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## 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

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*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.*

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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 arylsulphatase A (ASA)(1). This deposited material stains metachromatically with aniline dyes (toluidine 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).

### Case Reports

Case 1: A 2-year-old female child, born to first degree consanguineous parents, was reported to have developed normally till 18 months 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

which started 3 months prior to the admission. On examination, she was alert and normocephalic. There was bilateral early optic atrophy. The other cranial nerves were normal. Spasticity was evident in all four limbs. The deep tendon reflexes were elicitable except the ankle jerks. The plantar reflexes showed extensor response. EEG showed generalized epileptiform discharges and at places focal sharp discharges over right mid and posterior temporal regions. Motor nerve conduction was prolonged and no sensory nerve action potential (SNAP) was elicited (Table I). The cranial scan had early features of leucodystrophy (diffuse low attenuation of white matter). Urine could not be examined for metachromasia. Nerve biopsy was not done. She was subsequently lost to follow up and was reported to have died at 2Vi years of age following a severe respiratory infection.

Case 2: A 2V2-year-old male sibling of Case 1 was seen at the University Hospital nearly 2 years after the admission of the elder sibling. He had achieved motor milestones normally until IV2 years of age and had monosyllable speech. Over the next 1 year, he developed progressive stiffness of legs with difficulty to sit and stand. There was no history of seizures. On examination the child was normocephalic. His cranial nerves were normal. There was no optic atrophy. There was mild clumsiness in upper limbs, spasticity, with scissoring of lower limbs. Bilateral ankle jerks were absent and all other tendon jerks were present. Both plantars showed extensor response. The blood counts were normal. Urine was positive for metachromasia when tested with toluidine blue. Fresh urine sample, collected in the morning was centrifuged and the sediment was deposited on a clean slide. Toluidine blue was added to

TABLE I—Nerve Conduction Velocities in the Two Cases

Patient	Nerve	Latency in ms		Amplitude in mv		NCV (meters/sec)
		dl	Pl	dl	Pl	
AFM	<i>Motor</i>					
	Right Peroneal	11.7	17.2	0.21	0.25	24
	<i>Sensory</i>					
	Right sural	NR	—	—	—	—
AMM	<i>Motor</i>					
	Right median	12.2	23.3	3.03	1.51	9
	Right peroneal	12.0	23.7	0.52	0.88	11
	<i>Sensory</i>					
	Right median	NR	—	—	—	—
	Right sural	NR	—	—	—	—

MCV: Nerve conduction velocity; dl: distal latency; Pl: Proximal latency; ms: milliseconds; mv: millivolts; NR: not recordable.

this which stained brown. Normally, the dye stains everything blue but substances like sulphatide and amyloid react differently and stain shades of orange to brown. Cerebrospinal fluid (CSF) showed occasional lymphocytes, normal glucose and elevated proteins 0.8 g/dl (0.15-0.5 g/dl). Motor nerve conduction was markedly prolonged and no SNAP was obtained (*Table 1*). Brainstem auditory evoked responses were delayed bilaterally. The cranial scan revealed little differentiation between grey and white matter. Sural nerve biopsy showed scattered metachromatic purplish brown granules within Schwann cells. There was extensive demyelination and break down of myelin with normal axons. The granular metachromatic material was PAS positive. The child was discharged with a diagnosis of metachromatic leucodystrophy. Three months later, when the child was reviewed in the clinic, his neurological status had deteriorated considerably with increased spasticity.

### Discussion

Inherited metabolic disorders of nervous system may lead to progressive psychomotor retardation, morbidity and death of the children. The most distinct members of this category are the so called lysosomal storage diseases. There is a genetic deficiency of the enzymes, that are necessary for the degradation of glycoproteins, glycolipids and mucopolysaccharides within the cells. It is the type of enzyme deficiency and accumulated metabolite, as well as the tissue distribution of the undergradable substrate, that impart a distinctive biochemical and clinical character to the disease(7). These diseases can be diagnosed prenatally and prevented. Detection of carrier state is also possible. Leucodystrophies constitute a significant proportion of the

inherited metabolic disorders. They manifest as psychomotor retardation, optic atrophy and spasticity with abolished tendon reflexes (peripheral neuropathy). MLD is easy to differentiate from the other leucodystrophies by detection of metachromatic bodies in urine and nerve biopsy.

There are at least five distinct disorders of MLD depending on age of presentation and clinical features. Late infantile MLD begins between 1 and 4 years, usually between 15 and 18 months with normal antecedent development. The siblings reported here fit into this category of MLD. Hagberg(2) divided the course of the disease into 4 stages. Walking difficulties, unsteady gait, inability to stand, weakness of feet, hypotonia in lower limbs and retardation of mental development are seen in the first phase. In the second phase ataxia, more pronounced hypotonia with weakness of legs, inability to sit without support, hyporeflexia, spasticity and seizures are seen. Central nervous symptoms like speech impairment, apathy, vision loss predominate in third stage. In the fourth and fatal stage decerebrate rigidity, bulbar symptoms, deafness, blindness and hypertonic seizures are seen. In the present report the first child died possibly in second stage of illness with intercurrent infection and the second sibling is nearing second stage. Elevated CSF proteins with reduced nerve conduction velocities and reduced or absent SNAP are seen in this condition(8). The CSF study in second case showed elevated proteins while nerve conduction velocities were markedly decreased, and no SNAPs were seen in both cases. In addition, brainstem evoked potentials latencies were prolonged in Case 2. This association has not been reported earlier. A rapid and accurate diagnosis of MLD is possible by

pathological study of the nerves(4,5). A nerve biopsy was possible in the second case.

Extensive segmental demyelination with metachromatically staining material within Schwann cells and macrophages and abnormally thin myelin are seen in peripheral nerves in all types of MLD(9) and provides rapid and accurate diagnosis(4,5). Ultrastructurally inclusions comprising myelin figures, prismatic inclusions, Zebra bodies and tuft stone bodies are seen in nerves. The cause of demyelination in MLD is not fully understood. Sulphatide storage could potentially interfere with Schwann cell function or an abnormal composition of myelin may give rise to instability(10). Multiple sulphatase deficiencies of ASA B and C may resemble late infantile MLD(10) but additional clinical features of ichthyosis, flaring of ribs and hepatosplenomegaly differentiates the two. A further variant of MLD in which ASA and B activity is normal has been recognized(11). These are rare, have early infancy onset, protracted course and are diagnosed on nerve biopsy. Diffuse symmetrical white matter and low attenuation of the cerebral parenchyma are common features on CT scan(12). However, this is not characteristic of MLD only, as it can be seen in other leucodystrophies. Confirmatory diagnosis is from nerve biopsy. The CT scan in the first case showed mild low attenuation changes of the white matter while in the second case there was poor differentiation between white and grey matter.

The treatment is mainly supportive. Replacement therapy with exogenous enzymes has been unsuccessful. Low sulphur diet (to diminish the rate of sulphatide accumulation), vitamin A free diet (vitamin

A acts as a cofactor in synthesis of sulphatide) have been of no help(8). Since prenatal diagnosis is possible, the disease can be prevented, by first trimester diagnosis of MLD by assaying ASA in chorionic villi or cultured fibroblasts at 0°C(6) and possible intervention thereafter.

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## Congenital Primary Cerebral Neuroblastoma

**J. Mondkar**  
**A. Kalgutkar**  
**Y. Nalavade**  
**A. Fernandez**

Although brain tumors constitute the second largest group of tumors in children, they are extremely uncommon in the neo-

*From the Neonatal Division of Department of Pediatrics, Departments of Pathology and Radiology, LTMG Hospital and LTM Medical College, Sion, Bombay 400 022.*

*Reprint requests: Dr. JA. Mondkar, 22, 24, Vaibhav Apartments, SK Bole Road, Dadar, Bombay 400 028.*

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natal period and account for about 1% of all childhood brain tumors(1). Moreover, a difference in the pattern of disease from that seen in older children is observed which includes a high incidence of teratomas and a predominance of tumors in supratentorial sites(2).

A case of supratentorial neoplasm in a neonate of the nature of a "Primary Cerebral Neuroblastoma" is described. The tumor in itself is rare and this is probably the first case in literature with presentation at birth and which was diagnosed antenatally.

### Case Report

A 30-year-old primi gravida with seven months amenorrhea was referred for an ultrasound report suggestive of congenital hydrocephalus in the fetus. The patient was examined in the antenatal clinic and referred to the radiologist for a repeat ultrasonography (USG).

Repeat USG confirmed the diagnosis of congenital hydrocephalus and also sug-