SHORT REPORT

Late onset globoid cell leukodystrophy

R P Grewal, N Petronas, N W Barton

Abstract

A 29 year old male with onset of globoid cell leukodystrophy at age 14 is described. This is the first case of enzymatically confirmed globoid cell leukodystrophy with onset of symptoms after the age of ten. This patient is unique because of the late onset and slow progression and extends the clinical spectrum of globoid cell leukodystrophy.

Globoid cell leukodystrophy is caused by the deficiency of galactocerebrosidase beta-galactosidase, a lysosomal enzyme.¹ Clinically, it is characterised by psychomotor deterioration, pyramidal signs and visual loss. Eighteen case reports of "late onset" globoid cell leukodystrophy with enzymatic confirmation have been published to date and in all these patients, signs and symptoms were present by the age of ten. In thirteen of these patients, the onset of the disease was before the age of five and in the remainder, neurological signs and symptoms began before the age of ten years.² No case of enzymatically proven globoid cell leukodystrophy with onset after age ten has been diagnosed antemortem.

Case report

A 29 year old male first sought medical attention at the age of 14 complaining of difficulty in walking. His birth and delivery were uncomplicated and his developmental milestones were normal. He was an average student and a good athlete who had no difficulty walking, running or playing sports. At the age of 14 he was initially noted to have a "swing" to his gait.

After clinical examination, a myelogram was performed which was reported to be normal. He was told that he had Schilder's disease. He was first evaluated at the National Institute of Health in 1984 when, at the age of 24, he presented with worsening gait. On examination he was alert and oriented with a normal mental status. The abnormalities detected on the cranial nerve examination included pallor of the optic discs and a brisk jaw jerk with clumsiness of tongue movements. His muscle tone was increased in all extremities although more in the lower extremities. All stretch reflexes were brisk bilaterally with sustained clonus at both ankles and bilateral extensor plantar responses. His sensory examination was normal. His muscle bulk was diminished in the legs. On

testing muscular strength, he had diffuse (Grade 4/5 Medical Research Council) weakness in his legs with normal strength in his arms. His gait was spastic. His cerebrospinal fluid was acellular with a protein of 32 mg/dl, glucose of 69 mg/dl and with no oligoclonal bands.

Electromyogram and nerve conduction studies were normal. A sural nerve biopsy, including an examination under light and electron microscopy, was normal. An MRI with T2 weighted techniques showed abnormalities in the periventricular white matter of both cerebral hemispheres (fig). A CT scan with and without contrast was normal. Visual evoked responses revealed bilateral prolongation of the P-100 latencies. Somatosensory evoked responses showed prolonged conduction time with stimulation of the right peroneal nerve but were normal when the right median nerve was stimulated. Brainstem auditory responses were normal. Skin fibroblasts showed a beta-galactocerebrosidase activity of 0.08 nanomoles/mg hour/protein (control: 1.5 + 0.4). This test was repeated on two occasions with similar results. The father refused to be tested and his mother had died of trauma when the patient was eight years old. However, his sister's fibroblasts were tested for beta-galactocerebrosidase activity which fell in the "carrier" range. Attempts are being made to further characterise the enzyme from this patient.

Over the course of five years, his brainstem auditory responses became abnormal with prolonged latencies bilaterally. Also, the somatosensory evoked responses were slowed following stimulation of both upper and lower limbs. His cerebral MRI examinations showed slowly progressive disease bilaterally. Physical examination at the age of 29 disclosed a normal mental status with a normal sensory examination but severe spasticity in both legs and the left arm.

Our patient initially presented with spastic paraparesis without clinical, electrophysiological or pathological evidence of a peripheral neuropathy. Kolodny *et al* reported four patients with enzymatically proven globoid cell leukodystrophy who presented with spastic paraparesis.³ Three of these patients had no evidence of peripheral neuropathy. All of their patients became symptomatic in late childhood and had a more aggressive course than our patient. It was suggested that globoid cell leukodystrophy be considered in patients with spastic paraparesis. Later onset patients may not have

National Institutes of Health, Bethesda, Maryland, USA

Developmental and Metabolic Neurology Branch, NINDS
R P Grewal
N W Barton

Department of Radiology, Clinical Center
N Petronas

Correspondence to:
Dr Grewal, Building 10,
Rm 3D03, DMNB, NINDS,
NIH, 9000 Rockville Pike,
Bethesda, Maryland,
USA 20892

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Figure MRI scan of the brain using T2 weighted technique (TR: 2000 ms, TE: 80 ms). Three consecutive sections of brain (A, B) show abnormal areas of increased signal in the periventricular white matter of both cerebral hemispheres consistent with demyelination. Similar abnormalities are also noted in the white matter fibres of the internal capsule.

a peripheral neuropathy and the absence of a neuropathy should not exclude this disease from the differential diagnosis.⁴ Thomas *et al* reported a 34 year old woman with globoid cell leukodystrophy who at three years developed ataxia of gait with a subsequent course of slow spinocerebellar degeneration.⁵ Similar to our patient, she did not manifest dementia or visual impairment. The cranial MRI of our patient revealed high signal intensities in the periventricular white matter bilaterally (fig). This was not seen on the CT scan of the head, carried out simultaneously, which was normal. This corroborates the previously reported finding of the higher sensitivity of MRI in globoid cell leukodystrophy.^{6,7}

Electrophysiological tests have been shown to be useful in the investigation of patients with leukodystrophy.⁸ The visual evoked responses were abnormal early in our patient's course and provided evidence of the extent of nervous system involvement. The somatosensory responses initially demonstrated prolonged conduction time from stimulation of the lower extremity but not from the upper extremity. This correlated with the early and more extensive involvement of the lower extremities. As the disease progressed, the evoked responses produced by stimulation of the upper extremity also became abnormal. The brainstem auditory response was initially normal but over a five year period became abnormal providing evidence of disease progression. These observations suggest that evoked responses are useful both diagnostically and in monitoring for disease progression.

Before the discovery of the enzymatic defect, two cases of presumed globoid cell

leukodystrophy with onset in adulthood were diagnosed at necropsy.^{9,10} However, pathological description is not as reliable as enzymatic confirmation.¹¹ Nevertheless, globoid cell leukodystrophy should be a diagnostic consideration in selected patients, regardless of age. Our patient may represent a distinct form of globoid cell leukodystrophy separate from infantile and late infantile onset types. The clinical heterogeneity of the disease may arise from heterogeneity of the mutations causing the disease. With increased awareness of the clinical variability of this disease more patients may be recognised.

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