Late Infantile Metachromatic Leucodystrophy

Effect of Low Vitamin A Diet

Late infantile metachromatic leucodystrophy (MLD) is a genetically determined, generalized, sulphatide lipidosis, in which lipid metachromatic substances accumulate in the nervous system and other organs, due to a deficiency of the lysosomal enzyme, arylsulphatase A (Austin et al., 1964; Mehl and Jatzkewitz, 1965).

The disease is characterized by a slowly progressive course which has been divided into four stages according to the degree of motor handicap (Hagberg, 1963). The first symptoms and signs generally appear between 1 and 2 years in a previously normal child, and consist of hypotonia, unsteady gait, and valgus deformity of feet. The child gradually loses the ability to walk, sit, or crawl, and develops spasticity, with diminished or absent tendon reflexes, and may in addition show ataxia and tremor (stages I and II). Mental regression, hypertonic spasms, violent root pains, and total aphasia follow (stage III), and the child eventually dies between 3 and 6 years in a state of decerebrate rigidity, with cortical blindness and deafness (stage IV).

Attempts to alter the course of this disease by various therapeutic means have so far not met with any success. Because vitamin A is necessary for one of the metabolic steps in the synthesis of sulphatide (Sundaresan, 1966), Melchior and Clausen (1968) tried a vitamin A deficient diet in the treatment of a child with advanced MLD, but did not obtain any clinical improvement. We report a further case of MLD in which we tried a vitamin A deficient diet, with some apparent success.

Case Report

A girl presented at the age of 2½ years with delay in walking.

She was born normally at 37 weeks' gestation weighing 2920 g. The neonatal period was normal. In the first year she reached her developmental milestones quite normally—she sat unsupported at 6 to 7 months and pulled herself to a standing position at 9 to 10 months—but did not achieve the ability to walk independently, and at the age of 2 years 3 months, she could just take two to three steps unsupported. Her intellectual development seemed quite normal. She could talk well, making sentences of 4 to 5 words.

On examination at that stage, the only abnormal findings were slight hypotonia, especially in relation to the knee joint which would go into recurvatum when weight was taken on them; absent knee and ankle jerks; and a convergent concomitant squint. The fundi were normal. Her intelligence was difficult to assess because of poor co-operation. Delayed motor development with possible laxity of ligaments around the knee joints was diagnosed and she was given a course of physiotherapy.

Three months later there was no obvious change but she was reluctant to walk unless supported. The hypotonia was more pronounced. The knee jerks were still absent. Ankle jerks and the plantar response were equivocal. She was irritable and readily distressed when examined.

Four months later she was described by her parents as being 'ever so nervous', trembling all the time, would not sit or stand, was uncooperative, and 'not bothering to do anything'. The parents attributed to the arrival of the new sib. On examination, she was unable to maintain a sitting or standing position without support. It was noted that intermittently her right hand would hyperextend and the whole leg would go stiff. Because of definite weakness in her limbs at that stage, it was decided to do a muscle biopsy to exclude an underlying neuromuscular disorder.

On routine histological stain the quadriceps muscle showed no striking abnormality. There was an obvious variation in fibre size, falling into two populations, one about 30µ in diameter and the other about 60µ. However, on histochemical stains it was apparent that there was selective atrophy of type 1 fibres, and a denervation process was suspected. Motor nerve conduction velocity was then done and was very slow, confirming the presence of a peripheral neuropathy.

When assessed again six months later, there was an obvious deterioration in her condition. She was completely unresponsive and would not speak any words. She had difficulty in swallowing food and tended to choke. She was constantly grinding her
touched were and legs tase she still follows. Table in conduction velocities, confirmed by the following dystrophy with associated creatine 87 repeatedly positive and attempted to chew bed clothes. When examined she was extremely irritable, and cried whenever one touched her. Her hands were tightly clenched and her legs and arms were hypertonic. The tendon reflexes were still absent and the plantar responses unequivocally extensor. Bilateral nystagmus was also present. The fundi were normal.

The tentative diagnosis of metachromatic leucodystrophy with associated peripheral neuropathy was confirmed by the following investigations.

**Investigations.** The results of the motor nerve conduction velocities, and blood and urine arylsulphatase estimations on the patient and her family are shown in Table I. The remaining investigations were as follows. The blood lead was 10 µg/100 ml; the serum creatine phosphokinase 87 mIU/ml (normal 0–70 mIU/ml); and the WR negative. The routine blood count was normal. The CSF protein was 100 mg/100 ml, sugar 87 mg/100 ml, with 1 RBC/mm³ and 1 WBC/mm³, and a Lange curve of 012233210. The urine was repeatedly positive for intracellular metachromatic granules (according to the von Hirsch and Peiffer (1955) method). Skull x-ray was normal. EEG showed diffuse, bilateral, high voltage, slow wave activity.

**Sural nerve biopsy.** Frozen sections showed extensive accumulations of metachromatic material (von Hirsch and Peiffer stain). Paraffin-fixed and teased preparations showed segmental demyelination and remyelination, with characteristic metachromatic material in the Schwann cells. The original muscle biopsy was then also stained with cresyl violet (von Hirsch and Peiffer method) and this showed metachromatic material in the terminal nerves.

**Course and therapy.** After confirmation of the diagnosis, she was given a diet low in vitamin A (approximately 500–900 IU/day), with supplementary vitamins C and D.

When reassessed 6 weeks later there was an undoubted improvement. She had become more responsive, and attempted to smile and to speak when spoken to. She was able to chew and swallow without difficulty. Her hands were more relaxed and she opened them more frequently. When examined, she was more alert, was cheerful and did not become distressed when touched. The nystagmus was no longer present, and though her legs were still hypertonic and extended, it was easier to overcome the resistance than before. The reflexes were still absent.

She has now been followed up for over 2 years since starting the low vitamin A therapy. After the initial improvement her condition remained fairly static. She is still unable to sit or stand and has complete aphasia. She is unable to swallow solids but manages semisolids quite well. She is responsive and alert and turns to her father when spoken to. Extensor spasms, especially of her leg, still occur occasionally and the reflexes are all absent. Her nerve conduction velocities remain very slow (Table II).

**TABLE I**

*Results of Motor Nerve Conduction Velocities and Blood and Urine Arylsulphatase A Levels in Patient and Family***

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Ulnar (m/sec)</th>
<th>Posterior Tibial (m/sec)</th>
<th>Urinary Arylsulphatase A (µm 4NC/hr per g creatinine)</th>
<th>Blood Leucocyte Arylsulphatase (IU/1000 IU N-acetyl-β-glucosaminidase used as reference enzyme)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>3</td>
<td>14-4</td>
<td>10-7</td>
<td>2-0</td>
</tr>
<tr>
<td>Sib</td>
<td>8/12</td>
<td>47-7</td>
<td>39-0</td>
<td>—</td>
</tr>
<tr>
<td>Mother</td>
<td>33</td>
<td>63-3</td>
<td>51-3</td>
<td>18-2</td>
</tr>
<tr>
<td>Father</td>
<td>33</td>
<td>60-0</td>
<td>50-6</td>
<td>23-8</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td>50-173</td>
</tr>
<tr>
<td>Normal (mean ± 1 SD)</td>
<td></td>
<td></td>
<td></td>
<td>224 ± 49 (SD)</td>
</tr>
</tbody>
</table>

**TABLE II**

*Motor Nerve Conduction Velocities of Patient (m/sec)***

<table>
<thead>
<tr>
<th>Date</th>
<th>Ulnar</th>
<th>Posterior Tibial</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 July 1968</td>
<td>14-4</td>
<td>10-7</td>
</tr>
<tr>
<td>10 August 1968*</td>
<td>11-3</td>
<td>—</td>
</tr>
<tr>
<td>22 October 1968</td>
<td>10-0</td>
<td>9-5</td>
</tr>
<tr>
<td>17 December 1968</td>
<td>8-0</td>
<td>18-1</td>
</tr>
<tr>
<td>11 March 1969</td>
<td>8-0</td>
<td>10-1</td>
</tr>
<tr>
<td>3 June 1969</td>
<td>6-8</td>
<td>8-6</td>
</tr>
<tr>
<td>16 December 1969</td>
<td>10-7</td>
<td>6-3</td>
</tr>
</tbody>
</table>

* Diet begun.

**Discussion**

MLD follows a steadily downhill course and invariably leads to a fatal outcome in early childhood. If any form of therapy is to be successful in this condition, it should be instituted as early as possible, before excessive sulphotide deposition has occurred and ideally before there is severe clinical deterioration. The failure to produce a
dramatic improvement in the clinical state and the motor nerve conduction velocity would not be surprising. It is unlikely that any damage already caused by the excessive sulphatide would be corrected and the most one could hope for with the low vitamin A therapy would be to reduce any further accumulation of sulphatide and thereby limit the progression of the disease.

Early diagnosis is therefore all important. Peripheral motor nerve conduction velocity measurement (Fullerton, 1964; Aziz and Pearce, 1968) could be useful in this regard as a screening test, especially in the early stage when the only abnormal signs may be a slight hypotonia, or a genu valgum deformity with depressed or absent tendon reflexes. The diagnosis should thus be suspected in any previously normal child developing hypotonia or delay in motor milestones in the 2nd year of life. If a slow motor nerve conduction velocity is found the diagnosis can then be confirmed by demonstrating low levels of arylsulphatase activity in the blood or urine (Percy and Brady, 1968; Austin, McAfee, and Shearer, 1965). In our family we have also been able to show some reduction in levels of arylsulphatase A in the blood and the urine in the parents as well as the younger sib. It is thus possible also to identify heterozygotes for the recessive gene.

While it is difficult to assess the value of any form of therapy in a slowly progressive condition on the basis of a single case, we have been sufficiently impressed by the change in this patient to direct attention to its possible value, and at the same time to stress the importance of early recognition of this condition for future therapeutic trials.

Summary

A 3-year-old girl with metachromatic leucodystrophy showed an apparent improvement when put on a diet low in vitamin A. During a 2-year follow-up she subsequently showed no progression of the disease. The importance of early diagnosis by nerve conduction velocity studies and measurement of arylsulphatase levels in the leucocytes or urine is stressed in order to try and arrest the disease at an early stage. Heterozygotes can also be identified by lowered arylsulphatase levels in leucocytes and urine.

We wish to thank Dr. B. D. Lake for estimating the arylsulphatase activity of urine, Dr. N. Raine for the leucocyte arylsulphatase estimation, Dr. A. D. Dayan for the histology on the teased preparation of the sural nerve, and Miss C. Heinzmann and Mrs. B. Lunn for technical assistance. Our neuromuscular research programme is supported by grants from The Muscular Dystrophy Group of Great Britain and The Medical Research Council.

References


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Simple Method for Cutting Transverse Sections of Hair

Comments on Shape of Hair in Hurler and Sanfilippo Syndromes

In past reports on the mucopolysaccharidoses the hair has been described as coarse, but no detailed studies have been made. This paper presents a simple method of preparing transverse sections of hair for microscopical examination, and describes some features of the hair of patients with the Hurler and Sanfilippo mucopolysaccharidosis syndromes.

Materials and Methods

Hair samples were collected from the crown of the head and cut at scalp level. Samples were obtained from 2 patients with Hurler’s syndrome, 5 patients with the Sanfilippo syndrome, and 10 randomly chosen normal people. Subsequently, 150 patients and staff of the Royal Children’s Hospital were examined and

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