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CASE REPORT

Haematopoietic stem cell transplantation does not retard disease progression in the psycho-cognitive variant of late-onset metachromatic leukodystrophy

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Abstract Haematopoietic stem cell transplantation has an unproven role in the management of late-onset metachromatic leukodystrophy: theoretically justified through the engraftment of enzyme-replete haematopoietic progenitors and restoration of capacity for sulphatide catabolism in neural tissue through enzyme recapture, the long-term outcome is unknown. The rarity of the psycho-cognitive variant and slow progression of late-onset disease impairs evaluation of treatment. We report detailed clinical and neuropsychological assessments after haematopoietic stem-cell transplantation in a patient with a late-onset psycho-cognitive form of metachromatic leukodystrophy. Cognitive decline, indistinguishable from the natural course of the disease, was serially documented over 11 years despite complete donor chimaerism and correction of leukocyte arylsulphatase A to wild type values; subtle motor deterioration was similarly noted and progressive cerebral volume loss was evident upon magnetic resonance imaging. Sensory nerve conduction deteriorated 17 months post-transplantation with apparent stabilisation at 11-year review. Haematopoietic stem-cell transplantation was ineffective for this rare attenuated variant of metachromatic leukodystrophy. In the few patients identified pre-symptomatically or with early-phase disease, clear recommendations are lacking; when transplantation is considered, umbilical cord blood grafts from enzyme-replete donors with adjunctive mesenchymal stem cell infusions from the same source may be preferable. Improved outcomes will depend on enhanced awareness and early diagnosis of the disease, so that promising interventions such as genetically modified, autologous stem cell transplantation have the best opportunity of success.

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Introduction

Haematopoietic stem cell (HSC) transplantation has been employed in the management of metachromatic leukodystrophy (MLD) [OMIM: 250100] for over 20 years (Bayever et al 1985). Predicated on repopulating the nervous system with donor microglial precursors and redressing the pathogenic arylsulphatase A (ARSA) [EC: 3.1.6.8] deficiency (Sevin et al. 2007; Biffi et al. 2008), outcomes are variable and the benefit in late-onset disease remains uncertain. However, different sources of donor cells, notably umbilical cord blood (UCB) and genetically transduced stem cells with enhanced ARSA expression,

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offer the possibility for improved therapeutic efficacy in this disorder (Sevin et al. 2007; Biffi et al. 2004, 2008; Martin et al. 2007).

Impaired cognitive functioning is usually a feature of MLD but has seldom been documented in detail using objective, standardised tests before and after treatment. We report progressive cognitive decline over 11 years, indistinguishable from the natural disease course, in a young woman with MLD of the psycho-cognitive type, successfully engrafted with haematopoietic stem cells from an HLA-matched donor, suggesting this treatment has little benefit in this form of late-onset MLD.

Case report

A previously fit, 23-year-old woman presented with acute cognitive decline over 5 years with progressive frontal lobe dysfunction and disordered executive functioning, short- and intermediate-term memory impairment, impulsivity, regressive behaviour and emotional lability. Pre-symptomatic academic performance was within the 5th percentile. At presentation, motor examination was normal. Electroencephalography showed anterior predominant, background slowing, and magnetic resonance imaging revealed mild volume loss with symmetrical frontal and periventricular white matter hyperintensities on T2-weighted sequences (Fig. 1). There was marked deficiency of leukocyte ARSA activity [2 nmol mg protein^{-1} h^{-1} (reference range 34–117)], and a sural nerve biopsy showed metachromatic deposits in Schwann cells and macrophages. Molecular analysis of the ARSA gene [HGCN: 713] found a novel mutation (D281Y) in combination with the previously described I179S mutation (Halsall et al. 1999). Neurophysiology indicated a mild demyelinating, sensorimotor polyneuropathy. Baseline and serial neuropsychological assessments are depicted (Table 1).

Allogeneic haematopoietic stem cells derived from the peripheral blood of an HLA-matched, unrelated donor with normal ARSA activity were infused 9 months from presentation following reduced intensity conditioning with busulphan, cyclophosphamide and anti-thymocyte globulin. Complete cellular engraftment with restoration of leukocyte ARSA activity [61 nmol mg protein^{-1} h^{-1} (34–117)] was confirmed after 6 weeks.

Since transplantation, leukocyte ARSA activity has remained within the normal range; full donor chimaerism has been sustained. The patient continues to reside with her parents and, although independent with routine self-care, requires close supervision. Limited insight is retained, reflected in episodic frustration and low mood. However, inappropriate familiarity and gregariousness dominate her behaviour. Neurological examination reveals mild dysmetria and symmetrically brisk myotatic reflexes; sensation is intact for all modalities. Deterioration of sensory nerve conduction occurred 17 months post-transplantation with apparent stabilisation at 11-year review. Serial magnetic resonance imaging shows persistent signal abnormalities with progressive volume loss. Cognitive decline has continued unabated (Table 1).

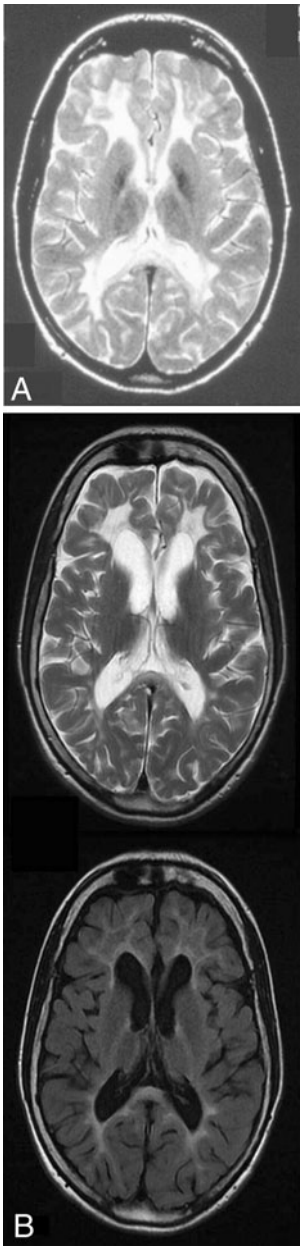

Fig. 1a, b Pre-transplantation and post-transplantation cerebral magnetic resonance imaging. **a** A T2-weighted axial image performed pre-transplantation shows white matter volume loss with symmetrically distributed high signal. A frontal predominance is seen with posterior involvement also present and sparing of the subcortical U-fibers. **b** T2-weighted and fluid attenuated inversion recovery sequences performed 10 years and 6 months posttransplantation show progression of white matter disease with further volume loss and persistence of signal abnormality; movement artefact is present

Discussion

In MLD, defective lysosomal digestion of sulphatide and other sulpholipids due to deficiency of the enzyme ARSA is linked to demyelination in the peripheral and central nervous system. Two principal clinical forms are recognised

Table 1 Neuropsychological assessment

	Date of assessment[a]						
	−5 Months	+4 Months	+13 Months	+20 Months	+30 Months	+75 Months	+122 Months
Mini Mental State Examination[b]	27*	26*	23**	21**	–	12**	–
Graded Naming Test[c]	21	19	–	–	–	8***	5***
Wechsler Adult Intelligence Scale[d]							
WAIS-R/III Vocabulary	11	9*	–	–	–	8*	–
WAIS-R/III Similarities	7*	7*	–	–	7*	5**	–
WAIS-R/III Arithmetic	6*	5**	2***	–	–	2***	–
WAIS-R/III Block Design	5**	4**	2***	–	–	1***	–
WAIS-R/III Digit Symbol	–	5**	–	–	–	2***	1***
WAIS-R/III/WMS-R Digit Span	5**	5**	3***	–	–	3***	4**

Asterisks indicate estimated degree of abnormality, taking into account patient's age and educational background: *mild impairment, **moderate impairment, ***marked impairment

[a] Assessment dates relative to haematopoietic stem cell transplantation

[b] Maximum score = 30

[c] Maximum score = 30

[d] Wechsler age-scaled scores shown (normal = 10, standard deviation = 3)

in adult-onset disease: an attenuated psycho-cognitive form characterised by psychiatric (usually psychotic) features with slow cognitive decline and a motor variant with pyramidal and cerebellar manifestations, commonly accompanied by progressive peripheral neuropathy. Overlap syndromes occur—especially with advancing disease (Rauschka et al. 2006).

HSC transplantation is theoretically justified by the phenomenon of secretion-recapture, in which complementing enzyme from donor cells is taken into the lysosomes of the deficient recipient from the extracellular milieu by receptor-mediated endocytosis; this is evidenced in MLD fibroblasts by correction of ARSA deficiency and clearance of stored sulphatide in vitro (Porter et al. 1971). Repopulating bone marrow with healthy haematopoietic progenitors replenishes the monocyte-macrophage lineage with microglial precursors competent for the degradation of myelin sulpholipids; additionally, donor microglia and migrating macrophages secrete ARSA, restoring capacity for sulphatide catabolism to neural tissue through enzyme recapture (Sevin et al. 2007; Biffi et al. 2008).

Whilst bone marrow transplantation is ineffective in early-onset MLD (Sevin et al. 2007), its therapeutic position in late-onset disease remains unclear; slower progression attributed to residual enzyme activity may favour transplantation, but reported outcomes vary and long-term data are limited. Despite slight improvement in the immediate post-transplantation period, our patient has shown unremitting cognitive decline. Cognitive dysfunction, with a relative lack of additional neurological features, is typical of patients heterozygous for the I179S mutation (Rauschka et al. 2006). Whilst we are unaware of any case where rapid deterioration has reverted to more indolent disease without intervention, this cannot be excluded. However, it appears more likely that early improvement reflected resolution of an acute psychotic episode or self-limiting delirium. Furthermore, the impact of transplant-associated immunosuppression cannot be discounted (Nevo et al. 1996), and the short time between transplantation and improvement cannot easily be attributed to the procedure itself.

Cognitive improvement has been reported in a 28-year-old woman with a slowly dementing phenotype; 4 years after transplantation, disinhibited behaviour decreased and full scale intelligent quotient increased marginally with particular effects on verbal performance (Solders et al. 1998). Peripheral nerve conduction also improved and MRI appearances were unchanged; 11 years later the disease appeared static (Ringden et al. 2006). In our patient, initial improvement in behaviour was also noted with strength in verbal skills an early feature. However, these abilities regressed alongside other cognitive parameters. Arrest of cognitive decline has also been reported in a 16-year-old boy with symptomatic juvenile disease, 8 years after bone marrow transplantation; imaging revealed a marginal increase in cerebral atrophy without altered leukodystrophy (Kidd et al. 1998). Similarly, 4-year follow-up in a 24-year-old patient with late-juvenile disease after bone marrow transplantation from a matched carrier sibling noted stabilisation of neurophysiological parameters and subtle improvement on neuroimaging; however, cognitive decline continued (Navarro et al. 1996). To our knowledge, the

longest follow up of a patient receiving bone marrow transplantation for late-onset was reported 13 years after transplantation; disease progressed for 2 years without further decline noted over this period (Gorg et al. 2007).

Failure to ameliorate late-onset MLD has also been documented (Ringden et al. 2006; Kapaun et al. 1999; Hoogerbrugge et al. 1995), and indolent progression cannot be excluded in any case. A review of the European Group for Bone Marrow Transplant Registry reported progression in all six cases transplanted for MLD, including three with juvenile-onset disease (Hoogerbrugge et al. 1995). A 20-year institutional experience of bone marrow transplantation included three patients with juvenile-onset disease and one of the previously reported adult-onset cases (detailed above) (Solders et al. 1998); after 12 years, one patient with early-phase juvenile disease appeared to stabilise, but the remaining patients progressed (Ringden et al. 2006).

Poor outcomes are attributed to restricted permeability of the blood-brain barrier to circulating enzyme, limiting supply to infiltrating microglia and macrophages (Sevin et al. 2007; Biffi et al. 2008); sequelae of incomplete engraftment and graft-versus-host disease may also play a role (Gaipa et al. 2003). Of particular importance is the 6–12 month delay between transplantation, engraftment and repopulation of ARSA replete microglia, during which progressive injury can obscure benefit gained from later increases in enzyme activity (Biffi et al. 2008). Whilst this effect is most critical in fulminating disease, it remains true for the slowly progressive, late-onset variants; such patients have appreciable residual enzymatic activity and ablation of endogenous cells may contribute to deterioration in the early post-transplantation period.

Despite less-than-conclusive results after standard HSC transplantation in late-onset MLD, there have been encouraging technical advances. Donor grafts utilising UCB stem cells sourced from relatives or registered tissue banks have shown early promise in several lysosomal diseases including MLD (Martin et al. 2007; Escolar et al. 2005; Pierson et al. 2008). When transplanted within the first month of life, pre-symptomatic children with infantile-onset Krabbe disease showed delayed symptom onset, retardation of disease and improved neuro-cognitive function; older patients with juvenile disease also benefited (Escolar et al. 2005). Similarly, among 14 MLD patients receiving UCB transplantation at a median age of 5.2 years (range: 0.17–16.4 years), those with mild disease maintained cognitive function at pre-treatment levels, although motor skills declined; no benefit was seen in children with more severe disease (Martin et al. 2007). Long-term results of UCB transplantation are not yet available, but these reports allow cautious optimism. Access to transplantation facilitated by UCB banks is improving and transdifferentiation of the more primitive stem cell content of UCB into neuronal tissue and glia as well as cells of haematopoietic lineage occurs. Improved engraftment, a decreased frequency of mixed chimaerism, lower rejection rates and reduced graft-versus-host disease may also contribute to improved outcomes (Boelens 2006).

Adjunctive mesenchymal stem cell (MSC) infusions from the same donor as the initial HSC graft have been advocated given their high enzyme activity, ability to enter the brain and capacity for transdifferentiation; in six patients with MLD, improved peripheral nerve conduction was temporally related to MSC infusion, although there was no impact upon cerebral disease (Koc et al. 2002). Nevertheless, restoration of the recipient's Schwann cell population through differentiation of donor stem cells has the potential to improve disabling peripheral neuropathy. In utero HSC transplantation has been considered attractive following success in congenital immunodeficiency states (Shields et al. 2002). However, in utero procedures carry high risk and are of limited practical use, requiring antenatal recognition of this rare disease. Perhaps the greatest promise for future patients is the application of gene transfer technology; autologous haematopoietic stem cells engineered to express supraphysiological levels of ARSA can be transplanted without risk of rejection. The success of this approach has been demonstrated in genetically modified mice with MLD; superior results compared to wild type HSC transplantation were seen (Biffi et al. 2004). Phase I/II clinical trials of this strategy are currently in development, and the outcomes are awaited (Biffi et al. 2008).

Current methods of HSC transplantation offer little benefit in late-onset MLD. In the few patients identified pre-symptomatically or with early-phase disease, clear recommendations are lacking; where transplantation is contemplated, UCB grafts from enzyme-replete donors with adjunctive MSC infusions from the same source may be preferable. Improved outcomes are dependent upon enhanced awareness of disease, with early diagnosis offering the best chance for effective intervention and perhaps the greatest opportunity for success resting with the development of genetically modified, autologous stem cell transplantation.

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