Case report

Improved peripheral nerve conduction, EEG and verbal IQ after bone marrow transplantation for adult metachromatic leukodystrophy

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Summary:

A 28-year-old woman with a 4 year history of slowly progressing 'frontal dementia' was diagnosed as having adult metachromatic leukodystrophy and was followed for 4 years after bone marrow transplantation (BMT). MRI, neurophysiological tests (EEG, ENeG, VEP, SEP and BAEP) and neuropsychological assessment were performed before, and repeatedly after BMT. MRI showed symmetrical white matter lesions in the frontal and parieto-occipital lobes and in the corpus callosum. EEG showed frontal and temporal slow wave abnormalities and nerve conduction was slow. Neuropsychological tests showed cognitive impairment in executive functions, decline in visuospatial-constructive and spatial memory tasks and disorganized thinking. IQ was low (52), with slightly better values for verbal IQ than for performance IQ. After BMT, the patient was followed for 4 years. Clear improvements were seen in EEG, in peripheral nerve conduction and in neuropsychological tests (especially in verbal IQ). MRI findings were unchanged. We believe that the improvement in our patient resulted from the bone marrow transplantation.

Keywords: metachromatic leukodystrophy; bone marrow transplantation

In metachromatic leukodystrophy (MLD), the accumulation of galactosyl sulphatide in lysosomes, due to an inherited deficiency of arylsulphatase A, causes demyelination in the central and peripheral nervous systems. Clinical symptoms vary. Depending on the age at onset of clinical symptoms and on the course of the disease, MLD is classified as late infantile (6 months to 2 years), early juvenile (4 to 6 years), late juvenile (6 to 16 years) and adult (>16 years) types. In adult MLD, psychiatric symptoms dominate with a change in personality, poor school or job performance and emotional lability. Disorganized thinking and impairment of memory functions then occur and hypomania/depression or psychosis is common.¹ Adult MLD may develop as a schizophrenic disorder² or it may present as polyneuropathy.³ Bone marrow transplantation (BMT) is recommended for presymptomatic cases in infants and children with a sibling with MLD and for early cases of juvenile MLD. BMT has been performed in only a few cases of adult MLD.⁴

Case report and methods

A 28-year-old woman with a 4 year history of slowly progressing 'frontal dementia' was diagnosed as having adult metachromatic leukodystrophy. She had previously been healthy, except for slight hypothyroidism, for which she had been treated. She had completed 12 years of school with excellent grades and had started university studies. At 24 years old, she gave birth to twins. After that, her parents noted a slow change in personality, with increasing difficulties in daily living and in caring for her children. Dyscalculia and inertia were observed. She appeared depressed for a while and then developed a schizophreniform state and was referred to a psychiatric clinic. She became progressively more impulsive and showed poor judgment and disinhibitory behaviour leading to pseudomania. Increased distractibility, attention problems, lack of initiative and difficulties in spatiotemporal orientation and planning were also observed. Arylsulphatase A in leucocytes was low $(2 \,\mu \text{kat/kg protein}, \text{ reference value } 9-19)^5$ and urinary excretion of sulphatide was high (1900 µmol/mol creatinine, reference value <25).

Her 3-year older brother had a similar, but more severe, clinical picture, low arylsulphatase A level in leucocytes $(1 \ \mu \text{kat/kg})$ and signs of widespread brain demyelination on CT scan.

The patient had a normal neurological state, except for a slight paresis in her right shoulder after a neonatal injury. She was examined with MRI, neurophysiological tests, neuropsychological tests and arylsulphatase A levels before transplantation and 1 year, 2 years and 4 years after transplantation. Neurophysiological tests and arylsulphatase A levels were also performed at 3 and 6 months after transplantation.

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MRI showed symmetrical white matter lesions, almost entirely in the frontal and parieto-occipital lobes and in the corpus callosum (Figure 1). The lesions did not enhance with contrast. Moderate cerebral atrophy presented with dilated lateral ventricles. Cerebellum and brainstem were normal on MRI.

Neurophysiological tests

EEG showed a marked frontal and temporal slow-wave (2–5 Hz) abnormality, more pronounced on the left side.

Peripheral nerve conduction was studied in the median, radial, peroneal, tibial and sural nerves. The results were expressed both as separate values of conduction velocities (m/s), shortest F-response to 20 stimuli (ms), compound muscle action potential (mV) and sensory nerve action potential (μ V) and also as an index (ENeG-Ix) based on 12 of these parameters and expressed as the mean deviation (in s.d.), standardized for age or height. The normal limit for ENeG-Ix is $\pm 2.5 \sqrt{n}$ number of recorded variables, in this study ie $\pm 0.72.^{6}$ Nerve conduction was uniformly slow, with an ENeG-Ix of -4.59.

Visual evoked potentials (VEP, pattern reversal stimuli and Oz to Fz recording) were delayed (123 ms right side, 127 ms left side, normal <112 ms). Somatosensory evoked potentials (SEP, median nerve stimulation with recording at Erb's point, cervical spine and contralateral parietal area and tibial nerve stimulation with contralateral parietal recording) were normal (median nerve stimulation) or borderline high (tibial nerve stimulation). Brainstem auditory evoked potentials (BAEP, 0.1 ms clicks at 10 Hz rate and recording between the vertex and the ipsilateral mastoid process) were normal.

Figure 1 Brain MRI images (T2-weighted image) 4 months before BMT showing symmetric demyelination in the frontal and parieto-occipital white matter and moderate brain atrophy with dilated lateral ventricles.

Neuropsychological assessment

The nature and degree of impairment were examined with a comprehensive test battery, including personality tests and screening tests as well as specific tests for memory and executive functions. The patient was assessed with the Wechsler Adult Intelligence Scale (WAIS-R), screening tasks from Luria's Neuropsychological Investigation, complex tests of attention functions (Trail-making Test, Wisconsin Card-sorting Test) and a test of verbal fluency (FAS word fluency). Memory tests, including verbal learning (Rev AVLT) and recognition, tests of perceptual organization and visual memory (Rey-Osterreith Complex Figure, the Benton Visual Retention Test, Corsi's Blocking-tapping test), line-marking tests (Line Bisection Test, Albert) and personality tests (Rorschach the Comprehensive System according to Exner, Draw-A-Person) were also given. Verbal IQ (VIQ), performance IQ (PIQ) and the full-scale intelligence quotient (FSIQ) were estimated from nine of the 11 WAIS-R subtests used.

Practice effects of the varied test battery are supposed not to be strong enough to outweigh the mental deterioration, and tests of motor, perceptual and memory functions show few training effects from repetition. Furthermore, no practice effects are seen when dementia is present.⁷

The neuropsychological assessments before the transplantation showed progressive cognitive impairments in executive functions, such as poor planning ability, distractibility and also an early decline in visuospatial-constructive and spatial memory tasks. FSIQ was 52, with slightly better values for VIQ (61) than for PIQ (52). The interpretation of the personality tests (Rorschach) revealed an oversimplified cognitive approach and disorganized thinking, and also showed a distinct resemblance to the records of schizophrenic patients.

Transplantation

The patient was conditioned with busulfan, 4 mg/kg/day, divided into four doses and given for 4 consecutive days. This was followed by cyclophosphamide, 60 mg/kg/day, for 2 days.⁸ In addition, she received thymoglobulin (Mérieux, France), 175 mg/day, for 5 days prior to BMT. On 1 June 1993, she received bone marrow from her 30year-old HLA-A, -B and -DR identical healthy sister, who had a normal arylsulphatase A level (11 μ kat/kg protein) and normal urinary excretion of sulphatide (19 μ mol/mol creatinine). Post-transplant immunosuppression consisted of cyclosporine and four doses of methotrexate.9 The posttransplant course was uneventful, with prompt engraftment $(>0.2 \times 10^9 \text{ WBC/1})$ on day 13 after transplantation. She was discharged from the hospital on day +22. She developed neither acute nor chronic graft-versus-host disease nor any serious infections.

Results

On repeated follow-ups for 4 years following the transplant, her clinical condition had stabilized, arylsulphatase A levels in leucocytes were normal (15–20 μ kat/kg protein) and her

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		Time after BMT (months)								
	0	3	6	12	24	48				
ENeG-Ix	-4.59	-4.80	-4.56	-3.51	-3.33	-2.90				
Median nerve MCV	45	47	44	44	40	50				
Median nerve F-lat	30	33	33	32	30	28				
Median nerve CMAP	7	5	6	5	9	10				
Median nerve SCV	31	32	31	44	42	39				
Median nerve SNAP	10	2	8	10	7	10				
Radial nerve SCV	NR	25	27	37	29	37				
Radial nerve SNAP	0	2	3	5	4	5				
Peroneal nerve MCV	NR	46	31	33	35	41				
Peroneal nerve CMAP	0	0.1	2	2	3	1				
Tibial nerve F-lat	64	69	69	65	58	59				
Tibial nerve CMAP	3	3	2	3	6	2				
Sural nerve SCV	NR	NR	22	30	NR	29				
Sural nerve SNAP	0	0	1	3	0	4				

 Table 1
 ENeG-Ix (mean deviation from normal values, in s.d., for 12 parameters) and nerve conduction values at various times after marrow transplantation

 $MCV = motor nerve conduction velocity (m/s); F-lat = F latency (ms); CMAP = compound muscle action potential (mV); SCV = sensory nerve conduction velocity (m/s); SNAP = sensory nerve action potential (<math>\mu V$); NR = not recordable.



Figure 2 Peripheral nerve conduction (ENeG-Ix = mean deviation from normal values, in s.d., for 12 parameters) before and at various times after BMT.

ability to adapt to social and emotional conditions had improved. At the 4-year follow-up, she could manage independent living and she also worked (although not in the open market). She saw her children regularly. The MRI findings were unchanged.

EEG showed a slight improvement after 2 years, with less slow-wave activity. Peripheral nerve conduction had improved significantly, starting 6 months after BMT (Table 1 and Figure 2). Evoked potentials were unchanged.

Neuropsychological assessments after transplantation showed the same deterioration of executive and complex cognitive functions, but less disinhibitory behaviour and she was sometimes capable of compensative functioning. Some new verbal learning was taking place. Four years after BMT, the FSIQ was 73, with a clear discrepancy between verbal (VIQ = 89) and performance (PIQ = 58)



Figure 3 IQ (FSIQ = full-scale IQ, VIQ = verbal IQ, PIQ = performance IQ) before and at various times after BMT.

functioning (Table 2 and Figure 3). The pattern at the 2and 4-year follow-ups resembled the situation of an arrested frontal lobe dementia.

The clinical condition of her brother who had not been transplanted had deteriorated further. He was unable to carry on a conversation.

 Table 2
 IQ values at various times after the bone marrow transplantation

		Time after BMT (months)						
	0	12	24	48				
FSIQ	52	63	63	73				
VIQ	61	76	76	89				
PIQ	52	56	56	58				

FSIQ = full-scale IQ; VIQ = verbal IQ; PIQ = performance IQ.

1122 Discussion

The pattern of behaviour and neurophysiological test results in our patient, as in other reported cases of adult MLD, resembled cases commonly associated with frontal lobe dementia,¹⁰ and those with white matter disease (ie more deficits in spatial than in verbal tasks).¹¹ There was also some resemblance to test results of schizophrenic patients. In some reported cases of adult MLD, the first manifestation is that of a psychiatric disease² or it may present as a polyneuropathy.³

Most cases of MLD treated with BMT have hitherto been infantile and early juvenile forms and the best results have been obtained in the presymptomatic cases.^{7,12,13} In slowly progressing late juvenile cases with only minor symptoms, a stable clinical, neurophysiological and neuropsychological state has been reported after BMT.^{4,14} However, deterioration may continue for up to 2 years after BMT and mental function stabilizes at a lower level than the baseline IQ.⁷

Only a few BMTs for adult MLD have been performed. After BMT, the condition of our patient stabilized and even improved slightly, ie the clinical and neuropsychological picture showed an improvement in the verbal IQ and an unchanged performance IQ. The MRI findings were typical of adult MLD¹⁵ and did not change after the transplant. A slight improvement in EEG, stable evoked potentials and a significant improvement in peripheral nerve conduction were also found. In reports of infantile and juvenile cases treated with BMT, nerve conduction has remained unchanged.^{14,16–18} The method used to assess peripheral nerve conduction in this study (ENeG-Ix) may be more sensitive for detecting changes over time.

Since her elder brother with adult MLD who was not transplanted has deteriorated further, we believe that the stable and, in some respects, improved, situation for our patient is a result of the BMT treatment.

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