Peripheral Neuropathy in Metachromatic Leucodystrophy

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Involvement of the peripheral nerves in metachromatic leucodystrophy has received increasing interest in recent years (Brain and Greenfield, 1950; Norman, Urich, and Tingey, 1960). Though definite pathological findings have been made there have been few clinical observations of peripheral neuropathy in this condition.

Case Report

This patient was born to unrelated parents without any family history of neurological disease. The birth history was without incident. She had normal milestones until the age of 1½ years, when she was noticed to be unsteady on her legs, and within the course of a few weeks was unable to support herself unaided. There was a history of recurrent attacks of infection of the upper respiratory tract. On examination at the age of 18 months she was mentally alert, there was a left sixth-nerve palsy, the arms were normal but the legs were hypnotic, with weakness of both proximal and distal muscles, and the reflexes were depressed. A lumbar puncture examination at the time showed cerebrospinal fluid (C.S.F.) protein 180 mg./100 ml. without cells, and a negative Lange curve. In view of these clinical and biochemical findings a diagnosis of postinfective peripheral neuritis was made.

Electrophysiological studies were done at this stage (Dr. D. Taverner). The conduction in the right lateral popliteal nerve was 15 metres per second. Electromyographic studies were done on the right anterior tibial and left extensor digitorum brevis muscles. There was discrete motor activity with spontaneous fibrillation potentials in both those muscles, confirming denervation in the muscles of the legs.

Prednisone 5 mg. b.d. was given, and in the following three weeks she made a definite but slight improvement, and at the time of her discharge from hospital could walk with support. While at home prednisone was increased to 30 mg. daily, but her neurological condition progressed. She could walk only with the aid of the furniture, and after six months from the onset of the illness she had become helpless and unable to stand. There was no change in the sixth nerve palsy. At this stage her hands were unsteady and she had a coarse tremor while feeding herself. She was mentally alert and would play with her brother.

On readmission, when the duration of her illness was 10 months, she was found to be mentally alert but very irritable. Sucking and grasp reflexes were absent. There was some intention tremor, and arm movements were clumsy. She could not support herself, and her legs were found for the first time to be spastic; the tendon jerks were normal in the arms, but the knee jerks were pathologically brisk. The abdominal reflexes were present, and the right plantar response was equivocal. Lack of co-operation precluded a sensory examination. During this admission she had a major epileptic attack. The C.S.F. protein was 130 mg./100 ml. with 40 leucocytes (75% lymphocytes). An air ventriculogram combined with brain biopsy was performed because of obvious cerebral involvement of recent occurrence. The size of the ventricles was normal, but there were excessive pools of air over the cortex. Repeated examinations of the urine did not show metachromatic granules.

During the next three months she became progressively withdrawn and irritable, had repeated attacks of major epileptic convulsions, and developed progressive cortical blindness. The spasticity in the legs increased and she developed contractures of her lower limbs in extension. The arms also became spastic with contractures in flexion. Twelve months after the onset of the disease she died of a fulminating bronchopneumonia. Permission for necropsy was withheld.

Brain Biopsy (Dr. D. Harriman).—The cortex was virtually normal. There was an excess of glial nuclei in the white matter. Some were swollen astrocytes; the remainder were oligodendroglia whose cytoplasm was distended. With periodic-acid-Schiff stain oligodendroglia showed filigree staining of the cytoplasm. In frozen sections the same cells were found to contain abundant metachromatic granules staining brown with both toluidine blue and crystal violet. Scarlet red did not stain this material but revealed a few lipid macrophages in the perivascular spaces. The myelin stained metachromatically with crystal violet but not with toluidine blue.

Discussion

The neurological manifestations of metachromatic leucodystrophy are mainly due to involvement of the central nervous system, and clinical involvement of the peripheral nerves has been largely overlooked. This is apparent from Hagberg's (1963) comment: "As the tendon reflexes in some cases were diminished or absent, and as early increase of the C.S.F. protein was nearly always found, polyradiculitis was the diagnostic error most easily made."

Greenfield (1933) reported on two children who complained of pins and needles in the legs and then in the arms. In his clinical description he noted that in one child the tendon reflexes were absent, while in the other they were feeble, and this was confirmed later by Brain and Greenfield (1950). Fullerton (1964) observed that the tendon reflexes were absent or depressed in six of the seven cases she described. The subjective symptoms of pins and needles or numbness in the limbs are usually unobtainable at this stage.

These clinical findings can be attributed to definite histopathological changes observed at necropsy and nerve biopsy (Thieffry and Lyon, 1959; Hagberg, Sourander, and Thorén, 1962; Webster, 1962).

The metachromatic granules accumulate predominantly in the Schwann cells of the peripheral nerves. Webster (1962) found that 95% of the Schwann cells were abnormal in the sections he examined. As the myelin sheath is formed by the Schwann cells it seems probable that a disturbance of the metabolism of the parent cell will cause degeneration of the myelin. This is confirmed further by the fact that such disintegration is more severe but patchy in the paranodal and sometimes internodal region, and that long stretches of myelin along the affected fibres may be normal, suggesting a relative sparing of some of the Schwann cells. This picture is one of segmental demyelination.

The diagnostic value of nerve conduction studies is recognized. Fullerton (1964) reported a marked reduction of motor-nerve conduction velocity in six patients. The amplitudes of the muscle action potentials were at the lower limit of normal. The nerve conduction rate of 15 metres per second in the case described here, with the presence of discrete motor activity and spontaneous fibrillation activity, establishes the site of the lesion in the peripheral nerves.

Peripheral neuropathy is an uncommon condition in infancy, and its diagnosis may be difficult. The object of this paper is to draw attention to the fact that metachromatic leucodystrophy may present as a polyneuropathy. This should be kept in mind in obscure cases. Electrophysiological studies supplemented by a peripheral nerve biopsy would establish the diagnosis in a suspected case. Other useful diagnostic measures used include examination of epithelial cells in the urine and rectal biopsy for metachromatic material. Cerebral biopsy may be needed if other investigations are negative.

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