Short reports

Archives of Disease in Childhood, 1975, 50, 735.

Juvenile onset metachromatic leucodystrophy
Failure of response on a low vitamin A diet

Metachromatic leucodystrophy (MLD) is an autosomal recessively inherited condition due to a deficiency of the heat labile fraction of cerebrosidase sulphatase, arylsulphatase A, a lysosomal enzyme. This leads to an accumulation of the sphingolipid sulphatide, particularly in Schwann cells of the nervous system, and in some visceral organs. Progressive demyelination and mental retardation occur. The first symptoms and signs appear most frequently in the second year of life, but juvenile and even adult onset of the condition are recognized.

Moosa and Dubowitz (1971) reported apparent improvement in a 3-year-old girl with MLD when given a diet low in vitamin A. The child with juvenile onset MLD reported here was given a similar diet, but in this case treatment failed.

Case report
A 9-year-old girl was admitted for investigation of progressive intellectual impairment and emotional problems. She was delivered by forceps at term, after an uncomplicated pregnancy, birthweight 3·5 kg. There were no neonatal problems, and developmental milestones during infancy were normal. She had both meases and mumps in her fourth year but was otherwise physically well. Her schoolwork was average up to the age of 7, but deteriorated over the next 2 years. She became emotionally labile and antisocial, with aggressive outbursts, day-time enuresis, and general naughtiness. Psychiatric supervision at this stage failed to influence her behavioural problems. In the 9 months before admission the deterioration appeared to accelerate, with difficulty in manipulation, unsteady gait, total failure to concentrate, and almost complete lack of speech. Her parents and 12-year-old sister were alive and well and of normal intelligence.

On examination she was prepubertal and overweight. She was emotionally labile, had a spastic gait and slurred speech. Her memory for recent and distant events remained good. There was a generalized increase in muscle tone in her limbs with brisk tendon jerks and bilateral extensor plantar responses. Cranial nerves appeared intact, fundoscopy was normal, and there were no signs of peripheral neuropathy.

Investigation. Routine blood counts, urea, electrolytes, calcium, glucose, proteins, and lead levels were normal. No abnormality could be seen on skull or chest x-rays. Wassermann reaction was negative and the measles complement fixing titre was 1 in 16. The plasma and urine amino acid pattern, white blood cell hexosaminidase and β-galactosidase levels were normal. Fresh urine specimens repeatedly contained intracellular metachromatic material and the urine and white blood cell arylsulphatase A activity was low (Table I).

<table>
<thead>
<tr>
<th>White blood cell arylsulphatase A (nmol/mg protein per h)</th>
<th>Urine arylsulphatase A (umol 4-nitrocatechol liberated/h per g creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>6</td>
</tr>
<tr>
<td>Mother</td>
<td>32</td>
</tr>
<tr>
<td>Father</td>
<td>19</td>
</tr>
<tr>
<td>Sister</td>
<td>106</td>
</tr>
</tbody>
</table>

TABLE I
White blood cell and urine arylsulphatase A in the patient and her first-degree relatives, showing low levels in the patient, intermediate levels in the parents, and normal levels in the sister

encephalogram showed a generalized abnormality, maximal in the frontal regions, though visual-evoked responses and the electroretinogram were normal. (R) lateral popliteal nerve conduction velocities were also normal.

Course and treatment
Diagnosis of juvenile MLD was made, and both parents were shown to be heterozygotes for the condition (Table I). In view of the encouraging report by Moosa and Dubowitz (1971) she was started on a diet low in vitamin A (no greater than 400 IU/day). Supplements were given as Ketovite tablets, calciferol (vitamin A free), cyanocobalamin, and ferrous sulphate. It was 2 months before a low serum vitamin A level was recorded, and urinary sulphatide levels remained high (Table II). There was a progressive and apparently rapid deterioration in her condition. After 4 months on the diet she had become totally incontinent, her speech was unintelligible, she could not sit, stand, or walk, dribbled continuously, choked...
Sulphatide after Changes in tion, possibly effective the tion in A2 Jan 5 and Percy of deficiency Age of the disease, to the problem of difficulties, and particularly neurological examination, particularly for early diagnosis if definitive treatment becomes available. Failure to develop signs of peripheral neuropathy is unusual, though is more consistent with late onset MLD.

Low arylsulphatase A levels in the urine and white blood cells of the parents (Table I) again confirms this method of detecting otherwise asymptomatic heterozygotes. Urine and serum levels of arylsulphatase A in the patient were well within the expected range for infantile onset MLD. Percy and Kaback (1971) showed that arylsulphatase A levels were no different in infantile and adult onset of the disease, and thus quantitative differences in the enzyme levels could not account for the different ages of presentation, confirming our experience.

There is no recognized treatment for this condition, which follows a steady downhill course ending in death in 2 to 10 years or more. Thus, any possibly effective therapy is worth trying, and may help the family to adjust to the fact that the child has a fatal and incurable disease.

The three possible approaches to therapy in single enzyme deficiency disease are as follows. (1) Correction of the defective gene by bioengineering (not a clinical possibility at present). (2) Replacement of the missing lysosomal enzyme, which has been achieved in vitro with fibroblast cultures from patients with MLD. Wiesmann, Rossi, and Herschkowitz (1972) showed that the cultured cells took up arylsulphatase A, probably by active pinocytosis, and partial correction of the degradation defect of sulphatide was observed. However, this technique cannot be readily applied to patients and when attempted has failed to restore the defect in metabolism (Greene, Hug, and Schubert, 1967). (3) Reduction of the accumulation of the metabolite by dietary control.

Sundaresan (1966) has shown that vitamin A acts as a coenzyme in the synthesis of active sulphate (PAPS).

\[
\text{Vitamin A} \\
\text{ATP} + \text{SO}_4^2- \rightleftharpoons \text{APS} + \text{PP} \\
\text{APS} + \text{ATP} \rightleftharpoons \text{PAPS} + \text{ADP}
\]

PAPS is then transferred to galactoceramide to form sulphatide. Melchior and Clausen (1968), in a single case report, showed a fivefold reduction in urinary sulphatide in an infant with MLD who had been on a vitamin A-deficient diet for 4 months, but with no arrest of clinical deterioration. Moosa and Dubowitz (1971), using a similar diet, suggested that in their case clinical decline was stopped after only 6 weeks of treatment, and their patient was maintained in an unaltered state for 2 years. However, periods of apparent remission do occur in MLD and in the latter case it may have been incidental to the therapy.

The case presented here showed no lessening of clinical deterioration and no reduction in urinary sulphatide after 4 months on a vitamin A-deficient diet, and in fact, clinical decline seemed more rapid and 24-hour urinary sulphatide levels rose (despite inadequate urine collections because of incontinence). Furthermore, the first low serum vitamin A level was recorded after 2 months and no therapeutic effect was expected until after this time.

Treatment may have failed because the myelin already formed was abnormal (Austin, 1973), and however much the sulphatide accumulation is reduced, demyelination proceeds. Furthermore, the condition may not be due entirely to metabolite accumulation but also to a deficit of substances formed beyond the arylsulphatase A stage of the enzyme system (Austin, 1973). Dietary control would then worsen the condition.

<table>
<thead>
<tr>
<th>Date</th>
<th>Plasma vitamin A (normal 70–200 IU/100 ml)</th>
<th>24-hour urine sulphatide (normal—undetectable) (mg/24 h)</th>
<th>Volume of urine (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Nov 72</td>
<td>140</td>
<td>0.775</td>
<td>455</td>
</tr>
<tr>
<td>8 Dec 72</td>
<td>100</td>
<td>2.29</td>
<td>670</td>
</tr>
<tr>
<td>5 Jan 73</td>
<td>53</td>
<td>3.34</td>
<td>355</td>
</tr>
<tr>
<td>2 Feb 73</td>
<td>109</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>28 Mar 73</td>
<td>53</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Discussion

This case illustrates several interesting features. Age of onset of symptoms is consistent with the juvenile form of MLD. Presentation as a behavioral problem with difficulties at school is characteristic of a number of childhood neurological conditions, and emphasizes the need for full neurological examination, particularly for early diagnosis when definitive treatment becomes available. Failure to develop signs of peripheral neuropathy is unusual, though is more consistent with late onset MLD.
The only satisfactory clinical approach to this disease at present is heterozygote detection with genetic counselling and antenatal diagnosis.

**Summary**

Treatment with a diet low in vitamin A failed to halt the neurological deterioration in a 9-year-old girl with juvenile onset metachromatic leucodystrophy.

Thanks are due to Drs. A. P. Norman and R. Stephens for allowing me to publish details of their case; to Dr. Patrick (Enzyme Department, Institute of Child Health) and Mr. Goodwin (Neurochemistry Department, National Hospital, Queen Square) for enzyme and sulphatide estimations; and to Miss C. Vincent for secretarial help.

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Correction of the defective sulfatide degradation in cultured 
fibroblasts from patients with metachromatic leucodystrophy. 

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**Lipodystrophy of limbs associated with insulin resistance**

In 1974 Dunnigan *et al.* described a new form of partial lipodystrophy occurring in several women from 2 families from the north of Scotland. They had loss of subcutaneous fat from the limbs and trunk, but with normal or increased facial fat. Other features were acanthosis nigricans, hyper- 
trophy of the labia minora, insulin resistant diabetes mellitus, and hypertriglyceridaemia.

We report a girl in whom the evolution of the disease has been observed over a 3-year period.

**Case report**

The patient was first seen here at the age of 11 years. She was born at term to healthy unrelated parents; birthweight was 3·5 kg. There were no neonatal problems. At the age of 8 the parents noticed that her legs and arms had become thin. This had developed over a few months, but then remained static. There was no family history of lipodystrophy, nor of diabetes, and there was no family link with the north of Scotland.

Examination showed that she was on the 50th centile for both height and weight. There was marked loss of subcutaneous fat of the lower limbs up to and including the buttocks, and loss of fat of the arms most marked in the forearms and hands (Fig. 1). Facial appearance was normal. Skinfold measurements over triceps, biceps, 
thigh, and calf were all below the 3rd centile, whereas measurements of abdominal, subscapular and suprailliac 
skin folds were all on the 50th centile. There was no hepatomegaly. At that time there was no abnormal 
pigmentation nor any genital hypertrophy. Physical 
examination was otherwise normal.

The patient has been seen on two further occasions. Examimation at the age of 12 was essentially unchanged, but at the age of 14 she was pubertal and had developed
Juvenile onset metachromatic leucodystrophy. Failure of response on a low vitamin A diet.

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