Dupuytren's contracture versus carpal tunnel release may account for less than one tenth of the 600% increase. It is also relevant that hypoxanthine concentrations were higher in the cellular areas of Dupuytren's contracture tissue as it is from these areas that the proliferative process is thought to arise.

Xanthine oxidase activity was also found in Dupuytren's contracture palmar fascia, establishing a potential for oxygen free radical production by the xanthine oxidase-hypoxanthine reaction.

These results support our hypothesis that in Dupuytren's contracture palmar fascia high concentrations of hypoxanthine may react with xanthine oxidase located in the endothelial cells[8] of narrowed microvessels[4] to release oxygen free radicals.[14] These free radicals may then damage the perivascular connective tissue and induce a reparative response by surrounding fibroblasts. Alternatively free radicals may directly stimulate proliferation of fibroblasts. We have added free radicals to fibroblasts cultured from Dupuytren's contracture palmar fascia and found, like others,[10 11] that high concentrations of free radicals are toxic, but that in contrast lower concentrations stimulate fibroblast proliferation.[16] The proliferating fibroblasts may then be responsible for the increase in type III collagen seen in Dupuytren's contracture and the early stages of normal wound healing.[17 18]

There is increasing evidence to suggest that acute ischaemic damage is mediated by oxygen free radicals.[12 13] We propose that free radical damage may also occur in chronic ischaemic settings, leading to fibroblast proliferation and localised fibrosis. Our findings also suggest that allopurinol by binding to xanthine oxidase and hence preventing free radical release may be useful in both chronic and acute ischaemia and in Dupuytren's contracture.[14]

We are indebted to the patients and surgeons of the Nuffield Orthopaedic Centre for the tissue specimens and to Dr James Crabbe and Dr Roger Smith for valuable advice. GACM is supported by the Rhodes Trust.

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(Accepted 25 September 1987)

Treatment of Niemann-Pick disease type B by allogeneic bone marrow transplantation

A VELLODI, J R HOBBS, N M O'DONNELL, B S COULTER, K HUGH-JONES

Abstract

Allogenic bone marrow transplantation was carried out on a 3 year old girl with Niemann-Pick disease type B. Successful engraftment was achieved, and nine months after the procedure there was definite clearing of the sphingomyelin from the liver and pronounced clearing from the bone marrow.

Any patient with Niemann-Pick disease type B complicated by early or severe hepatic impairment should be considered for bone marrow transplantation.

Bone Marrow Transplant Unit, Westminster Children's Hospital, London SW1
A VELLODI, MRCP, junior lecturer
J R HOBBS, FRCPATH, FRCP, professor and director of unit
K HUGH-JONES, MD, FRCP, senior consultant paediatrician

Department of Histopathology, Westminster Hospital, London SW1
N M O'DONNELL, MB, BAO, registrar

Alder Hey Children's Hospital, Liverpool L12 2AP, and Liverpool School of Tropical Medicine
B S COULTER, MD, FRCPI, honorary consultant paediatrician, senior lecturer in tropical paediatrics

Correspondence to: Dr Vellodi.

Introduction

Niemann-Pick disease type B is a lysosomal storage disorder characterised by a deficiency of sphingomyelinase resulting in the accumulation of sphingomyelin in tissues, particularly the bone marrow, liver, spleen, and lungs, but with no discernible neurological abnormality.[1]

We report a case of Niemann-Pick disease type B treated by displacement bone marrow transplantation.

Case report

An 8 month old white girl was diagnosed as having Niemann-Pick disease after investigations for an enlarged liver and spleen. The diagnosis was confirmed by finding a very low level of sphingomyelinase activity in her leucocytes. The absence of any obvious neurological impairment placed her

in group B. At the time of referral she was an only child and therefore not considered suitable for a transplant. A brother, however, was born a year later and was found to be HLA identical. The mixed lymphocyte reaction was non-reactive and we therefore decided that the patient should have a transplant.

At the time of admission the patient was aged 3 years 2 months. She was developmentally normal, and height and weight were between the third and 10th centiles. The liver was palpable 10 cm below the costal margin, and the spleen 14 cm. Examination of the central nervous system showed nothing untoward; the fundi were normal.

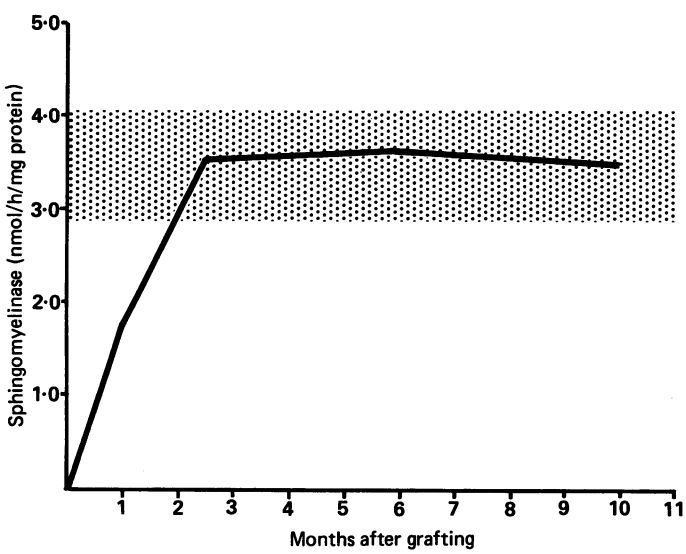
Investigations showed a normal full blood count but slightly raised liver enzyme activities (alkaline phosphatase 291 U/l, aspartate transaminase 43 U/l, alanine transaminase 72 U/l). On liver biopsy the parenchyma showed extensive accumulation of sphingomyelin in hepatocytes and Kupffer cells with early nodule formation. The architecture was comparatively well preserved, though there was some fibrosis between the lobules. Bone marrow trephine biopsy showed evidence of similar deposition with some normal haemopoeitic tissue. White cell sphingomyelinase activity was very low (0·44 nmol/h/mg protein; normal 2·17-5·27). Radiography showed a diffuse interstitial infiltrate in the lungs.

Displacement bone marrow transplantation was carried out after conditioning with busulphan and cyclophosphamide.[2] In between she received an infusion of donor buffy coat, an immunoprophylactic manoeuvre used while T cell help is still operational. Should any recipient lymphocytes have reacted to the normal enzyme and transformed they would have been destroyed by the ensuing cyclophosphamide regimen.[3] Intravenous cyclosporin was not begun until three days before grafting. The total nucleated cell dose that she received from her donor was $4{\cdot}2\times10^8$/kg.

The post-transplantation period was complicated by severe, predominantly cutaneous graft versus host disease, Gram negative septicaemia, and two episodes of interstitial pneumonitis, one of which was proved to be caused by cytomegalovirus. She continued to have problems with chronic graft versus host disease, hypertension, and fluid retention for several months after grafting. Successful engraftment was evidenced by finding male chromosomes on the 26th day and rising levels of leucocyte sphingomyelinase activity after grafting (figure).

On review at six months her liver and spleen were smaller. The liver showed little or no change in the amount of sphingomyelin with some fibrosis. There was a considerable reduction in the amount of storage material in the bone and normal haemopoiesis. At nine months the liver measured 7 cm and the spleen 8 cm below the costal margin, representing a substantial reduction in size. The liver showed a pronounced decrease in the amount of sphingomyelin, which appeared to be concentrated in the fibrous bands. Bone marrow trephine biopsy showed a dramatic decrease in "Niemann-Pick" cells. Radiologically there was definite clearing of the infiltration in the lungs. The patient's growth and development had remained entirely satisfactory throughout.

Staining techniques—Bone marrow trephine samples were fixed in Helly's medium for 24 hours, processed in absolute alcohol, and embedded in JB4 resin. Sections were cut at 1 μm and stained with haematoxylin and eosin, Gomori's reticulin, Giemsa, Perls's, Masson's trichrome, and toluidine blue. Liver biopsy samples were fixed in 10% buffered formaldehyde, routinely processed in paraffin wax, and sections cut at 3 μm and stained with haematoxylin and eosin, reticulin, Perls's, periodic acid Schiff with and without diastase, orcein, toluidine blue, and Masson's trichrome.



Rise in leucocyte sphingomyelinase activities after grafting. Shaded area represents 2 SD.

Discussion

Six types of Niemann-Pick disease have been described,[1] of which only types B and E are consistently free of neurological manifestations. Daloze *et al* attempted orthotopic liver transplantation in a patient with Niemann-Pick disease type A with less than satisfactory results.[4] Gartner *et al* attempted liver transplantation in a patient with neurovisceral storage disease with supranuclear ophthalmoplegia, a variant of Niemann-Pick disease in which sphingomyelinase activities are normal. No improvement was noted and the patient continued to regress.[5]

Sakiyama *et al* carried out bone marrow transplantation on Niemann-Pick mice.[6] Some reduction in sphingomyelin was obtained in the liver and a substantial reduction in the spleen and bone marrow. Sphingomyelin concentrations in the brain were not measured; however, neurological deterioration was not arrested.

In none of the above cases was immunoprophylaxis carried out. Possibly, therefore, the failure to modify the neurological manifestations was due to the formation of antibodies to the enzyme.[7]

Niemann-Pick disease type B is not associated with neurological disturbance but is associated with pronounced hepatic impairment.[8-12] It appears that children who present with early and severe liver disease die of this complication within a very short time.[8] We therefore decided that there were sufficient grounds for bone marrow transplantation in our patient.

We believe this to be the first recorded case of Niemann-Pick disease to have been treated by bone marrow transplantation. The three main objectives of transplantation in a patient with a lysosomal storage disorder are (*a*) to provide a lifelong source of the missing enzyme, (*b*) to prevent the formation of antibodies to the enzyme, and (*c*) to clear the abnormal storage material and prevent further accumulation. We think that we have achieved these objectives, albeit slowly. In Gaucher's disease we have noted more rapid clearing, though Gaucher cells are still evident up to three years after transplantation.[13]

In conclusion, we consider that bone marrow transplantation was justified in our patient. Nevertheless, Niemann-Pick disease is associated with reasonable life expectancy in the absence of liver disease. Clearly, therefore, bone marrow transplantation should be reserved for patients with early and severe liver disease.

We thank Dr G Besley, of Edinburgh, for the sphingomyelinase assay.

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(Accepted 29 September 1987)