Metachromatic Leukodystrophy Presenting with Extrapyramidal Disturbances

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

Metachromatic leukodystrophy (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.

Case Report

A 6-year-old male child, eldest of 2 sib-
lings, born of consanguinous union, deve-
loped progressive difficulty in walking,
since 2 years. He gradually developed cog-
nitive disturbances, slurred speech and in-
voluntary movements of the limbs. For the
last 6 months prior to admission, he re-
quired support to walk and had inconti-
nence of bowel and bladder. There was no
history of similar illness in the family. On
examination, head circumference was nor-
mal and he had no deformities. He was
conscious, restless and inattentive but com-
prehended simple commands. Speech was
scanty with marked dysarthria. Cranial
nerve examination and fundoscopy were
normal. Motor system examination re-
vealed 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
asymmetric 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 ophthalmic
evaluation including slit lamp examination,
which was normal. Serum copper, cerulo-
plasmin, 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 metachro-
matic granules (Fig. 2).

Discussion

MLD classically presents in 3 forms(6).
They are the infantile, juvenile and the rar-
er adult forms of MLD. The infantile vari-
ety is the commonest phenotype (1 in
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. Extrapyramidal 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 toluidine 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 toluidine blue demonstrated the darkly staining, brown colored metachromatic granules. In cases where sural nerve is processed by routine paraffin embedding, the cerebroside sulfatide gets leached 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

8. Polten A, Fluharty AL, Fluharty CB, Kappler J, Von Figura K, Gieselmann V. Molecular basis of different forms of
11. Austin JH, Balasubramaniam AS, Patabiraman TN, Saraswathi S, Basu -DK, 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

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