A preclinical case of late adult metachromatic leukodystrophy?

Manifestation only with lipid abnormalities in urine, enzyme deficiency, and decrease of nerve conduction velocity

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SUMMARY In a clinically unremarkable 39 year old sister of a patient afflicted with late adult metachromatic leukodystrophy, metachromatic deposits in the epithelial cells of the urine sediment, a high sulphatide excretion in the urine, and a deficiency of arylsulphatase A in urine and leucocytes were found. The motor nerve conduction velocity of the peripheral nerves in upper and lower extremities was distinctly decreased. Cerebral disturbances were not evident. It is surmised that this patient is a case of late adult metachromatic leukodystrophy in an early stage of the disease without obvious clinical signs. The peripheral neuropathy found by neurophysiological examination is interpreted as an early symptom of the disease.

Metachromatic leukodystrophy (ML) is a genetically determined, recessively inherited disorder which is characterized by a diffuse demyelination in the brain and peripheral nervous system (nonsudanophilic, metachromatic form of diffuse sclerosis). Since the investigations of Jatzkewitz (1958) and Austin (1958), ML has been classified with the sphingolipidoses. The cerebroside sulphuric acid esters (sulphatides), generally known as myelin constituents, are stored in the white matter of the central and peripheral nervous system. Sulphatide accumulation also takes place in the kidneys and, to a much lesser extent, in other body organs. This lipid storage is caused by an inherent defect of the enzyme cerebroside sulphatase— that is, arylsulphatase A (Mehl and Jatzkewitz, 1965; Austin, Armstrong, and Shearer, 1965).

According to the age of onset and the clinical duration, congenital, infantile, late infantile, juvenile and adult types of ML are differentiated (see Kahlke, 1967; Pilz, 1970). Infantile cases are accompanied by mental retardation and flaccid, later spastic paralysis. In juveniles, and also still noticeable in the adult type of illness, the alterations of character and personality are essentially non-specific. Neurological symptoms, as a rule, are initially only discrete; in further development a progressive dementia becomes obvious.

With one exception, the adult cases of ML (Müller, Pilz, and Meulen, 1969) were not diagnosed before necropsy. Only Austin, Armstrong, Fouch, Mitchell, Stumpf, Shearer, and Briner (1968) diagnosed an adult case during life by demonstrating the arylsulphatase A deficiency in a hospitalized brother of a man who had died of ML. Recently we reported on two patients in whom the diagnosis of late adult ML could also be established during life (Pilz, Paul, Müller, Volles, Hopf, Prill, and Krönke, 1971).

By systematic urine analyses of the siblings of both patients a strong sulphatide excretion and an arylsulphatase A deficiency in the urine was found in a 39 year old woman, who until then was clinically unremarkable. The neurophysiological examination, however, showed a distinct slowing of impulse conduction of the peripheral nerves. We consider this case an early stage of late adult ML. Since the first biochemical changes and initial clinical symptoms in the adult form are not yet exactly known, the presentation and discussion of this case appears justified.

CASE REPORT

Mrs. G.K. was born in June 1931 in Einbeck near
Göttingen. During childhood she had measles and mumps. After attending public school without failing a grade, she worked on the family farm. She was married in 1955 and in 1958 gave birth to a healthy son who is now attending lower grade secondary school.

For about seven years she has complained of pain in the back and shoulder joints thought to be due to rheumatism. This pain was increased by physical work and by stooping. She had occasional stiff feeling in the legs. There was no paraesthesia or numbness of the extremities, no headaches, and no dizzy spells or loss of memory. Now and then she had an unpleasant sensation of increased cranial pressure, especially after bodily strain. Like her mother and a brother she suffered from varicose veins and at the time of examination had a closed ulcer on the lower leg. Along with managing the household and tending a large garden, she sometimes helped out on her parents’ farm. In the 43 year old brother of Mrs. K. we had earlier discovered a clinically manifested metachromatic leukodystrophy (Pilz et al., 1971: case 2). After observing an increased sulphatide content in the urine of Mrs. K., a thorough clinical investigation was proposed. At first she refused such an examination. With the help of the family physician, an outpatient investigation in our clinic became possible. No mental alteration in the patient had been noticed by the family physician up to that time.

CLINICAL FINDINGS Marked varicosity of veins was present in both lower legs with healed cutral ulcer on the left side. Blood pressure (Riva Rocci) was 110/75 mm Hg. There was paravertebral tension of the lumbar musculature. Facial asymmetry was noted but no cranial nerve disturbances. Tendon reflexes were weakly present. The intensity of the left brachioradialis and biceps reflexes, left knee jerk, and right ankle jerk was decreased in comparison with the opposite side. Left upper abdominal skin reflexes were not detectable. There were no pyramidal signs and no paralysis. Superficial and deep sensations, including vibrational perception, were intact. There were no disturbances of coordination. Bladder and colon function were unremarkable. The patient appeared rather slow and with diminished facial expression, but other than that no mental changes were observed.

LABORATORY FINDINGS Serum creatinine was 0.7 mg/100 ml., blood sugar (11 a.m.) 105 mg/100 ml., GOT 9 mU/ml., GPT 4.5 mU/ml., alkaline phosphatase 31 mU/ml. Serum electrophoresis showed albumin 50%, alpha1 globulin 5%, alpha2 globulin 10%, beta globulin 12%, gamma globulin 23%. There was no marked protein and glucose excretion in the urine. Urinary sediment contained single leucocytes and epithelial cells, and large quantities of urate. After staining of the sediment with trypan-blue (Holländer, 1964) and contrasting with haemalaun, metachromatic substances were recognizable in the epithelial cells (Fig. 1). A quantitative

thin-layer chromatographic determination of the sulphatides in the urine (Fig. 2; for the method see Pilz et al., 1971) revealed an excretion of 0.45 mg in 24 hours (normal amount <0.01 mg). The semiquantitative determination of arylsulphatase A in the urine according to Austin, Armstrong, Shearer, and McAfee (1966) revealed no enzyme activity compared with a control urine. The arylsulphatase A activity of leucocytes (technique according to Percy and Brady, 1968) was 0.74 n-mole/mg protein (normal range between 38 and 126: see Pilz, 1972).

Cerebrospinal fluid contained: 3/3 cells; Pandy reaction was negative, total protein content 34 mg/100 ml., mastix-curve normal. After quantitative immunodiffusion of proteins there was no displacement within the immunoglobulin fraction.

EEG Regular 10 Hz alpha base activity with an amplitude of 30–50 nV was present in both occipital areas. Isolated theta waves of 5–7 Hz were superimposed. On opening the eyes there was definite blocking of the alpha rhythm. No lateralized differences or localized decrease of frequency were recognizable and no pathological wave forms. During the three minute hyperventilation test, the base activity showed no significant change.

ELECTRONEUROGRAM The maximum motor conduction velocity in the ulnar nerve was 35 to 36 m/sec and in the peroneal nerve 30-9 m/sec. The terminal latency was normal. The total duration of the muscle

FIG. 1. Intracytoplasmic accumulation of metachromatic substances in epithelial cells of urine sediment. Staining with acriflavine, × 720.
response of the hypothenar muscle was already increased to 16-3 msec with stimulation at the wrist, showing a further increase with stimulation at the upper arm (Table). The difference between fast and slow conducting motor neurones indicated a pathological range of motor fibre conduction velocity. The impulse conduction of the mixed nerve action potential (generally attributed to the conduction velocity of sensory fibres) was slowed down to 43-5 m/sec. The mixed nerve action potential itself at a 4-1 msec duration was broadened, and was also decreased in amplitude.

**ECHOENCEPHALOGRAM** The midline echo was not displaced; the third ventricle was 6 mm wide.

**RADIOGRAPHIC FINDINGS** Except for a hypoplasia of the frontal cavity and inconspicuous asymmetry, a skull series was normal. There was decreased lordosis and light scoliosis of the cervical spine, scoliosis of the thoracic and lumbar spine, and there was a lumbosacral transitional vertebra. In the lower lumbar and upper sacral region, osteochondrosis and spondylosis deformans were present. There were no particular heart and lung findings.

**TABLE**

<table>
<thead>
<tr>
<th>Neurophysiological Findings</th>
<th>Ulnar nerve</th>
<th>Peroneal nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td>motor neurones</td>
<td>mixed nerve action potential</td>
<td>motor neurones</td>
</tr>
<tr>
<td>Terminal latency</td>
<td>3-1 msec</td>
<td>5-2 msec</td>
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<tr>
<td>Maximum conduction velocity</td>
<td>35-3 m/sec</td>
<td>43-5 m/sec</td>
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<tr>
<td>forearm</td>
<td>36-7 m/sec</td>
<td>48-6 m/sec</td>
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<tr>
<td>upper arm</td>
<td>30-9 m/sec</td>
<td>9-4 m/sec</td>
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<tr>
<td>Overall duration of the</td>
<td>16-3 msec</td>
<td>2-5 msec</td>
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<td>evoked muscle response</td>
<td>19-1 msec</td>
<td>4-1 msec</td>
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<tr>
<td>distal response</td>
<td>11-0 mV</td>
<td>11-0 mV</td>
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<tr>
<td>proximal response</td>
<td>10-0 mV</td>
<td>8-5 mV</td>
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<tr>
<td>Overall amplitude of the</td>
<td>18-1 m/sec</td>
<td>—</td>
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<tr>
<td>evoked muscle response</td>
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<td>distal response</td>
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<td>proximal response</td>
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<tr>
<td>Difference in conduction</td>
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<tr>
<td>velocity of fast and slow</td>
<td>—</td>
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<tr>
<td>conducting motor neurones</td>
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**DISCUSSION**

This case of metachromatic leukodystrophy in a 39 year old woman was discovered by urine analyses of the siblings of a patient with the late adult form of ML (Pilz et al., 1971). A deficiency of the enzyme arylsulphatase A in urine and leucocytes, a distinctly increased sulphatide excretion in the urine and an accumulation of metachromatic substances in the epithelial cells of the urine sediment were found. The patient is socially well adjusted, has no subjective complaints pertaining to the central or peripheral nervous system, and is under the care of the family physician only for varicosity of the lower leg. Back pains which appeared through physical exertion are probably traceable to
degenerative changes of the spine. Until the
time of this examination mental changes had not
been noticed by relatives or the family physician.

The neurological examination showed a
definite decrease of the motor nerve conduction
velocity in the upper and lower extremities.
Since the patient appeared only for an outpatient
examination, no pneumoencephalogram or nerve
biopsy could be carried out. The echoencephalo-
gram revealed no enlargement of the third
ventricle, the EEG was normal. Noticeable in
the laboratory findings is the normal protein
content in the cerebrospinal fluid.

For the diagnostic classification of this case,
three possibilities must be discussed. There may
be (1) a latent or mildly progressing form of
ML; (2) slight symptoms of a heterozygote
genetic carrier; or (3) disturbances of an early
diagnosed case of ML, which has not yet
become clinically manifested.

Other sphingolipidoses also show differences
in the onset of the disease and severity of the
clinical picture. In analogy with enzymatic
studies of variously developing forms of
Gaucher’s disease (Brady, 1967) and GM2-
gangliosidosis (Okada, Veath, and O’Brien,
1970), the assumption would also seem plausible
that the infantile form of ML is caused by a
strongly marked enzyme defect, and that late
onset of the disease is due to a partial enzyme
defect. If it is furthermore taken into account
that the activity of cerebroside sulphatase and
arylsulphatase A steadily increases in the brains
of rabbits after birth, reaching its maximum
after the main constitution of myelin (Jatzkewitz,
1958), one would expect that the sulphatide
accumulation in ML would decrease with
increasing age of manifestation. In infantile and
juvenile cases, it has not been possible so far to
establish such a relationship (Jatzkewitz and
Mehl, 1969); however, several adult cases
showed a distinctly diminished amount of
accumulation in the brain as compared with the
earlier manifested cases (Pilz and Müller, 1969).
Nevertheless, for the patient described here, the
amount of sulphatides excreted in the urine in a
24 hour interval is definitely comparable with
that of her diseased brother and is even higher
than in another adult case of ML (Pilz et al.,
1971: case 1). The high level of urinary sulphatides
 correlates with a distinct arylsulphatase A
deficiency in urine and leucocytes. The extent of
these biochemical anomalies speaks against a
latent form of ML, and against a heterozygote
hereditary tendency as well. We are, therefore,
of the opinion that we are dealing with a case of
late adult ML, which has been discovered before
the onset of the first subjective disorders, and
that further symptoms of the disease will
develop in the future. Although the paper of
Austin dealing with an increased excretion of
metachromatic substances (Austin, 1957) and an
aryl sulphatase A deficiency in the urine (Austin
et al., 1966) of patients with ML has made it
possible to recognize the disease early, only two
preclinical cases of late infantile metachromic
leukodystrophy have been described until now
(Greene, Hug, and Schubert, 1967; Gabreëls,
Lamers, Kok, Loonen, and Lommen, 1971).

Because of the decreased nerve conduction
velocity, the involvement of myelin of peripheral
nerves can be detected earlier than in the central
nervous system. The peripheral neuropathy
without clinical symptoms obviously represents
an early sign of ML. Similar observations have
also been made by Yudell, Gomez, Lambert,
and Dockerty (1967) for several late infantile
forms, but in these cases examination did not
take place before the onset of flaccid paralysis.

The findings in the present case give no answer
to the question whether the enzyme defect had
existed since birth or, for still unknown reasons,
developed in later years (Jatzkewitz, 1970). In a
fully healthy 5 year old boy from a kin with
Fabry’s disease, we also found an increased
urinary excretion of the stored glycosphingo-
lipids (Pilz and Denden, 1972). A correlation of
this finding with adult ML is, however, not
permissible because of the different organ and
age manifestations of both diseases.

We wish to thank Mrs. R. Oberschmidt for her
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