2. Rao CVRM. Dengue fever in India. Indian Pediatr 1987, 54:11-14.
3. Pushpa V, Sheila M. Dengue hemorrhagic fever in Madras, 1989. (Unpub lished data).
4. darker DH, Casal J. Technique for hemagglutination and hemagglutination inhibition with nrthropod borne viruses. Am J Trop Med Hyg 1958, 7: 561-567.
5. Manchni G, Carbonara AO, Hereonara JF. Immunochemical quantitation of antigens by single radial immune diffusion. Int J Immunochemical 1965, 2: 235-254.
6. Fust G, Kavai M, Szegedi BY. Evaluation of different methods of detecting circulating immune complexes. "An International study. J Immunol Methods 1980, 12: 381-389.
7. World Health Organization. Dengue Hemorrhagic Fever. Diagosis, Treatment and Control, Geneva, 1986, pp 5-7.
8. Cedric A. Mechanisms of cell and tissue damage. *In:* The Pathogenesis of Infectious Diseases, III edn. London, Academic Press, 1987, pp 215-216.
9. Kuo CH. Liver biochemical tests and dengue fever. Am J Trop Hyg 1992, 47: 265-270.
10. Halstead SB. Arbo viruses of the Pacific and South East Asia *In:* Pediatric Infectious Diseases. Eds Feigin RD, Cherry WB. Philadelphia, W.B. Saunders Co, 1992, pp 1468-1492.

Metachromatic Leukodystropy Presenting with Extrapyramidal Disturbances

L. Pandit
R. Kapadia
P. Kini
S.Rao

Matachromatic leukodystropy (MLD) is a dysmyelinating disorder resulting from defective myelin synthesis. The basic abnormality localized in chromosome 22(1), is the absence of enzyme aryl sulphatase A, a deficiency which prevents the conversion of sulfatide to cerebroside. As a result sulfated lipids increase and the membranes of the myelin sheath break down in both central and peripheral nervous system.

It is the commonest of all dysmyelinating disorders, with at least 200 case reports(2). In our country the first case of leukodystrophy was reported by Taori *et al*.(3) from Vellore in 1971. Subsequently, there have been sporadic case reports of MLD(4,5). We are reporting a case of MLD with prominent extrapyramidal dysfunction. We believe that ours is the first report of extrapyramidal disturbances occurring with leucodystrophy, in India.

From the Departments of Neurology, Pediatrics and Pathology, Kasturba Hospital, Manipal, Karnataka.

Reprint requests: Dr. Lekha Pandit, Assistant Professor, Department of Neurology, Kasturba Hospital, Manipal 576119.

Received for publication: July 28, 1993; Accepted: February 23,1994

Case Report

A 6-year-old male child, eldest of 2 sib-

lings, born of consanguinous union, developed progressive difficulty in walking, since 2 years. He gradually developed cognitive disturbances, slurred speech and involuntary movements of the limbs. For the last 6 months prior to admission, he required support to walk and had incontinence of bowel and bladder. There was no history of similar illness in the family. On examination, head circumference was normal and he had no deformities. He was conscious, restless and inattentive but comprehended simple commands. Speech was scanty with marked dysarthria. Cranial nerve examination and fundoscopy were normal. Motor system examination revealed hypertonia in all 4 limbs. There was cog wheel rigidity demonstrable in both upper limbs with dystonic posturing of left upper limb on occasions. He had bilateral assymmetric foot drop. All deep tendon reflexes were absent. Plantar reflexes were bilaterally extensor. He had a high stepping gait and required support to walk. He underwent a detailed neuro opthalmic evaluation including slit lamp examination, which was normal. Serum copper, ceruloplasmin, calcium, phosphate and alkaline phosphatase were normal. Computerized tomography of the brain *(Fig. 1)* revealed bilateral white matter hypodensities in the cerebral hemispheres and diffuse brain atrophy. Nerve conduction studies revealed evidence of demyelinating sensory motor peripheral neuropathy. Sural nerve biopsy stained with toludine blue demonstrated the characteristic, dark staining metachromatic granules *(Fig. 2).*

Discussion

MLD classically presents in 3 forms(6). They are the infantile, juvenile and the rarer adult forms of MLD. The infantile variety is the commonest phenotype (1 in

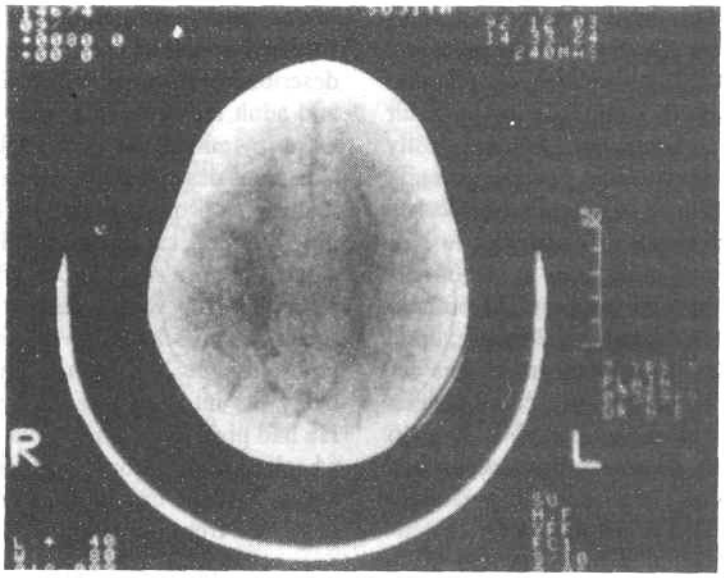

Fig. 1. Computerized tomography of the head showing bilateral cerebral white matter hypodensities and atrophy

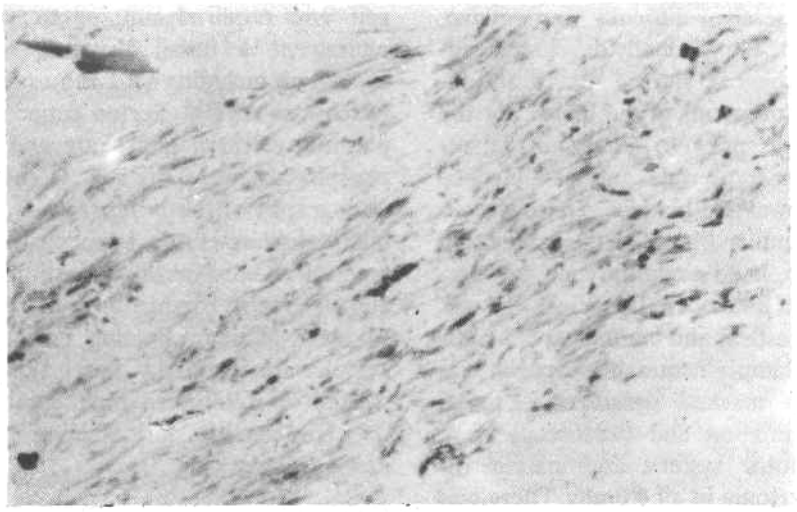

Fig. 2. Photomicrograph of the frozen section of the sural nerve showing the darkly staining metachromatic granules. (Toludine blue ×350)

40,0000) followed by the juvenile type (1 in 150,000)(7). The molecular basis of different types of MLD have recently been studied(8). It has been shown that the mutation in chromosome 22 responsible for infantile variety is different from that in the adult form, while compound heterozygosity seems to be responsible for the juvenile type of MLD. MLD of infantile type has its onset at 12-18 months of age with loss of previously gained milestones in use of legs for locomotion and support. Hypotonia predominates and later in the course, optic atrophy, dementia and long tract signs develop. The juvenile type presents between 3-21 years. Most are affected before 10 years and early cognitive disturbances are seen coupled with areflexia and pyramidal signs. The adult type presents with dementia often associated with ataxia and pyramidal disturbances.

Our case developed signs of disease at 4 years of age and had mental regression associated with generalized areflexia, pyramidal and extrapyramidal disturbance. Extrapyrawiidal signs are not a commonly described feature of MLD. Both juvenile and adult types of MLD may present with extra pyramidal and cerebellar signs(9). The cases described by Joshua *et al.* (4) had features of prominent and early optic atrophy, bilateral cataracts and delayed milestones. Chopra *et al.(5)* described a case of juvenile MLD with recurrent generalized seizures, myoclonic jerks involving the limbs, tongue and larynx. Our case probably fits into the juvenile type of MLD. He had prominent hypertonia of limbs, cog wheeling and dystonic posturing of upper limbs, which has not previously been described from our country.

Computerized tomography revealed selective white matter involvement suggestive of leucodystrophy. CT scan changes

are common to all types of MLD(10).

The diagnosis is established by the demonstration of metachromatic granules (accumulated sulfatides) in the urine or in biopsied specimens from peripheral nerves, skin, conjunctiva or nerves in the pulp of an extracted tooth. The term "metachromatic" has been coined in view of the distinct staining characteristics of sulfatides. Sulfate groups have strong negative charge and are capable of forming complexes with dyes that carry an opposing positive charge. Thus, dye molecules such as cresyl violet or toludine blue interact with sulfatide molecules and are re-oriented and change color. This phenomenon termed as metachromasia gives the disease its name. The frozen sections taken from sural nerve biopsy of this patient stained with toludine blue demonstrated the darkly staining, brown colored metachromatic granules. In cases where sural nerve is processed by routine paraffin embedding, the cerebroside sulfatide gets leeched off and may give a false negative staining with metachromatic dyes.

Alternative diagnostic methods are available. Austin and co-workers from Vellore(ll) showed for the first time that patients with MLD were deficient in lysosomal arylsulfatase A. This is now used for diagnostic confirmation and is totally absent in the infantile form and 0-10% of juvenile cases(7). Prenatal diagnosis is possible by study of arylsulfatase activity in the chorionic villi. However, the drawback to this test is that arylsulfatase activity may be absent or low in a sizable proportion of healthy individuals (0.5-2%). This pseudo deficiency can even co-exist with true MLD in the same family. Electrodiagnostic studies are also useful in differentiating leukodystrophies from other degenerative disorders(12). There has been no satisfactory treatment for this disorder, but attempts at bone marrow transplant have met with some success.

Metachromatic leukodystrophy is to be strongly suspected in infancy and childhood when they present with features of mental regression coupled with the unusual combination of pyramidal dysfunction and peripheral neuropathy.

REFERENCES

1. Adams RD, Victor M. Principles of Neurology, 4th edn. NewYork, McGraw-Hill Information Services Company, 1989, p 795.
2. Poser CM. Diseases of the myelin sheath. *In:* Clinical Neurology, Vol. 2. Ed Baker AB. Philadelphia, Harper and Row, 1981, pp 104-107.
3. Taori GM, Mammen KC, Kobrady S, Martin B, Bhaktaviziam Bachhawat BK. Globoid leukodystrophy (Krabbe's disease) Indian" J Med Res 1971, 58: 993.
4. Joshua GE, Jadhav M, Bhaktaviziam A, Mokashi S. Mental retardation in children—II. Leukodystrophies. Indian Pediatr 1974,11: 53-59.
5. Chopra JS, Banerjee AK, Sawhney BB. Juvenile metachromatic leukodystrophy (A case report). Neurology India 1974, 22: 184-187.
6. Austin JH. Metachromatic leukodystrophy. *In:* Merritt's Textbook of Neurology, 8th edn. Ed Rowland LP. Philadelphia, Lea and Febiger, 1989, pp 527-530.
7. Ogier H, Aicardi J. Metabolic diseases. *In:* Diseases of the Nervous System in Childhood, 1st edn. Ed Aicardi J. Oxford, Blackwell Scientific Publications, 1992, pp 388-389.
8. Polten A, Fluharty AL, Fluharty CB, Kappler J, Von Figura K, Gieselmann V. Molecular basis of different forms of

metachromatic leukodystrophies. N Engl JMedl991, 324:18-22.

9. Rosenberg RN, Pettegrew JW. Genetic neurologic diseases. *In:* The Clinical Neurosciences, Vol. 1,1st edn. Ed Rosenberg RN. Churchill Livingstone, 1983, pp 1-111.

10. Heinz ER, Drayer BP, Haenggell CA, *et al.* Computer tomography in white matter disease. Radiology 1979,130: 371-378.

11. Austin JH, Balasubramaniam AS, Pattabiraman TN, Saraswathi S, Basu -DK, Bachhawat BK. Controlled study of enzyme activities in three human disorders of glycolipid metabolism. Gargoylism, metachromatic and globoid leukodystrophy. J Neuro Chemistry 1963, 10: 805-816.

12. Taori GM, Iyer GV, Abraham J, Mammen KC. Electrodiagnostic studies in lipidosis, mucopolysaccharidosis and leukodystrophies. 1, Nerve conduction and needle EMG studies. Neurology 1973,21: 303-306.

Late Infantile Metachromatic Leucodystrophy in Two Siblings

R.L. Koul
A. Gururaj
A.P. Chacko
M.S. Elbualy
S.R. Bhusnurmath
P. Chand

Metachromatic leucodystrophy (MLD) is genetically heterogenous and comprises of at least five distinct autosomal recessive disorders. Demyelination in central and peripheral nervous systems is the hall mark in all of them. There is accumulation of galactosyl sulphatide in Schwann cells, macrophages and glia, due to deficiency of arylsulphatasa A (ASA)(1). This deposited material stains metachromatically with aniline dyes (toludine blue) and is hence named MLD. The patients of late infantile MLD manifest in the first two or three years of life and die at about the age of 6 years(2). The diagnosis is usually established by assay of ASA in leucocytes, cultured fibroblasts or urine(3) but nerve biopsy can provide extremely rapid and accurate diagnosis(4,5). Prenatal diagnosis by amniocentesis is possible in the first trimester of pregnancy(6).

From the Departments of Child Health (Neurology), Pathology and Medicine, Sultan Qaboos University Hospital, Al Khod, Sultanate of Oman.

Reprint requests: Dr. R.L. Koul, Consultant Neurologist, Department of Child Health, Sultan Qaboos University Hospital, P.O. Box 38, Al Khod, Sultanate of Oman, Postal Code 123.

Received for publication: January 12, 1994; Accepted: April 7, 1994

Case Reports

Case 1: A 2-year-old female child, born to first degree consanguinous parents, was reported to have developed normally till *VA* years of age when she presented with progressive difficulty in walking, stiffness of legs and later, inability to sit. In addition, she had generalized tonic clonic seizures