



Case report

Bone marrow transplantation does not correct the hyper IgE syndrome

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Summary:

Congenital immunodeficiency in hyper IgE syndrome is characterised by a markedly raised IgE level, recurrent staphylococcal skin infection and pneumatoceles. Standard treatments include anti-staphylococcal antibiotics. We report a severely affected patient in whom successful bone marrow transplantation was followed by reappearance of the immunodeficiency. We conclude that bone marrow transplantation does not cure the immunological features of the hyper IgE syndrome. *Bone Marrow Transplantation* (2000) 25, 1303–1305.

Keywords: hyper IgE syndrome; bone marrow transplantation

Case report

Our patient presented aged 1 year with persistent severely infected eczematoid dermatitis and a staphylococcal pneumonia with pneumatoceles. She had the typical facies with a bossed forehead, deep-set eyes and thickened nose and ears and a polyclonal raised total serum IgE (1500 kU/l, reference 0–52). She subsequently suffered recurrent staphylococcal skin infection, as well as recurrent long bone fractures. Despite flucloxacillin prophylaxis, high-dose intravenous immunoglobulin and IFN γ treatment, she required five hospital admissions over 6 months to treat methicillin-resistant staphylococcal and resistant pseudomonas skin infection. At 7 years of age, in view of increasing severity of infection despite adequate treatment, poor

The hyper IgE syndrome (HIE), a multisystem disorder of unknown underlying pathogenesis, is characterised by coarse facies, markedly raised serum IgE level, recurrent staphylococcal skin infection and pneumonia with pneumatoceles; poor dentition, slightly increased bone fragility and connective tissue disorders are also found.¹ Although the primary immunological defect in HIE has remained elusive, recent findings indicate a profound impairment in the regulation of interleukin 4 (IL-4)-dependent IgE production,² confirming previously published data showing defective interferon gamma (IFN γ) production.³ This pattern, however, seems not to be specific as it has been shown in chronic mucocutaneous candidiasis,⁴ another rare primary immunodeficiency of unknown aetiology. The mainstay of conventional management in HIE is aggressive antibiotic treatment and prophylaxis targeting *Staphylococcus aureus*, the known main pathogen in these patients. Both IFN γ ³ and cyclosporin A (CsA)⁵ have been tried as supplementary agents, but no treatment is curative. We present the case of a child with severe HIE in whom bone marrow transplantation (BMT) was performed in the expectation that at least the immunological defect would be cured by replacing the pluripotent haematopoietic stem cells.

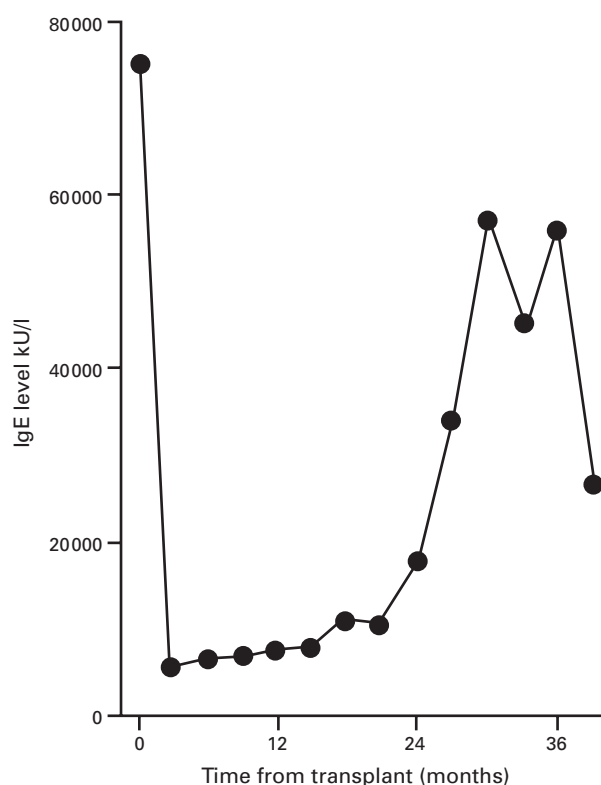


Figure 1 Serum IgE level after BMT. Normal age-related IgE level 0–52 kU/l, CsA stopped at 32 months after BMT.

Table 1 Pre- and post-transplant immunological data

	IgM g/l	IgA g/l	IgG g/l	Tetanus IU/ml	Hib µg/ml	CD3 ^a	CD4	CD8	CD19	NK	Anti-A	Anti-B	PHA ^b
Normal values	0.43–1.9	0.64–2.58	3.8–15.2	>0.1	>1	1400–2000	700–1100	600–900	300–500	200–300			Stimulation index
Pre-transplant	1.5	1.86	12.3	on IVIG	on IVIG	2238	1622	568	243	135			254
42 months post transplant	0.87	2.3	24.1	1.58	1.15	5014	1873	2645	165	331	1/32	1/32	175

^aCells/µl.^bPHA (phytohaemagglutinin) stimulation index: increase over background count.

life quality with increasing periods of school absence because of hospitalisation, and poor long-term outlook, her parents were counselled with regard to BMT. Following cytoreductive conditioning with busulphan 16 mg/kg, cyclophosphamide 200 mg/kg, and Campath 1G monoclonal antibody as *in vivo* T cell depletion, marrow from an unrelated donor matched for 11/12 antigens (DP mismatch) was infused. CsA was used as graft-versus-host disease (GVHD) prophylaxis. Engraftment was uneventful with a neutrophil count $>0.5 \times 10^9/l$ by day 28 post transplant and platelet independence by day 32 post transplant. The lymphocyte count exceeded $0.2 \times 10^9/l$ by day 70 post transplant and molecular DNA studies (PCR enhanced dinucleotide repeat polymorphism, courtesy of A Curtis Northern Genetic Service, Molecular Diagnostic Laboratory, Medical School, University of Newcastle upon Tyne) showed full donor chimerism in all leukocyte lineages (ie neutrophils, T and B lymphocytes, monocytes), as well as subsequently at 12, 24 and 42 months post transplant. Oral herpes simplex infection re-activating on day 56 post transplant was treated with acyclovir and donor-acquired disseminated cytomegalovirus (CMV) infection, indicated by positive urine culture, venous blood antigenaemia and staining of rectal biopsy, on day 146 post transplant was treated successfully with ganciclovir. Biopsy-proven mild gut GVHD on day 128 post transplant was treated with high-dose methylprednisolone (500 mg/m²) for 3 days; no further GVHD occurred. Initially the skin lesions cleared but now, almost 4 years after transplant, she has developed further staphylococcal and pseudomonal skin sepsis. The IgE level has returned to pre-transplant levels (Figure 1). Her main immunological parameters pre and post BMT are shown in Table 1.

Discussion

BMT was successful in so far as molecular DNA studies showed all the myeloid and lymphoid cells derived from haematopoietic stem cells are of donor origin. However, our patient still exhibits the immunological features of HIE. The resolution of symptoms in the immediate post-transplant period may have been secondary to CsA used to prevent GVHD.⁵ It has been suggested that the bony and connective tissue disorders described in HIE are due to cytokine-stimulated and abnormally activated cells of the

monocyte/macrophage lineage.⁶ It seems unlikely that the underlying defect is in the bone marrow haematopoietic stem cell itself, as osteopetrosis, a condition caused by defective macrophage-derived osteoclast function, can be successfully treated by BMT,⁷ but hyper IgE appears not to be. The failure of BMT to correct the immunological defect in HIE suggests another, as yet unrecognised, defect rather than one intrinsic to lymphocyte or monocyte-derived cells, is responsible for driving immunological cells in a Th2 and hence IgE producing direction.

To our knowledge, this is the first bone marrow transplant attempted for this condition. Our experience suggests that successful haematological and immunological reconstitution with donor bone marrow stem cells does not alter the disease process in HIE and invites intriguing questions regarding the underlying pathogenesis of the associated immunodeficiency.

Note added after submission

Since this manuscript was submitted, deficient IL-12/IFN- γ production has been postulated to be responsible for the elevated IgE levels and the variable defects in neutrophil chemotaxis in this disorder.⁸ The editorial article by ER Stiehm⁹ suggested, like our report, that cytokine defects described in this disorder may provide a clue both to its pathogenesis and rational treatment.

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