A preclinical case of late adult metachromatic leukodystrophy¹

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

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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 crural 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%, α_1 globulin 5%, α_2 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 trypanflavin (Holländer, 1964) and contrasting with haemalaun, metachromatic substances were recognizable in the epithelial cells (Fig. 1). A quantitative

FIG. 1. Intracytoplasmic accumulation of metachromatic substances in epithelial cells of urine sediment. Staining with acriflavin, $\times 720$.

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 semi-quantitative 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; Pandey 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 μ V 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

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.

FIG. 2. Thin-layer chromatogram of total lipid extracts from urine. Solvent: chloroform-methanol-water 73:28:4, 5. Detection for glycolipids: orcin/sulphuric acid. 1 = cerebroside, 2 = monohexose-sulphatides, 3 = dihexose-sulphatides. A = test mixture (free cholesterol, cerebroside, kersin type of cerebroside sulphate, sphingomyelin. Cholesterol and sphingomyelin non visible with the spray used). B = normal urine (1/20 of a 24-hour portion). C = urine (1/20 of a 24-hour portion) from case G.K.

TABLE
NEUROPHYSIOLOGICAL FINDINGS

	Ulnar nerve		Peroneal nerve
	motor neurones	mixed nerve action potential	motor neurones
Terminal latency	3.1 msec	—	5.2 msec
Maximum conduction velocity			
forearm	35.3 m/sec	43.5 m/sec	30.9 m/sec
upper arm	36.7 m/sec	48.6 m/sec	—
Overall duration of the evoked muscle response			
distal response	16.3 msec	2.5 msec	9.4 msec
proximal response	19.1 msec	4.1 msec	11.6 msec
Overall amplitude of the evoked muscle response			
distal response	11.0 mV	50.0 μ V	11.0 mV
proximal response	10.0 mV	10.0 μ V	8.5 mV
Difference in conduction velocity of fast and slow conducting motoneurones	18.1 m/sec	—	—

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 varicosis 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 echoencephalogram 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 arylsulphatase 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 metachromatic 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 glycosphingolipids (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.

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