Letters

Hexosaminidase A deficiency presenting as juvenile progressive dystonia

Sir: Hexosaminidase A deficiency is an inherited disorder characterised by the accumulation of GM₂-ganglioside in cerebral and other tissues. Infantile onset GM₂ gangliosidosis (Tay-Sachs disease) occurs almost exclusively in Ashkenazy Jews, typically presents within 6 months of birth with rapidly progressive psychomotor retardation, amaurosis and the macular cherry-red spot, and is fatal within 4 years.

Rarely cases in various ethnic groups have also been described with childhood onset between 1 and 10 years, of which only four were recorded to have survived beyond age 15.1 2 Presenting features of these cases have included spino-cerebellar3-6 and anterior horn cell syndromes7 8 as well as juvenile-onset encephalopathies and, in one case, generalised dystonia.8 We report a further case of GM₂ gangliosidosis presenting with progressive generalised dystonia in childhood.

An English girl was referred at age 16 years because of difficulty with fine manual tasks, lower limb weakness and frequent falls since childhood, although she remained functionally independent. She was born at term to healthy unrelated non-Jewish parents. Early development was normal but, at age 4 years, abnormal posturing of the right arm and inversion of the right foot whilst walking were noted. A paediatrician found lower limb spasticity and a presumptive diagnosis of athetoid cerebral palsy was made. She became unable to walk when aged 10 and had attended a special school for the physically handicapped since aged 12 because of frequent falls whilst walking and involuntary movements of the right upper limb which had caused increasing difficulty with hand grip and writing. There was no history of seizures or drug intake, and her general health was good. Her one 18 year old brother was normal, and there was no relevant family history.

General physical and ophthalmological examination was normal. There was intermittent blepharospasm, a spastic smile and moderate dystonic dysarthria, with writhing dyskinesia and slowness of repetitive tongue movements. Psychometric assessment revealed reduced attention span, verbal IQ 82, performance IQ 62, with selective weakness of visual memory and arithmetic. There was global muscle wasting and weakness, more marked in the lower limbs with bilateral foot drop. Tone at rest was reduced, but marked dystonia of either upper limb occurred during action with overflow to the contralateral limb but only mild impairment of fine finger movements. Moderate postural tremor with mild ataxia and action tremor affected the upper limbs. No involuntary movements of the lower limbs were seen.

Tendon reflexes were all brisk apart from at the knees, where they were only present with reinforcement, plantar responses were flexor and sensory examination normal. Stance was lordotic with a prancing high-stepping but independent gait with dystonic posturing of the upper limbs; she could walk at least 500 m unaided before she tired.

Electromyographic sampling showed widespread denervation without myopathic features. Nerve conduction studies were normal. Muscle biopsy showed marked fibre type grouping typical of anterior horn cell disease. Computed tomographic brain scan showed scattered areas of low attenuation in cerebral grey matter with mild atrophy. All routine biochemical investigations were normal, as were the lysosomal enzymes galactocerebrosidase, arylsulphatase A, beta-galactosidase and total beta-hexosaminidase. However, both leucocytes and plasma showed a deficiency of hexosaminidase A consistent with a diagnosis of GM₂ gangliosidosis (table).

Meck et al10 described a 10 year old boy who was severely disabled with generalised dystonia and dementia. The first symptoms of dystonia had begun in the third year of life, and by eight years he was anartric with dysphagia and urinary incontinence, unable to feed himself or to walk without assistance. In two other cases, one of which had deficiency of hexosaminidase A and B9 10 dystonia appeared only late in the course of the disease.

The subject of this report was much less severely disabled despite progressive generalised dystonia beginning at age 4 years. She also exhibited striking anterior horn cell involvement typical of other reported cases without dystonia,1 7 as well as mild dysarthria, tremor and ataxia. There are some similarities to case six described by Brett et al11 who, by the age of four years, had inversion of both feet with an unsteady high-stepping gait and frequent falls. However, that child showed rapid physical and mental deterioration, was unable to walk at six years and then developed seizures, myoclonus and frank dementia.

Our case confirms the variety and overlap of clinical features that may occur as part of a spectrum of childhood GM₂ gangliosidosis. Approximately one third of patients with progressive generalised dystonia have additional abnormalities implying that dystonia is secondary to another underlying condition.12 It seems likely that this proportion will increase as physicians become more aware of the possible causes of symptomatic dystonia. Accurate diagnosis of conditions such as GM₂ gangliosidosis is essential to permit screening and counselling of families, as well as to capitalise upon future therapeutic advances.

We thank Dr CH Hawkes for permitting us to describe this patient.

Table Hexosaminidase activity in patient and family

<table>
<thead>
<tr>
<th></th>
<th>Plasma (μmol/ml/h)</th>
<th>WBC (μmol/mg protein/h)</th>
<th>% hexosaminidase A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brother</td>
<td>0.5</td>
<td>0.9</td>
<td>11</td>
</tr>
<tr>
<td>Mother</td>
<td>0.6</td>
<td>1.3</td>
<td>55</td>
</tr>
<tr>
<td>Father</td>
<td>0.7</td>
<td>1.5</td>
<td>37</td>
</tr>
<tr>
<td>Normal range mean (n = 100)</td>
<td>0.9</td>
<td>1.7</td>
<td>56</td>
</tr>
<tr>
<td>TSD homozygotes mean</td>
<td>0.3-1.3</td>
<td>0.7-1.9</td>
<td>52-78</td>
</tr>
<tr>
<td>TSD heterozygotes mean</td>
<td>0.7</td>
<td>1.3</td>
<td>25</td>
</tr>
<tr>
<td>Obligate TSD mean</td>
<td>0.5-1.4</td>
<td>0.7-2.4</td>
<td>32-52</td>
</tr>
<tr>
<td>n</td>
<td>14</td>
<td>25</td>
<td>9</td>
</tr>
</tbody>
</table>

TSD = Tay-Sachs disease
to report the patient originally referred by him, and Dr RCG Rowe for making available histological material.

References


A compulsive movement disorder with cavitation of caudate nucleus

Sir: The movement disorders include a number of conditions in which the patient is conscious of a compulsion to move. In some, such as akinesis, the movement appears to be a response to an unpleasant sensation, but in others like Gilles de la Tourette syndrome, the compulsion less convincingly has such a provocation. Laplane et al reported three patients (two after an episode of carbon monoxide poisoning and one after coma following a wasp sting) who had CT scans showing bilateral cavitation in the basal ganglia who had psychic akinesia and two of whom had a movement disorder. In their first case the patient showed stereotyped activities such as mental counting and this was sometimes accompanied by gestures although it was difficult to tell if this was voluntary or involuntary. The patient also had chorea, tics and some Parkinsonism. Their third case had Parkinsonian signs. We wish to report a patient with cavitation in the region of the basal ganglia from an unknown cause who had a compulsion to move her hands simulating a typing exercise and who had no other form of movement disorder. She also displayed psychic akinesia.

The patient is a 48 year old lady who was employed as a manageress of a card shop but was forced to resign owing to the consequences of her current illness. Her present complaints began 2 years ago and coincided with her mother’s death; the patient thought that depression was the explanation for this illness. She had become apathetic, not rising till 1 p.m., and then watching television for the remainder of the day. She stopped doing any housework, shopping or social activities. She relinquished her previous interests, conversation became limited and so did her sense of humour. Her personal hygiene became poor and she had not had a bath for 18 months. One year previously she had begun to move her hands purposelessly. This was more obvious on the right than on the left. She could stop the movements happening for long periods if repeatedly asked to but if left to herself they would recur within a minute and persist. She said she found it comforting to move her fingers and described it as though she was practising typing exercises. The movements did correspond to the beginner’s exercise a s d f space bar, l j k space bar. In other words the movements consisted of flexion of her fingers towards the palm of her hand in repeated sequences running from the little to the first finger and then the thumb. Despite finding this activity comforting she thought it was “dreadful” that she did it. The movements would stop if she used her hands so they were not at all disabling. Apart from these movements and the impression of moderately impaired intellectual function neurological examination was normal. Psychometry showed on the Wechsler a verbal IQ of 96 and a performance IQ of 76.

The patient and her family denied any possible episode of carbon monoxide poisoning.

Her CT scan (fig) demonstrates cavitation in the region of both caudate nuclei also involving the putamen at least on the right. Haematological and biochemical screen were normal as were thyroid function tests. Treponemal serology and antinuclear factors were negative. Copper, caeruloplasmin and slit lamp examination of her cornea were all normal. CSF examination showed a normal protein with no cells. Serum and CSF pyruvate and lactate levels were within the normal range.

Her diagnosis is unclear. Of the known causes of cavitation in the region of the caudate nucleus carbon monoxide poisoning and Wilson’s disease have been excluded. Bilateral ischaemic lesions are possible. Leigh’s syndrome was considered but her CSF, pyruvate and lactate were normal.

The pathology is not germane to the more interesting phenomenon of an abnormal caudate and putamen in a patient with a compulsive movement disorder. We cannot prove that the lesions seen on CT scan are the cause of the movement disorder but as this part of the brain has so much to do with abnormal movements it seems likely that it is involved.