LETTERS

Farber's disease without central nervous system involvement: bone-marrow transplantation provides a promising new approach

K Ehlert, J Roth, M Frosch, N Fehse, N Zander, J Vormoor

Ann Rheum Dis 2006;**65**:1665–1666. doi: 10.1136/ard.2005.048322

Farber's disease is a lysosomal storage disorder caused by acid ceramidase deficiency.¹ The main symptoms in patients without central nervous system (CNS) involvement (type 2/3), are caused by leucocyte dysregulation,² with impaired apoptosis and signal transduction caused by intracellularly accumulated ceramide, leading to the inflammatory component of this disorder, with swelling of joints, granuloma formation, contractures and inflammatory airway involvement.⁶ Current treatment focuses on pain management, physical treatment, surgical correction of contractures and treatment with anti-inflammatory drugs. In rheumatoid disorders such as juvenile rheumatoid arthritis, immunosuppression or autologous haematopoietic stem cell transplantation (HSCT) can afford a substantial benefit, as treatment is based on suppression of abundant inflammatory

responses by autoreactive T cells. However, these options do not promise a cure for patients with Farber's disease, as the fundamental impairment of cell signalling cannot be influenced by immunosuppressants. Considerable and progressive joint involvement may result in the inability to walk and in repeated surgical procedures to improve mobility and patients usually die in the second decade of their lives as a result of respiratory insufficiency.¹

Two reports of HSCT in patients with Farber's disease were published in 1989³ and 2000.⁴ Both children had a Farber's disease subtype with CNS involvement (type 1) and died of neurological deterioration. HSCT did not provide a benefit, as it could not reduce ceramide neurotoxicity. However, a new immune system by HSCT may correct the abnormal inflammation and thus be an option in Farber's disease, type

Table 1 Transplant-related data

Patient	1, female (MS)		2, male (MS)		3, female (MS)		4, female (HH)	
Age at Tx	3 years, 11 months		3 years, 10 months		2 years		21 years	
Preparative regimen, cumulative dose in mg/kg bw	Bu 12.8 iv/Cy 120 iv		Bu 12.8 iv/Cy 120 iv/ATG 40 iv		Bu 12.8 iv/Cy 120 iv		Bu 12 po/Cy 120 iv/ATG 90 iv	
Donor-stem cell source, dose/kg bw	MRD-BM, 11.3×10^6 CD34		MUD-PBSC, 25×10^6 CD34		MRD-BM, 5.6×10^6 CD34		MRD-BM, 4.2×10^6 CD34	
GvHD prophylaxis	CsA, MTX		CsA, MTX		CsA, MTX		CsA, MTX	
Day of neutrophil engraftment	14		12		18		14	
Acute/chronic GvHD	Grade II of GIT/none		Grade I of GIT/none		Grade II of skin/none		None	
Treatment of acute GvHD	Steroids		Steroids		Steroids and tacrolimus		None	
Infections	<i>Clostridium difficile</i> enteritis, bacteraemia with staphylococci		CMV reactivation		CMV colitis		None	
Toxicities	CsA neurotoxicity		None		CsA-neurotoxicity		Suspected VOD	
Chimerism (%)	91		96		90		99	
Time point of follow-up	Before Tx	Day 450	Before Tx	Day 200	Before Tx	Day 270	Before Tx	Day 958
ESR (1 h)	38	9	53	12	25	13	No data available	
Number of nodules	58	8	39	14	18	0	Pre-Tx nodules mainly dissolved, no new nodules	
Joints with restricted mobility	26	2	24	4	10	4	Almost all joints affected; improvement after HSCT	

ATG, anti-thymocyte globulin; BM, bone marrow; Bu, busulfan; bw, body weight; CsA, ciclosporin A; Cy, cyclophosphamide; ESR, erythrocyte sedimentation rate; GIT, gastrointestinal tract; GvHD, graft-versus-host disease; HH, Hamburg; iv, intravenous; MRD, matched related donor; MS, Muenster; MTX, methotrexate; MUD, matched unrelated donor; PBSC, peripheral blood stem cells; Tx, transplantation; VOD, veno-occlusive disease.

Figure 1 Pre-transplant (A and B) and post-transplant (C) pictures of affected hands (patient 1). Parental/guardian consent was obtained for publication of this figure.

2/3. So far, three patients from Muenster⁵ and one patient from Hamburg⁶ have had transplantation. Table 1 shows their transplant-related data.

A busulfan-based, myeloablative regimen was chosen for all patients, as reduced-intensity conditioning regimens are probably associated with a higher rejection rate in patients with storage disorders.⁷ Treatment-related toxicities were moderate (table 1). Neutrophil engraftment was rapid and permanent. Graft-versus-host-disease (GvHD) prophylaxis consisted of ciclosporin A and a short course of methotrexate either with or without anti-thymocyte globulin. Acute GvHD was controlled by steroids, and no chronic GvHD was observed. In contrast with the natural course of disease, all patients with transplants showed an improvement in mobility, less pain and a considerable gain of function. Before transplant, patient 1 was almost a regular wheelchair user, owing to severe contractures. Figure 1 shows the benefit of HSCT in this patient. Patient 4 was a young woman at the time of her transplant, having a milder course of disease compared with the other patients, which might reflect a different subtype on a molecular basis. The reason for HSCT was the need for numerous surgical procedures in her legs to improve mobility.

Currently, all patients are seen at least twice yearly by the outpatient BMT unit; additionally, all children are evaluated by pediatric rheumatology once yearly. Inflammatory markers (erythrocyte sedimentation rate, leucocyte count, and C reactive protein) are checked regularly; however, no data are available with regard to specific granulocyte activation markers.

Despite these preliminary data and limited experience of haematopoietic stem cell transplantation in patients with Farber's disease without involvement of the central nervous system, the results indicate that for the first time a new and promising treatment modality may be available.

Authors' affiliations

K Ehler, J Vormoor, Department of Pediatric Hematology and Oncology, University Hospital Muenster, Muenster, UK

J Roth, M Frosch, Department of General Pediatrics, University Hospital Muenster, Muenster, UK

N Fehse, N Zander, University Hospital Hamburg-Eppendorf, Hamburg-Eppendorf, Germany

Competing interests: None.

Correspondence to: J Vormoor, Newcastle University, Northern Institute for Cancer Research, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK; h.j.vormoor@ncl.ac.uk

Accepted 4 August 2006

REFERENCES

- 1 Moser HW, Linke T, Fensom AH, Levade T, Sandhoff K. Acid ceramidase deficiency: Farber lipogranulomatosis. In: Scriver CR, ed. *Metabolic and molecular bases for inherited disease*. New York: McGraw-Hill, 2001:3573–85.
- 2 Burek C, Roth J, Koch HG, Harzer K, Los M, Schulze-Osthoff K. The role of ceramide in receptor- and stress-induced apoptosis studied in acidic ceramidase-deficient Farber disease cells. *Oncogene* 2001;**20**:6493–502.
- 3 Souillet G, Guiband P, Fensom AH, Maire I, Zabol MT. Outcome of displacement bone marrow transplantation in Farber's disease: a report of a case. In: Hobbs JR, ed. *Correction of certain genetic diseases by transplantation*. London: COGENT, 1989:137–41.
- 4 Yeager AM, Armfield-Uhas K, Coles CD, Davis PC, Krause WL, Moser HW. Bone marrow transplantation for infantile ceramidase deficiency (Farber disease). *Bone Marrow Transplant* 2000;**26**:357–63.
- 5 Vormoor J, Ehler K, Groll AH, Koch HG, Frosch M, Roth J. Successful hematopoietic stem cell transplantation in Farber disease. *J Pediatr* 2004;**144**:132–4.
- 6 Burck U, Moser HW, Goebel HH, Gruttnar R, Held KR. A case of lipogranulomatosis Farber: some clinical and ultrastructural aspects. *Eur J Pediatr* 1985;**143**:203–8.
- 7 Peters C, Balhazor M, Shapiro EG, King RJ, Kollman C, Hegland JD, et al. Outcome of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. *Blood* 1996;**87**:4894–902.

Pyridoxine toxicity courtesy of your local health food store

C D Silva, D P D'Cruz

P yridoxine or vitamin B6 is a highly water-soluble vitamin that plays an important part in the functioning of many enzymes, especially those involved in amino acid metabolism. A normal adult will require 1–2 mg of pyridoxine per day. This is adequately supplied by a normal diet. Requirements are increased in pregnancy, in malnourished patients and in patients who are taking drugs that cause a depletion of pyridoxine—for example, isoniazid, theophyllines and penicillamine.

Pyridoxine toxicity is a recognised cause of sensory neuropathy. Schaumburg *et al* described sensory neuropathy after pyridoxine misuse in 1983.¹ It can occur with chronic use of pyridoxine supplementation over several years, and also with acute over-dosage with parenteral pyridoxine.² It is used to produce an animal model of sensory neuropathy, because unlike drugs such as cisplatin, which also cause sensory neuropathy, it does not cause systemic toxicity.

We recently saw a patient who had been taking vitamin B supplements from a health food store for the past 10 years. She had developed a peripheral sensory neuropathy affecting her hands and feet. She has had systemic lupus erythematosus for 20 years, which was initially thought to be the underlying cause of her neuropathy although her disease seemed to be in

remission. However, when her vitamin supplements were reviewed, it was noted that they contained 50 times the recommended daily amount of pyridoxine.

She was advised to stop the vitamin B supplements, and in the following months, her neuropathy slowly resolved.

Patients with systemic lupus erythematosus are at risk of peripheral neuropathy, and pyridoxine toxicity should be considered in the differential diagnosis, especially if no other cause is identified. This case highlights the problems with over-the-counter drugs, which are often not mentioned by the patients. When there is a possibility of toxicity with excessive intake of supplements, the recommended daily allowance should not be exceeded.

Authors' affiliations

C D Silva, D P D'Cruz, The Louise Coote Lupus Unit, St Thomas' Hospital, London, UK

Competing interests: None declared.

Correspondence to: D P D'Cruz, The Louise Coote Lupus Unit, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK; david.d.cruz@kcl.ac.uk

Accepted 20 May 2006