

Importance of neurological assessment before bone marrow transplantation for osteopetrosis

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Abstract

Neurological complications of malignant infantile osteopetrosis are well recognised; successful bone marrow transplantation, when performed early in life, can prevent or halt some of them. In a subgroup of infants osteopetrosis is associated with primary retinal degeneration and/or generalised neurodegeneration. Bone marrow transplantation, in spite of being successful in correcting the osseous and haematological abnormalities, does not influence the progressive course of the neurodegenerative disorder. Thus, the recognition of this subgroup of infants with a very poor prognosis is essential before deciding on bone marrow transplantation.

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Keywords: osteopetrosis; retinal degeneration; generalised neurodegeneration; bone marrow transplantation

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Autosomal recessive infantile ("malignant") osteopetrosis is a group of rare inherited diseases caused by defective bone resorption by osteoclasts resulting in increased bone density. The clinical expression is variable and affected children usually have severe manifestations of abnormal bone remodelling (poor growth, brittle bones, delayed tooth eruption, macrocephaly, and frontal bossing), deficient and extramedullary haematopoiesis (anaemia and hepatosplenomegaly), neurological impairment (blindness, deafness, developmental delay, and hydrocephalus), and susceptibility to infections; early death is common, with only 30% survival at 6 years of age.¹ The only effective treatment is bone marrow transplantation (BMT), which corrects the osseous and

haematological abnormalities and can also halt or prevent the neurological complications caused by nerve entrapment.² However, in some children primary retinal degeneration (either isolated or as part of a generalised neurodegenerative disorder), rather than compression of the optic nerve, has been described as a cause of blindness.^{1,3,4} Because it has been shown that successful BMT has no effect on the progressive course of the neurodegenerative disorder associated with infantile osteopetrosis,^{1,5} careful neurological evaluation of children referred for BMT is essential before reaching a decision about this procedure.

Patients

Five infants with infantile osteopetrosis were referred to us for BMT between 1992 and 1996. All had radiographically demonstrated generalised osteosclerosis, anaemia, hepatosplenomegaly, and normal renal tubular function. Bone marrow examination revealed overproliferation of osteoclasts in three patients, but virtually no osteoclasts were present in two patients (patients 4 and 5). Patient 3 had undergone bilateral surgical optic nerve decompressions before being referred to us. Their presentations varied and included hypocalcaemic convulsions (patients 1 and 5), recurrent upper respiratory infections (patients 2, 3, and 5), and lethargy and poor feeding (patients 4 and 5). Table 1 shows the results of the detailed neurological assessments.

Patient 4, a male infant of consanguineous parents, had severe visual impairment with optic atrophy, abnormal retinal pigmentary changes, absent visually evoked responses, hypertonicity, microcephaly, and marked cerebral atrophy. Because of the early onset of severe neurological impairment, his

Table 1 Neurological assessments of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at diagnosis	3 weeks	5.5 months	6 weeks	2 weeks	3 months
Age at referral	4 months	6 months	9 months	7 weeks	5 months
Sex	Female	Male	Male	Male	Male
Neurological findings					
OFC (centile)	75	90	3	< 3	> 90
Length (centile)	25	50	3	3	9
Features	Normal	Delay in head control	Mild motor delay	Spastic tetraplegia	Developmental delay
Brain imaging					
CT	Normal	Ventricular dilatation	Normal	Marked cerebral atrophy	Mild cerebral atrophy
MRI	NA	NA	NA	Cerebral atrophy	NA
Ophthalmological findings					
Clinical	Normal	Normal	Roving nystagmus	Roving nystagmus	No eye contact/"blind"
Fundoscopy	Normal	Normal	Optic atrophy	Optic atrophy, retinal depigmentation	Normal
VER	Normal	Normal	Delayed/attenuated	Absent	Delayed/ broadened
ERG	Normal	Normal	Normal	NA	Normal
ENT findings					
AER	Normal	Normal	Absent	Normal	Normal

AER, auditory evoked response; CT, computed tomography; ENT, ear, nose and throat; ERG, electroretinogram; MRI, magnetic resonance imaging; NA, not available; OFC, occipitofrontal circumference; VER, visually evoked response.

investigation was broadened to include neurodegenerative disorders, but his electroencephalogram, white cell lysosomal enzyme assays, and electron microscopy of skin biopsy showed no abnormalities. Our joint decision was that BMT was not indicated for this infant and he was discharged to his referring hospital with suggestions of palliative treatment with limited calcium intake and corticosteroids. Patient 5 had signs of developmental delay with visual impairment but normal hearing and his brain computed tomography results showed mild cerebral cortical atrophy. His fundi appeared normal, his visually evoked potential showed delayed and broadened flash responses, and his electroretinogram showed a normal response under photopic conditions but an attenuated response under scotopic conditions, possibly as a result of the less than ideal light exclusion at the time. After detailed evaluation, the joint opinion was against the diagnosis of neurodegenerative disorder and the patient underwent BMT, as did the first three patients from our series. Although successfully engrafted, unfortunately, patient 5 died on day 22 after transplantation of progressive veno-occlusive disease of the liver. His postmortem examination, including neurohistology, showed no evidence of lysosomal storage disorder.

Discussion

Generalised neurological impairment has been recognised in children with osteopetrosis and can vary from mild motor delay, often with macrocephaly and mild ventricular dilatation, to severe psychomotor retardation.¹ Sensorineural deafness can occur owing to bony compression of the VIII nerve; however, conductive deafness has been reported more commonly either as a result of sclerosis of the middle ear ossicles or poor drainage of the eustachian tube.⁶ The commonest and often earliest neurological manifestation of infantile osteopetrosis is visual impairment, which is present in 75% of patients by the 1st year of life.¹ In the largest reported series of patients, 87% had irreversible visual impairment despite successful BMT and bone clearing; this indicates the need for BMT as soon as possible after diagnosis, preferably before 3 months of age.^{1,2} Surgical decompression of the optic nerves has been shown to improve visual function in some patients; however, this procedure should not delay BMT.² Although the visual loss has usually been attributed solely to optic atrophy secondary to bony compression of the optic nerve, it can be caused by primary retinal degenera-

tion, either isolated or as a part of a progressive generalised neurodegenerative disorder.^{1,3,4} In some children, the association of osteopetrosis with neuronal ceroid lipofuscinosis has been documented,⁴ and in others osteopetrosis was associated with infantile neuroaxonal dystrophy.³

The form of infantile osteopetrosis associated with retinal or generalised neurodegeneration characterises a separate disease entity with a very poor prognosis.² A report of two such patients who died, after successful BMT, of progressive neurodegenerative disease emphasises the importance of recognition of this disorder,^{2,5} and two of our patients (patients 4 and 5) demonstrated the need for very careful and detailed evaluation before the decision about BMT is made. To determine the cause of visual loss, even in the presence of optic atrophy, full ophthalmological assessment including electrophysiological testing (measurement of visually evoked responses and electroretinography) is required.⁷ Cranial imaging is mandatory, preferably with magnetic resonance scanning because it is better than computed tomography at detecting white matter degeneration.⁶ Tests to exclude known neuronal storage disorders (vacuolated lymphocytes on the blood film, white cell enzyme assays, skin or rectal biopsy for electron microscopy and histochemical analysis, and electroencephalography) should be considered if children present early and with major neurological abnormalities. A paediatric neurologist, ophthalmologist, and otorhinolaryngologist should be involved in the clinical evaluation of these patients.

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