Adult Metachromatic Leucodystrophy

GILLIAN COLE, N. S. F. PROCTOR

SUMMARY

A case of adult metachromatic leucodystrophy, the first described in South Africa, is reported. A 28-year-old, White South African-born male developed mental and neurological signs which started 4 years prior to his admission to Sterkfontein Hospital. His course was progressively downhill, and by the time of his death he was profoundly demented. An autopsy was performed, and the diagnosis of adult metachromatic leucodystrophy was made histologically. A brief summary of the disease is given.

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CASE REPORT

History

The patient was a White South African male, and his illness first became apparent in 1967, at the age of 28 years. He had passed standard 7 at the age of 16 years, and was a plumber by trade. He was married and had 4 sons who are all well. His mother is alive and well, and his father died many years ago from coronary artery disease. He had 4 sisters and 3 brothers. Two brothers and 2 sisters are apparently well. One sister died at the age of 30 years, another brother died in his early adult years, and a sister who was 27 years old died recently in an institution. According to members of the family all 3 deceased siblings exhibited the same symptoms as the patient reported here.

The patient's history prior to his admission to hospital was mainly obtained from his wife. In 1967 he became dull, uninterested in life and idle, and complained that his legs felt weak, although she noticed no change or abnormality of his gait. His condition gradually worsened, and sometimes he talked to himself. There was decline in his intellectual abilities, and he became irritable and aggressive on occasions. He gave up his job in December 1970, and by then his gait was noticeably unsteady. His wife found him increasingly difficult to cope with. He assaulted her on several occasions, and accused her of infidelity, although there were no grounds for such an accusation.

In August 1971 he was admitted to Sterkfontein Hospital. On admission he was found to be childish and fatuous, and was unable to answer simple questions or to do simple numerical calculations. There was considerable fluctuation in mood, which varied from a fatuous euphoria to depressive episodes. He stated that six different voices spoke to him, and exhibited paranoid ideas. Although his insight was poor, he still retained some awareness of his condition, and complained of loss of concentration, and that there was something wrong with his mind. He complained of weakness of his legs and bladder. This complaint sometimes led to incontinence.

Physical examination showed a markedly spastic gait. He had bilateral pes cavus, but it was not clear how long this had been present. There was increased tone of the lower limbs, very brisk patellar and ankle reflexes and flexor plantar responses. The cranial nerves were intact, and the fundi normal. No other abnormalities were detected at this stage.

During his stay in hospital the patient progressively deteriorated. His gait became more ataxic, and he was eventually confined to a wheelchair. He became totally incontinent and developed bilateral ankle clonus and extensor plantar responses. He was severely demented and virtually mute.

Neurosurgical opinion was sought, and the following examinations were carried out; an air encephalogram was attempted, but lack of co-operation rendered it valueless; bilateral carotid angiography performed under general anaesthesia was reported normal; bilateral burr holes were made, followed by contrast ventriculography, but no gross abnormality was found. Following these procedures the patient developed status epilepticus, which was extremely difficult to control. He never regained full consciousness, and died 3 weeks later.

Autopsy Findings

There were no significant findings at postmortem examination. The brain weighed 1 300 g, and no obvious cortical atrophy was present. On sectioning, in the coronal plane at 1-cm intervals, the centrum semiovale had a yellowish discoloration, and a slightly spongy appearance (Fig. 1). This change was present in varying degree throughout the white matter of the brain stem and cerebellum. The ventricles were slightly enlarged. The spinal cord was not available for examination.

Histological Examination

Gross destruction of myelin (Fig. 2) was apparent in sections taken from the frontal, parietal, temporal and occipital regions. In all these areas sparing of the cortical U-fibres (Fig. 3) was evident. Large numbers of macrophages were present in the areas of destroyed white matter,

Department of Neuropathology, School of Pathology, South African Institute for Medical Research and University of the Witwatersrand, Johannesburg

GILLIAN COLE, M.B. B.CH., D.P.M.

N. S. F. PROCTOR, M.B. B.CH., F.R.C. PATH.

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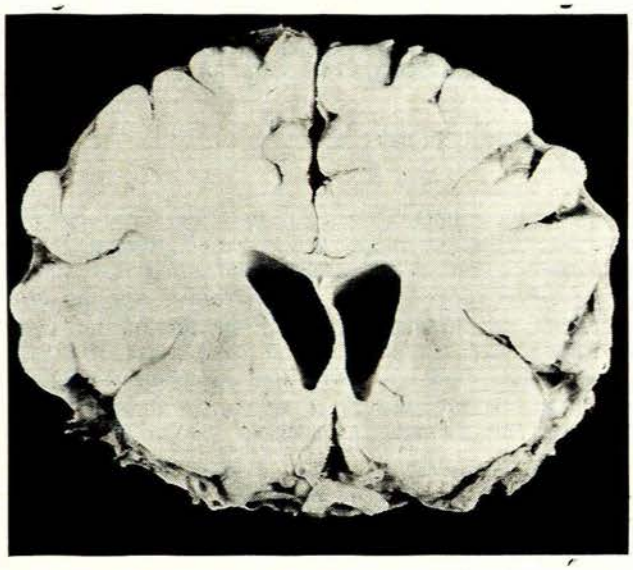

Fig. 1. Coronal section of brain showing spongy appearance of white matter (level of optic chiasma).

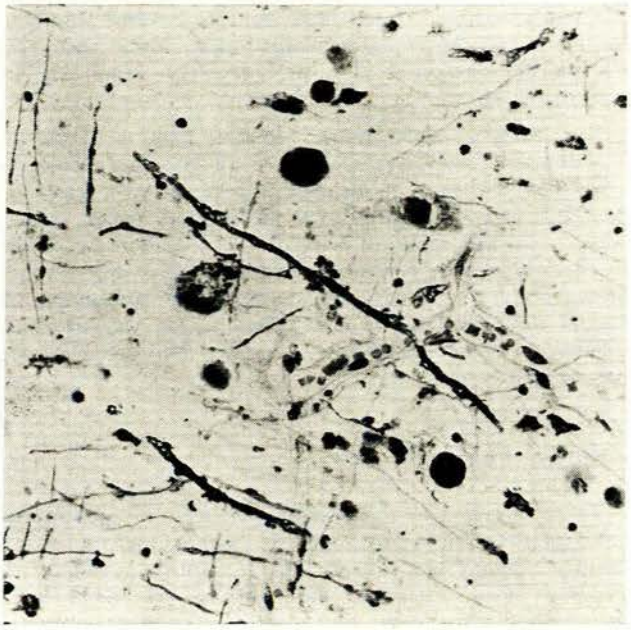

Fig. 2. Kluver-Barrera stain for myelin showing severe demyelination and macrophages containing granular material (× 240).

and they contained granular material, blue-grey in colour, with haematoxylin and eosin staining. This material was also lying free in the brain tissue.

Special stains showed that this material was strongly PAS-positive (Fig. 4), and produced a golden-brown metachromasia with the Hirsch-Pfeiffer stain (Fig. 5). Sudanophil lipid stains were negative, and stains for neutral fat

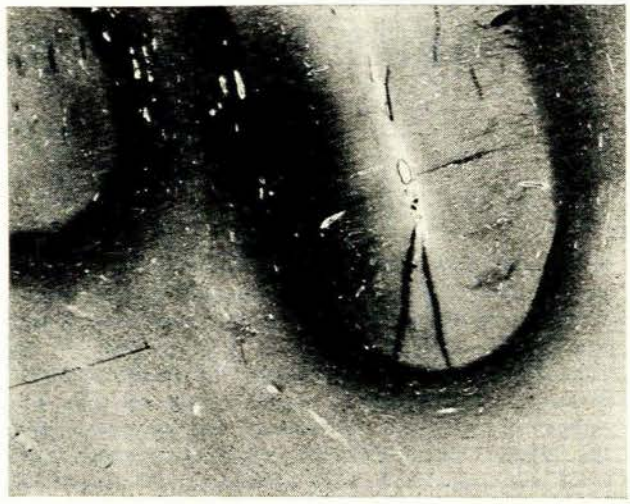

Fig. 3. Kluver-Barrera stain showing preservation of cortical U-fibres (× 8).

showed very scant positivity. Oligodendroglial cells were decreased in number. The demyelinated areas showed marked gliosis, and many swollen astrocytes were present. These histological changes were also present in the white matter of the midbrain, especially in the crus cerebri, pons and medulla. The changes were also present in the cerebellum and marked in the region of the dentate nucleus. The putamen, pallidum, thalamus and internal capsule were also involved. Examination of sections from the kidney showed metachromatic material in the epithelium of the renal tubules (Fig. 6). Sections of lung confirmed the presence of oedema, congestion and haemorrhagic infarction. The liver had small focal areas of necrosis and scattered fatty change, but no metachromatic material was observed.

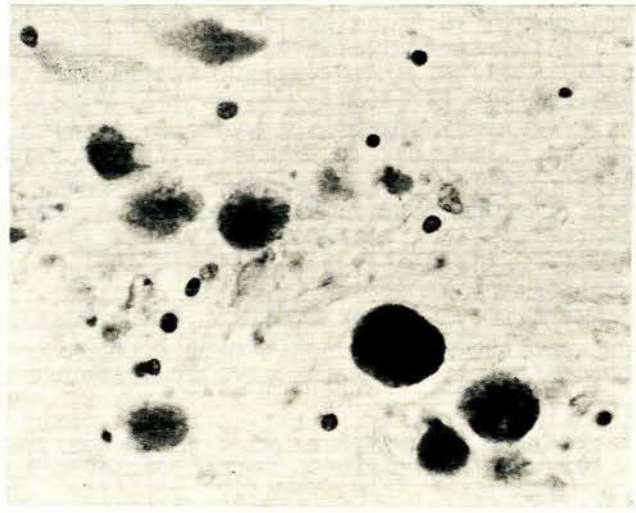

Fig. 4. Strongly PAS-positive material in macrophages and lying free in white matter (× 375).

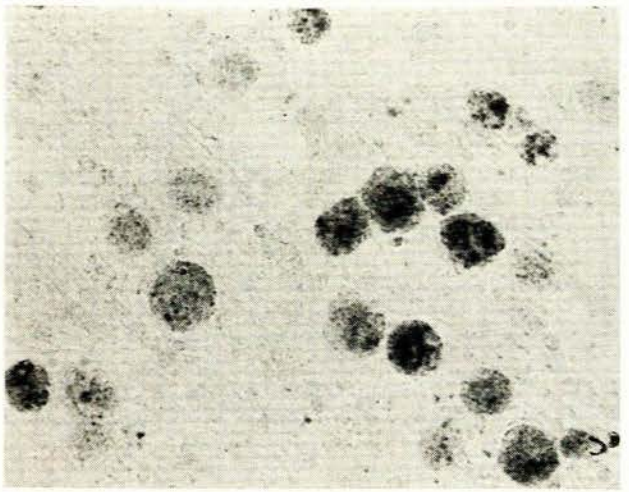

Fig. 5. Hirsch-Pfeiffer stain showing metachromatic deposits in white matter (× 240).

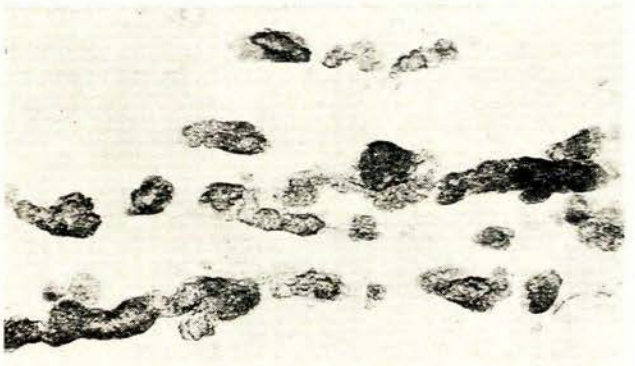

Fig. 6. Hirsch-Pfeiffer stain showing metachromatic material in renal tubular epithelium (× 95).

The histological findings were diagnostic of adult metachromatic leucodystrophy.

DISCUSSION

Metachromatic leucodystrophy occurs in three different age groups. The late infantile form is the most common. Greenfield and Norman[1] quote Lyon *et al.* who described the usual age of onset in the second year of life, with termination in the third or fourth year. The juvenile type has its onset between 13 and 20 years, while the adult type (the most rare) occurs at 21 years or later.

The disease (classified by many as a lipoidosis) results from an inherited disorder where there is deficiency of the enzyme arylsulphatase A. Sulphatide thus accumulates in the nervous system and it is this substance which is responsible for the golden-brown metachromasia with cresyl violet. Demyelination is associated with this process. Sulphatide accumulation occurs in systematic organs and, among other investigators, Wolfe and Pietra[2] reported 2 cases of late infantile metachromatic leucodystrophy, where sulphatide accumulations were found in the liver, gallbladder, pancreas, lymph nodes, kidney, adrenal gland and ovary. This supported their contention that this is a generalised metabolic disorder, possibly affecting multiple sites of sulphatide synthesis. The pathological changes are characterised by destruction of myelin and the accumulation of metachromatic material which may be found within macrophages, glial cells, and neurones, and also lying free in the tissue. In the adult type the preservation of cortical U-fibres may be a prominent feature.

Webster,[3] in an electron microscopic study of the sural nerve from patients with metachromatic leucodystrophy, observed that about 95% of Schwann cells contained cytoplasmic inclusions. These inclusions corresponded in size and distribution to the metachromatic material seen on frozen sections of the same nerve. The inclusions were present in Schwann cells surrounding both myelinated and unmyelinated axons. This observation suggests that the process of myelination occurs normally. In later stages of the disease myelin destruction is more severe, and macrophages are very numerous. Austin *et al.*[4] discussed the question of mitochondrial insufficiency in Schwann cells and oligodendroglia and elaborated on the nature and significance of low sulphatase activity. They assayed three different sulphatases in the organs of 4 patients with metachromatic leucodystrophy. Sulphatase A was markedly reduced in all 4 patients, and the deficiency was multicentric, found in cerebral cortex, white matter, kidney and liver. They describe sulphatase B and C, the patterns of which differ in different types of metachromatic leucodystrophy, and in the various organs.

Stumpf and Austin[6] pointed out that the late infantile, juvenile and adult forms, plus the variant forms, each tend to have subtly different clinical, neuropathological and biochemical variations. Stumpf *et al.*,[6] in an immunological investigation, used a precipitating antibody produced by immunising rabbits with normal human sulphatase A. They demonstrated that the rabbit antibody precipitated both the normal and MLD sulphatase A. In the MLD samples there was negligible sulphatase A activity. Their findings indicated that the enzyme protein is present in metachromatic leucodystrophy but that it is functionally abnormal. They point out that the existence of an enzyme protein in metachromatic leucodystrophy is of interest, since the activity of the protein might be increased by a therapeutic agent.

The clinical picture may vary among the different age groups, but essentially the features are those of a progressive neurological involvement due to destruction of myelin, and accompanied by mental deterioration.

A family study by Hirose and Bass[7] supports an autosomal recessive mode of inheritance for both adult and juvenile forms of the disease. From their investigations it seemed that the juvenile and adult forms had a specific pattern of inheritance which excluded the late infantile form. They point out that they could find no reported cases where infantile and late onset forms affected different members of the same family.

Diagnosis

Few adult cases have been diagnosed during life. As in the case reported here, most have been diagnosed at autopsy, and then a live member of the family with a similar history is likely to be specifically investigated. The diagnosis can be made by demonstrating absence or reduction of arylsulphatase A activity in urine, leucocytes or skin fibroblasts. Urinary excretion of sulphatides is often raised.

A useful rapid test for sulphatase A deficiency in urine is described by Austin *et al.*[8] Sural nerve biopsy is a relatively simple procedure, and Hirose and Bass[7] describe an effective technique of microdissection which enables intact nerve fascicles to be obtained. This procedure allows microchemical analysis to be more easily performed. Their cases demonstrate that formalin-fixed, paraffin-embedded sural nerve shows segmental demyelination in both adult and infantile metachromatic leucodystrophy. Frozen sections show metachromatic granules in Schwann cells, in macrophages and free in tissues. Rectal biopsy may also be useful for the detection of metachromatic material.

A probable preclinical case of adult metachromatic leucodystrophy was reported by Pilz and Hopf.[9] In a clinically well, 39-year-old sister of a patient with the disease, metachromatic deposits were found in the epithelial cells of urinary sediment, with a high urinary sulphatide excretion. Deficiency of arylsulphatase was found in urine and leucocytes. Motor nerve conduction velocity of peripheral nerves was decreased. This is a useful procedure for early diagnosis. The authors felt that she exhibited an early stage of metachromatic leucodystrophy, where clinical signs had not yet become evident.

Da Silva and Pearce[10] recently reported on 2 children with late infantile metachromatic leucodystrophy, who presented with peripheral neuropathy, and who had no evidence of central nervous system involvement at that stage. They point out the importance of early recognition of the disease from the point of view of possible therapy and genetic counselling. They stress the value of peripheral nerve biopsy in cases of peripheral neuropathy, where the cause is not evident.

Treatment

Sundaresan,[11] in an article on vitamin A and the sulphate-active enzymes, found that an acidic metabolite of vitamin A and vitamin A acid is attached to, and can activate, the enzyme ATP sulphurylase. Since vitamin A is necessary for synthesis of active sulphate, Melchior and Clausen[12] attempted to alter the course of the metachromatic leucodystrophy of the late infantile type in a child who exhibited symptoms at the age of 6 months. She was fed a diet low in vitamin A for 4 months. The diet appeared to reduce the amount of glycolipids in the urinary sediment but did not change the sulphatase activity.

Moosa and Dubowitz[13] reported the effect of a low vitamin A diet in a 3-year-old girl with late infantile metachromatic leucodystrophy. Clinical improvement occurred, and during a 2-year follow-up period she showed no progression of the disease.

At the present time about 20 cases of adult metachromatic leucodystrophy have been reported in the literature. It is possible that a fair number of cases are never diagnosed. The case described here is the first reported in South Africa. Three siblings had died without an autopsy, but from the history it is very likely that they suffered from the same condition. It is of interest that the first symptoms shown by this patient were mental. Investigations into the pedigree of this family have commenced, and it is hoped that further contributions to the knowledge of this disease will be documented.

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