

## Peripheral neuropathy detected on electrophysiological study as first manifestation of metachromatic leucodystrophy in infancy

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**SYNOPSIS** A case of infantile metachromatic leucodystrophy is described in which symptoms started at 1 year of age with weakness and hypotonus in the lower extremities. The electrophysiological status was typical of a polyneuropathy, showing fibrillation and a reduction of the nerve conduction velocity to 30% of the average for normal children of the same age. Clinical signs of a central lesion and mental regression were not evident until a year later. Nerve biopsy showed metachromatic granules in the phagocytes and in the Schwann cells, confirming the diagnosis of metachromatic leucodystrophy. In peripheral neuropathy in infancy without obvious cause, a nerve biopsy is the most appropriate method for diagnosis of the metachromatic leucodystrophy.

The metachromatic form is one of the most common manifestations of the leucodystrophies (Yudell *et al.*, 1967). Although its onset may be established at different stages in life, it is most commonly before the age of 2 years, particularly between 6 and 18 months (Gamstorp, 1970). It is likely that some forms of the disease, such as the late-infantile metachromatic leucodystrophy, are transmitted by a recessive autosomal gene (Gustavson and Hagberg, 1971).

Reduction of the nerve conduction velocity compatible with polyneuropathy was demonstrated in metachromatic leucodystrophy, generally severe, by Fullerton (1963, 1964) and Moosa and Dubowitz (1971). Marked reduction of motor nerve conduction velocity has also been observed in other forms of leucodystrophy, such as in Krabbe's disease (Hogan *et al.*, 1969).

The electrophysiological alterations are paralleled by the structural changes consisting of segmental demyelination observed in nerve biopsy (Dayan, 1967; Aziz and Pearce, 1968). Since the first findings of metachromatic substance in the nerve (Thieffry and Lyon, 1959), sural nerve biopsy has proved to be the most appropriate method for the diagnosis of metachromatic

leucodystrophy. The metachromatic granules are found in the Schwann cells and also in the perivascular phagocytes (Hagberg *et al.*, 1962; Webster, 1962).

Polyneuropathy is uncommon in infancy and, although it is a recognized component of the picture of metachromatic leucodystrophy, it is not usual to establish the diagnosis before the onset of mental symptoms and a lesion of the central nervous system.

However cases of metachromatic leucodystrophy have been described with apparent onset as a peripheral neuropathy, clinically manifested by hypotonus and hyporeflexia with an electrophysiological study compatible with demyelination of the peripheral nerve (Yudell *et al.*, 1967; De Silva and Pearce, 1973).

We present in this paper the case of an infant diagnosed as metachromatic leucodystrophy by nerve biopsy, seen for the first time when the infant was 2 years old. At that time, the clinical picture and electrophysiological studies were compatible with a pure polyneuropathy.

### CASE REPORT

S.D., a female child, was born to unrelated parents with no family history of neurological disease. The

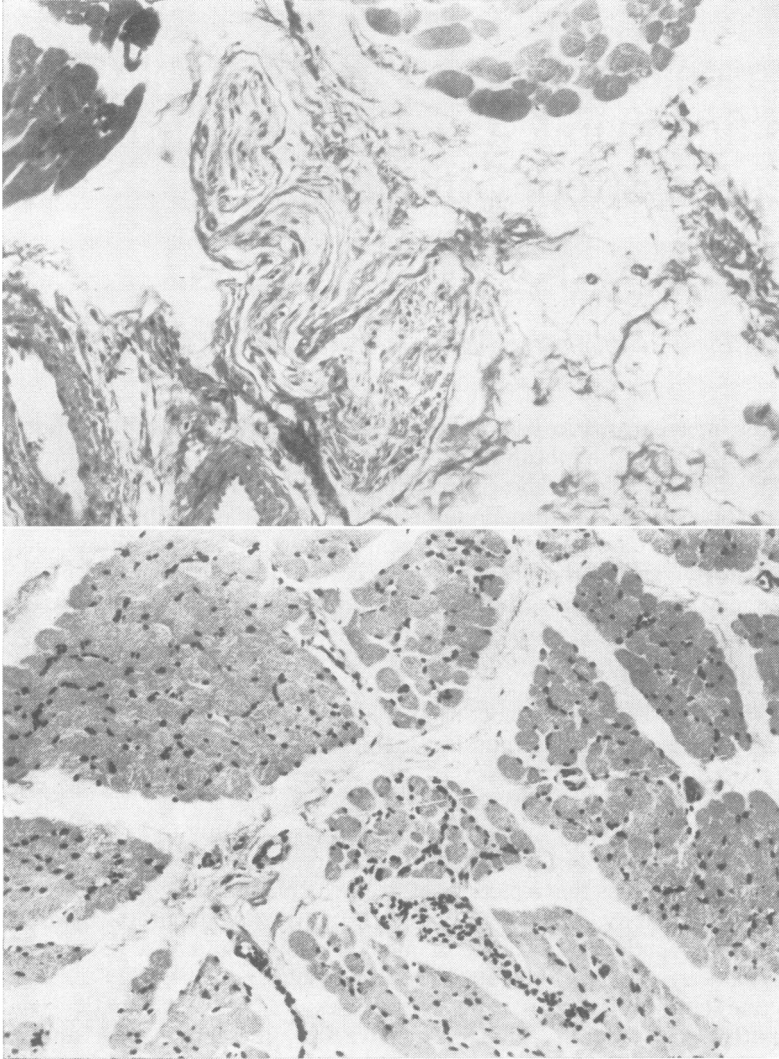


FIG. 1 *Internal hamstring biopsy. (a, top) Muscular atrophy. Thinness of the fibres and increase in the number of nuclei. H and E,  $\times 10$ . (b, bottom) Demyelination of intramuscular nerve fibres. Landum,  $\times 10$ .*

birth history was without incident. There are no data of interest in the family history, the parents being healthy as well as two brothers, 4 and 13 years old. When she was 12 months old, without previous antecedent, the infant showed weakness in the lower extremities, with unsteady step and frequent falling down. Weakness in her upper extremities was not present then and her mental state was normal too. A diagnosis of cerebral palsy was made in another hospital and she underwent a rehabilitation treatment without apparent improvement at first. She later developed paresis of the lower extremities.

One year after the onset of the disease the child

was brought to this hospital. She was mentally alert. Her walking was ataxic with bilateral steppage gait, requiring a walking aid. Generalized hypotonia, with marked kyphosis when she was seated, was evident. The tendon reflexes were feeble in the four extremities and muscle weakness was present, particularly in the legs. Sensory tests were unreliable because of lack of cooperation. Other abnormal neurological signs were not found. The provisional diagnosis reached at that time was infantile spinal muscular atrophy or myopathy. She was referred to our department for electromyography (EMG). The electrophysiological study, which is described later in detail, was com-



FIG. 2 Sural nerve biopsy. Metachromatic granules.

patible with a peripheral neuropathy. Since the reduction in the conduction velocity was over 50%, a marked nerve demyelination was suggested. Several causes of polyneuropathy in infancy were rejected. EMG studies on her mother and two brothers were also performed with normal results.

Routine tests including radiological studies, red blood cell count, white blood cell count, erythrocyte sedimentation rate, urine analysis, muscle enzymes, blood urea and glucose were normal. Total plasma lipids were 406 mg/dl and the lipidogram was normal. Retinal appearances, electroencephalography (EEG), and electrocardiography were also normal. The serum transaminases were elevated when first estimated (SGOT, 182 units; SGPT, 205 units) but, in a second investigation, they were found to be within normal limits. In the cerebrospinal fluid (CSF) study there was 1 cell/mm<sup>3</sup>; glucose 36 mg/dl; chloride 111 mEq/l; total protein 68 mg/dl and Pandy reaction positive.

Without a precise diagnosis, the infant was placed

under treatment in the rehabilitation department without observing any improvement. The child began to have pains in her legs that very often started with the least movement.

After two months stay in hospital a growing deterioration in her general condition was observed, accompanied by paleness of the skin, although her nutritional condition was maintained. The facies was apathetic and the infant's character changed, as she became irritable and wept often without apparent cause. She could not walk even with an aid and the standing position was held with support; a tendency to the scissors sign appeared, with bilateral Babinski responses; meanwhile, the upper limbs remained hypotonic. Muscle atrophy in distal groups of legs was already evident.

Mental tests then showed a motor behaviour appropriate to 8 months and an adaptive behaviour of 15 months; her speech was that of a child of 24 months and a developmental age of 18 months with a quotient of 72; her IQ was 63. Cholecystography demonstrated an excluded gall-bladder. Pneumoencephalography showed left frontal cortical atrophy and ventricular dilatation. Foamy cells were observed in a rectal biopsy. Muscle biopsy *vide infra* (and Fig. 1) confirmed the neurogenic atrophy detected in the EMG. Sural nerve biopsy (Fig. 2) by the Hirsch-Peiffer technique revealed metachromatic substance inside the macrophages and Schwann cells. Metachromatic granules were sought repeatedly by urinary cytological investigation but without any success.

These results positively confirmed the diagnosis of metachromatic leucodystrophy, but the clinical suspicion was established only when the patient manifested central nervous symptoms, hypertonia, and mental impairment.

Two months after the diagnosis was established and the infant had ostensibly improved from a pneumonia, she began to present an apathetic facies with half-opened mouth, lack of gaze fixation, easy weeping, dysphagia, and loss of comprehensible speech, emitting sounds only. The hypertonus was very much marked when the legs were extended and in the equinus posture; there was no voluntary control of the right lower extremity. Increase of muscle tone was also appreciated in the arms where active mobility had been diminished. There was a trunk rigidity which prevented the seating position although opisthotonos was not evident. Deafness and blindness were not apparent either. Repeated EEG and retinal studies proved normal again. Urine analysis, performed for the third time, was negative without any findings of intracellular metachromatic granules.

The possibility of a diet poor in vitamin A was considered, although the dysphagia and the lack of

cooperation about eating necessitated a soft, mainly milky, diet.

**ELECTROPHYSIOLOGICAL STUDY** The right anterior tibial muscle was explored with concentric needle electrodes. Profuse fibrillations and positive sharp waves were observed at rest. During maximal effort the interference pattern was reduced to 1.5 mV, with a 20% increase of the average duration of the motor unit potentials and 40% of the motor unit action potentials were polyphasic.

The right peroneal nerve gave a motor distal latency of 7.7 ms and a motor conduction velocity (knee-ankle) of 17.7 m/s. The evoked muscular potential in extensor digitorum brevis had an amplitude of 1 mV (coaxial needle). The left peroneal nerve gave 6.5 ms of distal latency and a motor conduction velocity (knee-ankle) of 16.9 m/s, with polyphasic muscle action potential of 2 mV amplitude.

The sensory conduction velocity of the right median nerve was explored with surface electrodes at the wrist. When the second digit of the hand was stimulated with ring electrodes 7 cm from the detection point no sensory potential could be detected.

The mother and the two brothers of the patient also underwent EMG investigations. The mother, aged 40 years, gave normal voluntary patterns in the EMG. The peroneal nerve gave a distal latency in extensor digitorum brevis of 3.4 ms and motor conduction velocity of 46.3 m/s (knee-ankle). The muscle action potential in the extensor digitorum brevis muscle was biphasic of 10 mV amplitude. The sensory latency in the median nerve (second finger-wrist, 13 cm) was 2.8 ms, and the amplitude of the sensory evoked potential was 15  $\mu$ V. The data obtained from one of the two brothers of the infant were also normal. The motor conduction velocity of the peroneal nerve (knee-ankle) was 53.2 m/s, distal latency 3.4 ms and the muscle action potential in the extensor digitorum brevis was biphasic of 8 mV amplitude. The sensory conduction latency of the median nerve (second finger-wrist, 11 cm) was of 2.5 ms and amplitude 20  $\mu$ V. The other brother, 4 years old, also had a normal electromyogram. The motor peroneal nerve conduction was normal: 3.4 ms of distal latency and 54.2 m/s velocity (knee-ankle), with a biphasic potential evoked in extensor digitorum brevis of 5 mV amplitude. The sensory potential of the median nerve had a latency of 2.4 ms (second finger-wrist, 9 cm) and 20  $\mu$ V amplitude.

The electrophysiological study in the affected infant was considered to show neurogenic atrophy and severe disturbance of the nerve conduction in its motor and sensory components, compatible with a polyneuropathy with significant demyelination of the

peripheral nerve. The mother and brothers of the patient were considered normal.

**MUSCLE BIOPSY** The essential findings of the left internal hamstring muscle biopsy were: thinness of all the fascicles with homogeneous reduction in diameter of the muscle fibres, proliferation of the nuclei which seemed to be enlarged, and increase of the interstitial collagen. The intramuscle nerve fibres appeared not to be uniform, with a great number of Schwann cells and absence of myelin. The findings were interpreted as showing neurogenic atrophy suggestive of peripheral nerve lesion (Dr C. Liñan) (Fig. 1).

**SURAL NERVE BIOPSY** Severe demyelination with myelin sheath disintegration was found. Sections were stained with PAS, Hirsch-Peiffer, luxol blue, Sudan III, scarlet red, and toluidine blue stains. The most surprising finding was the presence, with the Hirsch-Peiffer stain, of a metachromatic golden-brown material in the macrophages and Schwann cells (Dr S. Ramon y Cajal and Dr A. Martinez) (Fig. 2).

#### DISCUSSION

The clinical suspicion of metachromatic leucodystrophy is established usually only in the presence of central neurological disturbance and mental regression (Yudell *et al.*, 1967; De Silva and Pearce, 1973). As the first clinical presentation in our patient consisted of weakness and hypotonia the possibility of either spinal atrophy or myopathy was considered. Because of the alterations in the cerebrospinal fluid, these diseases, together with Guillain-Barré polyradiculoneuritis, are the initial diagnosis most frequently mentioned (Yudell *et al.*, 1967; De Silva and Pearce, 1973).

The electrophysiological study definitely established the presence of polyneuropathy. Peripheral neuropathy is an uncommon condition in infancy and, as sensory testing in infants rarely provides any conclusive data, diagnosis of polyneuropathy becomes very difficult (Aziz and Pearce, 1968). The measurement of nerve conduction velocity is simple and does not require cooperation on the patient's part, so it is an excellent method for the detection of peripheral nerve pathology. Our patient showed neither palpable nerves nor retinal alterations. Other causes of polyneuritis mentioned as frequent in

infancy by Gamstorp (1968) were eliminated by the clinical history and supplementary tests. The cerebrospinal fluid was not considered specific and the familial component was also rejected in the light of the clinical exploration and electromyographic results performed. On the other hand, it has been said (Tasker and Chutorian, 1969) that a great deal of chronic polyneuritis in infancy remains without defined aetiology. During her stay in hospital the patient showed an evolution towards hypertonus in lower extremities which, together with the change in character, were the symptoms that led us to establish the possibility of leucodystrophy, which was confirmed by the nerve biopsy.

Polyneuropathy in metachromatic leucodystrophy, even at an early stage is now familiar and in recent years has received increasing interest (Yudell *et al.*, 1967; Aziz and Pearce, 1968; Gamstorp, 1968, 1970; Tasker and Chutorian, 1969; De Silva and Pearce, 1973). The electrophysiological study is usually the first test to confirm the polyneuritis, and is therefore of great orientation value. The marked reduction of motor nerve conduction velocity, commonly by more than 50%, has been described by Fullerton (1963, 1964), Yudell *et al.* (1967), Aziz and Pearce (1968), Gamstorp (1968, 1970), and De Silva and Pearce (1973). Our results show figures of motor nerve conduction velocity that are equivalent to about 30% of the average values in normal children of the same age, the distal latency was more than doubled. The voluntary EMG pattern is described more rarely in the literature. We detected profuse fibrillations indicative of axonal degeneration and we agree at this point with some previous authors (Austin, 1958; Taori *et al.*, 1971). The absence of evoked sensory potential, observed in our patient, has been pointed out by Yudell *et al.* (1967). We did not explore the H reflex in the upper extremities but Yudell *et al.* have obtained it, supporting the possibility of an upper motor neurone lesion.

The confirmation of the diagnosis during the patient's life is by histology and requires the finding of metachromatic material. The pathology of metachromatic leucodystrophy consists of accumulation of sulphatides in several tissues, particularly in the nervous system where a demyelination of the white matter takes place; this

is attributed to deficiency of the enzyme arylsulphatase A, perhaps as a consequence of a congenital metabolic anomaly. Absence of this enzyme has been demonstrated in the urine of affected infants (Melchior and Clausen, 1968). This enzymatic deficiency has also been observed in some clinically healthy relatives of patients affected by late-infantile metachromatic leucodystrophy, which would suggest that they might be in a preclinical state of the disease (Pilz, 1972). The enzymatic activity in our patient has not been determined at the time of carrying out this study. As vitamin A takes part in the active synthesis of sulphates necessary for the biosynthesis of sulphatides, a diet poor in vitamin A has been proposed for the treatment of metachromatic leucodystrophy (Melchior and Clausen, 1968; Moosa and Dubowitz, 1971).

Metachromatic granules have been found in the brain at necropsy of affected children. The same finding is described more recently in cerebral biopsies as a diagnostic confirmation of this disease (Greenfield, 1933; Aziz and Pearce, 1968). The metachromatic material is also deposited in other tissues and organs such as salivary glands, ovaries, pancreas, and gall-bladder; the accumulation in the biliary ducts might account for the excluded gall bladder shown in our patient. Metachromatic granules may also be observed in the urinary sediment (Austin, 1957), although in the patient we describe such demonstration was not possible. Deposition of sulphatides in nerve roots has also been demonstrated (Brain and Greenfield, 1950); involvement of the dorsal roots (Gamstorp, 1970), would explain the painful symptoms in our case. Phosphatides also accumulate in the peripheral nerve, especially in the Schwann cells.

The secondary degeneration of the cerebral white matter would account for the alterations in the pneumoencephalogram and, without considering them specific, these alterations are similar to those mentioned by De Silva and Pearce (1973). The deposit of metachromatic granules in the Schwann cells suggests that this is the cause of the nerve demyelination seen in biopsies (Dayan, 1967; Aziz and Pearce, 1968; Olsson and Sourander, 1969) and the myelin degeneration accounts for the marked reduction of motor nerve conduction velocity. In our

patient there was a good correlation with the severe demyelination observed in nerve fibres on biopsy of muscle and nerve (Figs 1 and 2). But the most important fact of the nerve biopsy is that it allowed positive confirmation of metachromatic leucoencephalopathy in this infant. It is imperative to find metachromatic granules in the Schwann cells and phagocytes (Hagberg *et al.*, 1962; Webster, 1962; Olsson and Sourander, 1969), since small deposits of metachromatic substance among the nerve fibres may also be observed in children with Krabbe's disease and familial amaurotic idiocy (Olsson and Sourander, 1969).

We wish to stress the importance of nerve conduction studies. Having demonstrated polyneuropathy, it is important to appreciate that, during the first 18 months of life, metachromatic leucodystrophy is one of the most common causes of peripheral nerve lesion and that polyneuritis might be its presenting form. In these circumstances, sural nerve biopsy is the most appropriate investigation, superior to rectal biopsy and urine investigation, to confirm or reject the presence of metachromatic granules, so that the diagnosis can be made as early as possible before the appearance of symptoms of central and mental regression.

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## REFERENCES

- Austin, J. H. (1957). Metachromatic form of diffuse cerebral sclerosis. 2. Diagnosis during life by isolation of metachromatic lipids from urine. *Neurology (Minneapolis)*, **7**, 716-723.
- Austin, J. H. (1958). Observations in metachromatic leucoencephalopathy. *Transactions of the American Neurological Association*, **83**, 149-152.
- Aziz, H., and Pearce, J. (1968). Peripheral neuropathy in metachromatic leucodystrophy. *British Medical Journal*, **4**, 300.
- Brain, W. R., and Greenfield, J. G. (1950). Late infantile metachromatic leuco-encephalopathy, with primary degeneration of the interfascicular oligodendroglia. *Brain*, **73**, 291-317.
- Dayan, A. D. (1967). Peripheral neuropathy of metachromatic leucodystrophy: observations on segmental demyelination and remyelination and the intracellular distribution of sulphatide. *Journal of Neurology, Neurosurgery, and Psychiatry*, **30**, 311-318.
- De Silva, K. L., and Pearce, J. (1973). Neuropathy of metachromatic leucodystrophy. *Journal of Neurology, Neurosurgery, and Psychiatry*, **36**, 30-33.
- Fullerton, P. M. (1963). Motor nerve conduction velocity in metachromatic leucodystrophy. (Abstract.) *Electroencephalography and Clinical Neurophysiology*, **15**, 913.
- Fullerton, P. M. (1964). Peripheral nerve conduction in metachromatic leukodystrophy (sulphatide lipidosis). *Journal of Neurology, Neurosurgery, and Psychiatry*, **27**, 100-105.
- Gamstorp, I. (1968). Polyneuropathy in childhood. *Acta Paediatrica Scandinavica*, **57**, 230-238.
- Gamstorp, I. (1970). Metabolic neuropathies and myopathies in infancy and childhood. *Acta Neurologica Scandinavica*, **46**, 109-119.
- Greenfield, J. G. (1933). A form of progressive cerebral sclerosis in infants associated with primary degeneration of the interfascicular glia. *Journal of Neurology and Psychopathology*, **13**, 289-302.
- Gustavson, K. H., and Hagberg, B. (1971). The incidence and genetics of metachromatic leucodystrophy in northern Sweden. *Acta Paediatrica Scandinavica*, **60**, 585-590.
- Hagberg, B., Sourander, P., and Thoren, L. (1962). Peripheral nerve changes in the diagnosis of metachromatic leucodystrophy. *Acta Paediatrica*, **51**, S135, 63-71.
- Hogan, G. R., Gutmann, L., and Chou, S. M. (1969). The peripheral neuropathy of Krabbe's (globoid) leucodystrophy. *Neurology (Minneapolis)*, **19**, 1094-1100.
- Melchior, J. C., and Clausen, J. (1968). Metachromatic leucodystrophy in early childhood. Treatment with a diet deficient in vitamin A. *Acta Paediatrica Scandinavica*, **57**, 2-8.
- Moosa, A., and Dubowitz, V. (1971). Late infantile metachromatic leucodystrophy. Effect of low vitamin A diet. *Archives of Diseases in Childhood*, **46**, 381-383.
- Olsson, Y., and Sourander, P. (1969). The reliability of the diagnosis of metachromatic leucodystrophy by peripheral nerve biopsy. *Acta Paediatrica Scandinavica*, **58**, 15-24.
- Pilz, H. (1972). Late adult metachromatic leukodystrophy. *Archives of Neurology*, **27**, 87-90.
- Taori, G. M., Iyer, G. V., Abraham, J., and Mammen, K. C. (1971). Electrodiagnostic studies in lipidoses, mucopolysaccharidoses, and leukodystrophies. I. Nerve conduction and needle myographic studies. *Neurology (Minneapolis)*, **21**, 303-306.
- Tasker, W., and Chutorian, A. M. (1969). Chronic polyneuritis of childhood. *Journal of Pediatrics*, **74**, 699-708.
- Thieffry, S., and Lyon, G. (1959). Diagnostic d'un cas de leucodystrophie métrachromatique (type Scholz) par la biopsie d'un nerf périphérique. *Revue Neurologique*, **100**, 452-456.
- Webster, H. de F. (1962). Schwann cell alterations in metachromatic leucodystrophy: preliminary phase and electron microscopic observations. *Journal of Neuropathology and Experimental Neurology*, **21**, 534-554.
- Yudell, A., Gomez, M. R., Lambert, E. H., and Dockerty, M. B. (1967). The neuropathy of sulphatide lipidosis (metachromatic leukodystrophy). *Neurology (Minneapolis)*, **17**, 103-111, and 127.