

Letter to the Editor

Successful bone marrow transplantation for DOCK8 deficient hyper IgE syndrome

Dear Editor,

We report a girl with AR-DOCK8 deficiency treated successfully with allogeneic bone marrow transplantation (BMT). She was born to consanguineous parents (cousins) originating from and living in eastern Turkey. The first two children of the family were not diagnosed as immunodeficient despite hypereosinophilia and high IgE levels. They had neonatal onset pruritic eczematous dermatitis, food allergies, recurrent and severe pneumonias (LRTI) when they died at five and six yr old, respectively. Sibling 6 (the proband) who was born after three healthy children, presented with severe neurological disease: beginning nearly 6–8 months ago with mild ataxia and gradual deterioration with restlessness, spasticity, progressive hearing, speech and vision loss, hyperactive deep tendon reflexes, Babinsky and clonus. Radiological diagnosis of progressive multifocal leukoencephalopathy (PML) with serial MRI was supported by high JCV-DNA in serum and cerebrospinal fluid (2200 copies/mL). He also was diagnosed with hyper IgE syndrome (HIES) caused by the dermatitis of neonatal onset, severe food allergies, LRTIs and high peripheral blood eosinophilia and serum IgE. There were no pneumatoceles despite recurrent pulmonary infections and cold abscesses nor joint hypermobility. We treated him with i.v. immunoglobulin (IVIG) 400 mg/kg/day for 15 days with no clinical response. As the response to rh-interferon-gamma (rhIFN- γ) stimulation is shown in Tyk-2 deficient patient (1), we gave rhIFN- γ to this patient with PML using 50 μ g/m², $\times$ 3/wk, by sc route. He died at the age of seven yr with sepsis in our intensive care unit.

The last child (DOB: 25 October 2006) of this family also presented with neonatal rash. She developed severe eczema with lichenification since the first months of life. She had multiple food, environmental and drug allergies, including lentil anaphylaxis. At the age of 18 months, she

underwent further investigations after the diagnosis of her brother's JCV infection. She presented with severe disseminated ichthyosiform eczema, ectropion of the eyelids, recurrent LRTI, oral, cutaneous and ungual candidiasis. Fortunately, her brain CT was normal and the serum and CSF did not reveal JCV infection as her brother. High levels of IgE (>10 000 IU/mL) and hypereosinophilia (>5000/ μ L) were persistent. Serum immunoglobulin levels (G: 1580, M: 71 and A: 8.7 mg/dL) were normal except for low IgA for age while lymphocyte phenotyping revealed CD4+ T cell lymphopenia (absolute: 250/ μ L) with CD3+ T cell 28%, CD19+ B cell 60%, CD16+ 56+ NK cell 5% in the peripheral blood. Her serum anti-HBs, antipolio, anti-HSV, anti-CMV, anti-EBV, anti-IgM and anti-IgG antibodies and isohemagglutinins were absent. The girl was also clinically diagnosed as autosomal recessive-HIES and treatment was initiated with IVIG, itraconazole, sulfamethoxazole-trimethoprim and rhIFN- γ for prophylaxis and immune modulation. She was not responding to topical steroids, emollients and oral antihistamines. Genomic DNA of the patient, parents and her brother who died with JCV infection were evaluated for the DOCK8 gene as the possible cause for the phenotype at the Department of Immunology and Molecular Pathology of Royal Free Hospital (London, UK). Engelhardt et al. identified a homozygous large deletion up to and including exon 25 of the DOCK8 gene (c.?_3121-?del), deleting the first half of the gene (JACI 2009;124:1289, patients with codes of ARH016.6, ARH016.7) (2). It could not be understood where the exact beginning of the deletion was; the first deleted exon they detected was exon 3, but as they did not analyze exon 1 and 2, it was concluded that the deletion began before or at the start of the DOCK8 gene.

Because of recurrent sibling deaths, she was considered for hematopoietic stem cell

transplantation (HSCT); however, her LRTI was not responding to antibiotics, diagnosed as pulmonary tuberculosis (TB) by the PCR yield of *Mycobacterium tuberculosis*. After six months of treatment for TB, BMT was performed from her healthy, HLA-identical 17-yr-old sister on 17 March 2011. The conditioning regimen consisted of intravenous busulfan (16 mg/kg, total 280 mg, on days -10 to -7) and cyclophosphamide (200 mg/kg, total 3500 mg, on days -5 to -2). Graft-versus-host disease (GvHD) prophylaxis consisted of cyclosporine A and methotrexate. Cyclosporine was given intravenously until day +21 and then orally. Methotrexate dosage was 10 mg/m²/day, on day +1; +3; and +6. A total of 4.6×10^8 nucleated cells/kg including 6.77×10^6 CD34+ cells/kg was infused. On day +12, she developed disseminated maculopapular rash suggestive of grade 2 GvHD and resolved after an extra dose of i.v. 2 mg/kg of methylprednisolone and continued with tapering 20% per week. Skin biopsy confirmed GvHD. Neutrophil engraftment was achieved on day +20 and platelet engraftment, on day +25. Bone marrow aspiration showed normal maturation on day +30. Immunosuppressive therapy was being tapered after four months and planned to stop at six months; substitutive therapy with IVIG was continuing if IgG level was below 400 mg/dL. A stable 100% donor chimerism was observed at the first and third months after BMT. On the third month after BMT, she was admitted with the complaints of non-febrile seizure, headache, fever, fatigue, dizziness and vomiting. First possible diagnosis was encephalitis or pseudotumour cerebri. However, CSF pressure, culture, biochemistry and cell count in lumbar puncture were all normal. Contrasted BT and MRI and MR venography showed thrombosis in the dural sinus. The symptoms related with dural sinus thrombosis improved within a week and recanalized in the second month with low molecular weight heparin-enoxaparin sodium (dosage: 1 mg/kg/dose; two times per day). Severe ichthyosiform eczema and erythroderma resolved completely within one month after BMT and no infection then occurred. The reintroduction of mixed food did not reveal any allergy except lentil. Nine months after BMT, she is doing well with enoxaparin sodium treatment and with stable engraftment. Anti-TB therapy was discontinued after three months of BMT. The serum IgE level has decreased down to 600 IU/mL and peripheral eosinophils to normal values.

This is the first report of central nervous system thrombosis as a complication of BMT in

a patient with DOCK8 deficiency which is also seen during the disease course of patients with autosomal recessive (AD) and AR-HIES as CNS complications and is usually associated with septic embolus (3). Dural sinus thrombosis developed after the beginning of steroid treatment because of to grade 2 skin GvHD in our patient. She underwent an HLA-identical HSCT after conventional myeloablative conditioning with no toxicity. Complete clinical remission is sustained at the fifth month of BMT. The patient is maintained on a prophylactic dose of enoxaparin which is planned to be continued for six months. This report is the first patient who underwent BMT and also showing the value of BMT as a curative treatment for HIES because of DOCK8 deficiency as in the recent literature (4–7).

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References

1. MINEGISHI Y, SAITO M, MORIO T, et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity* 2006; 25: 745–755.
2. ENGELHARDT KR, MCGHEE S, WINKLER S, et al. Large deletions and point mutations involving the dedicator of cytokinesis 8(DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. *J Allergy Clin Immunol* 2009; 124: 1289–1302, e4.
3. FREEMAN AF, COLLURA-BURKE CJ, PATRONAS NJ, et al. Brain abnormalities in patients with hyperimmunoglobulin E syndrome. *Pediatrics* 2007; 119: 1121–1125.
4. McDONALD DR, MASSAAD MJ, JOHNSTON A, et al. Successful engraftment of donor marrow after allogeneic hematopoietic cell transplantation in autosomal-recessive hyper-IgE syndrome caused by dedicator of cytokinesis8 deficiency. *J Allergy Clin Immunol* 2010; 126: 1304–1305.e3.
5. BITTNER TC, PANNICKE U, RENNER ED, et al. Successful long-term correction of autosomal recessive hyper-IgE syndrome due to DOCK8 deficiency by hematopoietic stem cell transplantation. *Klin Padiatr* 2011; 222: 351–355.
6. GATZ SA, BENNINGHOFF U, SCHUTZ C, et al. Curative treatment of autosomal-recessive hyper-IgE syndrome by hematopoietic cell transplantation. *Bone Marrow Transplant* 2010; 46: 552–556.
7. GALAMBRUN C, CHAMBOST H, LAMOUREUX-TOOTH S, et al. Successful allogeneic hematopoietic stem cell transplantation for DOCK8 deficiency. *J Allergy Clin Immunol* 2011; 128: 420–422.