the basis of dermatological lesions.

CASE REPORT

An 8-year-old boy presented with a history of severe atopic disease, including generalized atopic dermatitis, asthma and different food allergies (cutaneous rashes after ingestion of peanut, mustard and soya, and an anaphylactic reaction after ingestion of egg white). He was the oldest of his siblings. There was no significant familial medical history. He was born of a non-consanguineous marriage. From an early age, he also had repeated ear-nose-throat and pulmonary bacterial infections, none of which led to hospitalization. A failure to thrive (-1.5 standard deviation (SD)) was noted. When he was 3 years old, dermatological examination revealed many flat warts, profuse molluscum contagiosum, resistant *Candida* intertrigo and onychomycosis. One year later, he presented with very profuse flat warts on the face and neck, molluscum contagiosum on both axilla and genital areas, eczema skin lesions of the anterior flexural crease of the elbow (Fig. S1¹) and failure to thrive (body mass index (BMI) 15.86 kg/m²; -1.5 SD).

Based on the cutaneous lesions, an immune deficiency syndrome was suspected. Laboratory results revealed hyper eosinophilia at 8.2 G/l (normal <0.5 G/l), a lymphopaenia CD4 at 400/mm³ (normal $>4,500$ /mm³), a low immunoglobulin M (IgM) level at 0.12 g/l (normal 0.49–1.81 g/l) and a hyper IgE at 607 IU/ml (normal = 1–124 IU/ml). A diagnosis of HIES was made and confirmed by the presence of *DOCK8* mutations and the lack of *STAT3* mutations. Two different heterozygous mutations were detected in the affected child and each parent was carrier of one heterozygous mutation. The patient thus carried a double heterozygous mutation: one from his paternal side (deletion of exons 2–46 of the *DOCK8* gene) and one from his maternal side (deletion of exons 21, 22 and 23). The patient then received a haematopoietic stem cell transplantation (HSCT) from his human leukocyte antigen (HLA)-matched sister. We quickly observed an improvement in the clinical and biological anomalies, de-

spite the use of immunosuppressive drugs. Six months after the transplantation, immunosuppressive drugs were stopped and after one year of follow-up, no recurrence of atopic dermatitis, molluscum contagiosa and flat warts and no ear-nose-throat or pulmonary bacterial infections were observed.

DISCUSSION

Severe atopic disease, repeated viral and bacterial infections and cancer susceptibility are the main characteristics of *DOCK8* mutation syndrome (4, 5), which is associated with a high morbidity and mortality rate.

Aydin et al. (5) recently reported a large international retrospective survey describing the detailed clinical and immunological phenotypes of 136 patients with *DOCK8* gene deficiency. The majority of patients (73%) were from consanguineous Turkish or Arabic families. It should be noted that our patient was born of a non-consanguineous Caucasian family. The most common manifestations were eczema (99%), recurrent respiratory infections (91%) and skin abscesses (84%). A high incidence of life-threatening infections was observed (58%). The causative organisms mainly included *Staphylococcal aureus*, streptococcal pneumonia, *Haemophilus influenzae* and *Pseudomonas aeruginosa*. Among 34 patients who died, 17 (50%) succumbed to severe pneumonia, cerebral infection or sepsis. However, mucocutaneous candidiasis and fungal fingernail infections were more frequent (92%) of cases. Acquired viral infections occurred in 81%, mostly caused by human papillomavirus, herpes simplex virus, varicella zoster virus, or pox virus. Different prophylaxis approaches have been proposed, including immunoglobulins, antibiotics, antiviral and antifungal drugs (5). Allergic disorders were also frequent (71%), including food allergy (85%), followed by asthma (54%), allergic rhinitis (23%), anaphylaxis (16%) and drug allergy (9%). Autoimmune manifestations were observed in 13% of patients (vasculitis and autoimmune haemolytic anaemia). In this large series (5), the authors also reported cerebral events in 14% of patients, mostly vascular (57%), that can be related to the involvement of Dock8 protein within the nervous system (6). Twenty-three patients (17%) had malignancies at a median age of 12 years, including lymphoma (48%) and epithelial tumours (39%), resulting in death in 26% of patients. Almost all patients had eosinophilia (96%) and the me-

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dian serum IgE level was 2,175 IU/ml (normal = 1–124 IU/ml) in 98% of patients. Although our patient did not demonstrate such a high level of IgE, it should be noted that 3 patients with *DOCK8* gene deficiency were previously reported to have normal levels of IgE (5).

Loss-of-function mutations in the *DOCK8* gene are responsible for most forms of autosomal recessive HIES (2, 4, 5). Dock8 protein was found to play an essential role in humoral immune responses and to be important in the proper formation of the B-cell immunological synapse (6). Dock8 protein itself is highly expressed within the immune system. Thus, not surprisingly, patients with *DOCK8* gene deficiency present with multiple abnormalities of the immune system, including defective CD8 T, Natural Killer T cell and natural killer (NK) cell survival and function, impaired generation of Th17 cells, impaired production of antiviral cytokines, and impaired production of antigen-specific antibodies (4, 5, 7). Atopic manifestations can be explained by skewing towards Th2 CD4⁺ T-cell responses that promote allergic disease (8, 9). Similar to many other primary immune deficiencies, *DOCK8* gene deficiency is associated with an increased likelihood of developing cancer (3, 5). In addition to direct oncogenic effects of certain viruses, the increased incidence of cancers in *DOCK8* gene-deficient patients might reflect impaired tumour surveillance resulting from defective CD8 T-cell functions. The possibility that Dock8 protein might have a tumour suppressor function has also been suggested (4, 10).

In contrast to Job's syndrome, *DOCK8* mutation is associated with severe atopic manifestations, such as asthma, eczema, food allergies and severe mucocutaneous viral infections (11). Patients with Job's syndrome more frequently develop cutaneous rash, facial dysmorphism, skeletal abnormalities, and *Candida* infections (Table I). The prognosis of *DOCK8* mutation syndrome is worse than that of Job's syndrome, which justifies an aggressive treatment such as HSCT (12, 13).

In conclusion, early diagnosis of primary immune deficiencies may be based on cutaneous lesions, emphasizing the role of dermatologists. Knowledge of the 2 forms of HIES is important, since the severity of *DOCK8* mutation syndrome justifies bone marrow transplantation.

The authors declare no conflicts of interest.

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Table I. Clinical differences between *DOCK8* deficiency and Job's syndrome (5, 10, 11)

Clinical features	DOCK 8 deficiency	Job's syndrome
Eczematous dermatitis	++++	++++
Newborn rash	+	+++
Coarse facies	–	+++
Retention of primary teeth	–	++++
Joint hyperextensibility	+	+++
Minimal trauma fractures	+	+++
Asthma	+++	+
Allergies	+++	++
Skin staphylococcal abscesses	+++	+++
Mucocutaneous viral infections	+++	+
Mucocutaneous candidiasis	++	+++
Sinopulmonary infections	++++	++++
Elevated serum IgE levels	++++	++++
Eosinophilia	++++	++++
Cerebral event	++	–
Squamous cell carcinoma	++	–
Lymphoma	++	+

Frequency: + (<25% of patients); ++ (25–49%); +++ (50–75%); ++++ (>75%).