Saudi Variant of Multiple Sulfatase Deficiency

A. Al Aqeel, MD, MRCP; P.T. Ozand, MD, PhD; J. Brismar, MD, PhD; G.G. Gascon, MD; G. Brismar, MD; M. Nester, PhD; N. Sakati, MD

Abstract

We describe eight patients with multiple sulfatase deficiency (MSD, or Austin's disease) who differ phenotypically from classic neonatal-, childhood-, or juvenile-onset MSD. The age of onset was in childhood. The patients presented with somatic and facial features of mucopolysaccharidosis reminiscent of Maroteaux-Lamy and Morquio syndromes. They differed from classic MSD by the presence of corneal cloudiness, macrocephaly, severe dysostosis multiplex, and gibbus and the absence of ichthyosis, retinal degeneration, severe deafness, severe mental retardation, and dementia. The main neurologic presentation was cervical cord compression due to axis abnormalities. Despite neuroradiologic evidence of white-matter changes, neurologic presentation was not like metachromatic leukodystrophy. The sulfatase deficiencies were more marked than in the classic juvenile form of MSD, but less marked than in the classic childhood-onset form of MSD. Steroid sulfatase activity was spared except in one patient. This Saudi variant of MSD accounts for 5% of all lysosomal storage diseases in the Cell Repository Registry of our Inborn Errors of Metabolism Laboratory. (*J Child Neurol* 1992;7(Suppl):S12–S21.)

Multiple sulfatase deficiency (MSD, or Austin's disease) is an autosomal recessive disease of unknown etiology, characterized by the deficient activity of many sulfatases and lysosomal storage of sulfatides, glycosaminoglycans, glycolipids, and sulfated steroids. The storage of glycolipids may be caused by the inhibition of other lysosomal hydrolases due to the accumulation of mucopolysaccharides.[1] Since its description by Austin et al,[2,3] more than 31 patients have been identified.[4] Initially, the deficiency of three sulfatases, arylsulfatases A, B, and C, were reported.[3] The number of sulfatases now known to be involved is at least nine.[1,4] The clinical presentation of patients with MSD combines features of the individual enzyme defects.[4,5] In its usual or classic form, it may present during early childhood with the progressive myelin degeneration of metachromatic leukodystrophy[5] or in the neonatal period with features of a severe mucopolysaccharidosis (MPS).[6] A mild juvenile form has been reported.[7] This report describes another phenotype observed in eight patients.

Received July 23, 1991. Received revised August 19, 1991. Accepted for publication Oct 9, 1991.

From the Departments of Pediatrics (Drs Al Aqeel, Ozand, Gascon, and Sakati), Biological and Medical Research (Dr Ozand), Radiology (Dr J. Brismar) and Ophthalmology (Dr G. Brismar), King Faisal Specialist Hospital and Research Centre, and the Riyadh Armed Forces Hospital (Dr Al Aqeel), Riyadh, Saudi Arabia.

Address correspondence to Dr P.T. Ozand, Department of Pediatrics, King Faisal Specialist Hospital and Research Centre, PO Box 3354, Riyadh 11211, Saudi Arabia.

Methods

We performed general physical, neurologic, and ophthalmologic evaluations and developmental assessments. Radiologic studies included radiographs of the skeleton, ultrasound studies of abdomen, a computed tomographic (CT) scan (GE 9800; 10-mm consecutive tomograms) or magnetic resonance imaging (MRI) scan (Picker 1.5 T; SE 2000/40, 80; 7-mm consecutive slices) of the brain and cervical spinal cord.

The collection of lymphocytes, growth and harvesting of fibroblasts, and the enzymatic procedures used have been described previously.[8] The activity of steroid sulfatase was measured according to Fedde and Horwitz[9] and Conary et al.[10]

Case Descriptions

Patient 1

This 6-year-old boy was referred for work-up of proptosis, failing vision, hydrocephalus, and dysmorphia. He

showed facial features of MPS (Figure 1A). His skin was thick but without ichthyosis. His height and weight were below the 2nd percentile, while the dolichocephalic head was 2 SD above normal. Bilateral diffuse haziness of cornea and moderate optic atrophy were found. Retina and lens were normal. He had a grade 4 to 6 pansystolic murmur at 5th intercostal space and umbilical hernia. Liver was 5 cm, and spleen 3 cm, below costal margins. He had a crouched stance, with flexion contracture of joints. Deep-tendon reflexes were hyperactive, with bilateral Babinski signs. He showed a moderate developmental retardation. Hematologic studies revealed Alder-Reilly granules in polymor-

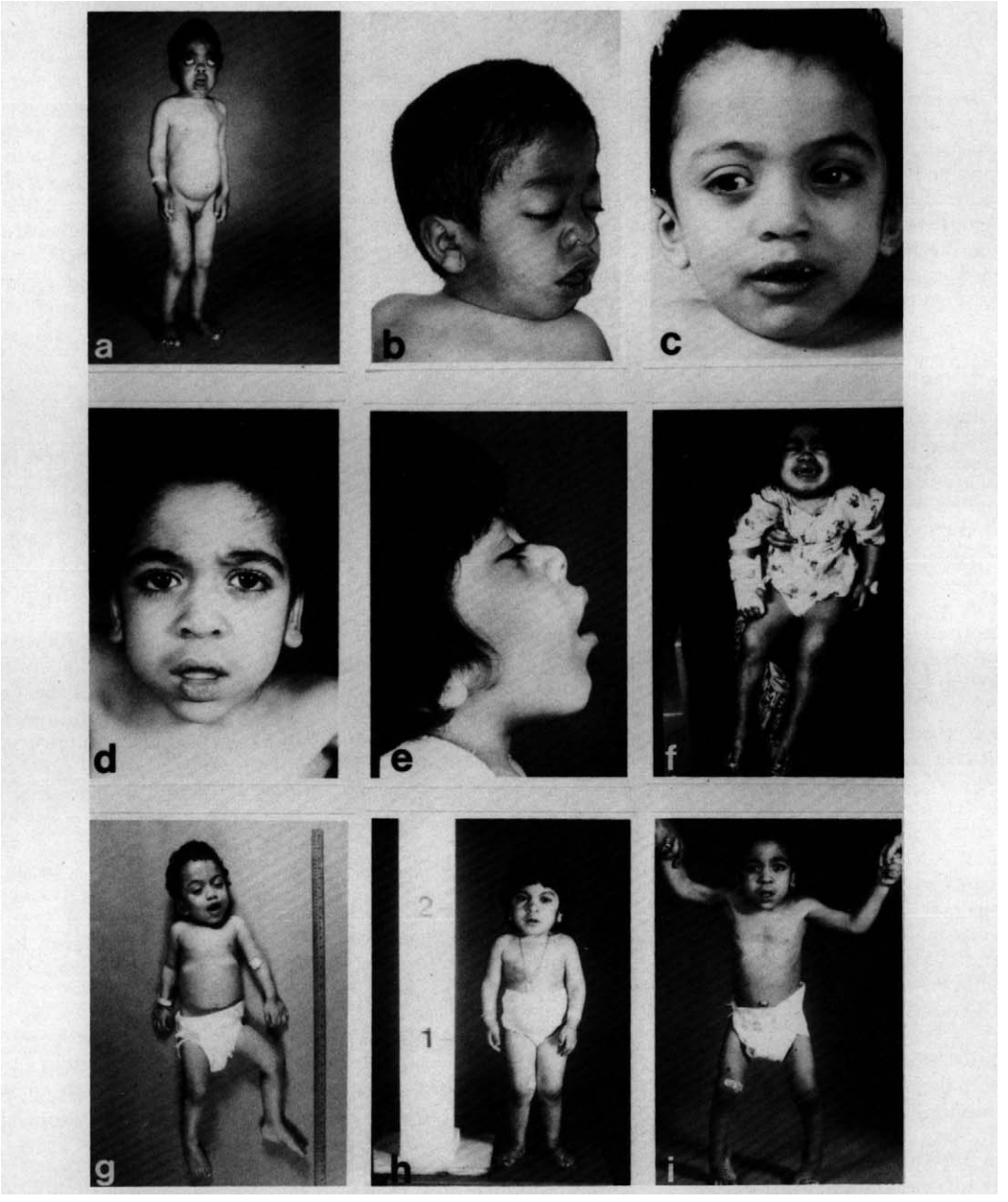

FIGURE 1
Appearance of patients. **A.** Patient 1: MPS, dwarf, proptosis, hydrocephalus. **B.** Patient 2: MPS, macrocephaly with abnormally shaped head. **C.** Patient 7: abnormally shaped head with frontal crest, short neck. **D.** Patient 7: MPS, short neck. **E.** Patient 4: coarse facial appearance. **F.** Patient 6: MPS. **G.** Patient 7: dwarf, Morquio-like appearance. **H.** Patient 3: dwarf, Morquio-like appearance. **I.** Patient 8: dwarf, pes equinus, Morquio-like appearance.

phonuclear neutrophil leukocytes, in basophils, in monocytes, and in lymphocytes on light microscopy, and excess lysosomal vacuoles with autophagic debris on electron microscopy. Urine screening indicated excessive mucopolysaccharides. Skeletal survey revealed bone involvement suggestive of Hurler or Maroteaux-Lamy syndrome (Table 1). Echocardiogram revealed mitral valve prolapse with mild mitral insufficiency. Parents refused further follow-up.

Patient 2

This 7-yr-old boy was referred with a presumptive diagnosis of Maroteaux-Lamy syndrome. He walked at 18 months and started speaking at 2.5 years, at which time parents noted proptosis and stertorous breathing. At 3 years of age, he was studied for poor vision and difficulty hearing. He had numerous chest infections from age 3 years on. At 6 years of age, he had bilateral inguinal herniorrhaphy. Growth arrested at age 5 years. He was referred because an ophthalmologist noticed corneal cloudiness. His height and weight were below the 2nd percentile, and his head circumference was at the 50th percentile. He had a crouched stance, with flexion contracture of joints, and the appearance of MPS (Figure 1B). Skin was thick but was without ichthyosis. Echocardiogram revealed thickened mitral valves with prolapse and mild regurgitation. He had an umbilical hernia. Liver was 4 cm, and spleen 3 cm, below costal margins. Neurologic examination showed no motor signs, and psychometric assessment showed developmental level of 5 years at age 7 years. Ophthalmologic examination showed bilateral pronounced corneal cloudiness with whitish dots in stroma. Retina could not be visualized. Glaucoma was present bilaterally. Hematologic examination revealed metachromatic granules, and electron microscopy showed vacuolated lymphocytes. There was significant mucopolysaccharidurie. Skeletal survey showed severe bone involvement characteristic of MPS (Table 1). Brain-stem auditory evoked response showed normal left side but poorly identifiable waves on right side. The patient was followed for 2 years, at which time bilateral ankle clonus appeared. Parents refused further studies.

TABLE 1
Radiologic Findings in Cranium, Axis, and Vertebrae

Patient	Cranial Vault Findings	Atlantoaxial Axis	Other Vertebral Findings
1	Total cranial synostosis; trigonocephaly, shallow orbits, deep chiasmatic sulcus, J-shaped sella	Hypoplastic dense axis; small foramen magnum	Globular vertebral bodies with anterior notching and posterior AP diameter of D12 and L3 are short, with mild gibbus at these levels; L2 and L5 are slightly hooked
2	C1 normal; sagittal upper part of coronary and lambdoid sutures closed; J-shaped sella	Broad and irregular growth zone of apophysis of dense; no antlantoaxial dislocation	Ovoid bodies, anterosuperior ossification defects especially in cervical vertebrae; dorsal excavation of L3–L5
3	All except temporoparietal sutures closed, dense bones; J-shaped sella	Cord atrophy due to compression by the posterior arch of C1	Hypoplastic anterior parts with bowing of L2–L3 bodies; marked kyphosis at L3; rounded bodies of lower thoracic spine
4	Sagittal suture totally, lambdoid suture partially, closed; J-shaped sella	C2 dens is hypoplastic; posterior arch of C1 impinges on posterior surface of cord	Kyphosis at L1–12; hyperplastic L1–L2; ovoid vertebral bodies; L1–L3 hooked
5	Microcephaly; synostosis of sagittal and lambdoid sutures; J-shaped sella; elongated calvaria	Posterior arch of C1 is located 1 cm anterior, compressing the cord against C2; the AP diameter of cord at this level is less than 30% of normal	The AP diameter of L1 short; L2 hooked, with marked gibbus at L2
6	Brachiocephaly; C1 lower than normal; sagittal coronary and lambdoid sutures closed; temporoparietal suture partially open; J-shaped sella	Parents refused the study	Anteriorly rounded up L2–L3, slight gibbus at L2; mild scoliosis; only four sacral segments
7	Synostosis of sagittal suture; J-shaped sella	Anterior subluxation of atlas; hypoplastic dense spinal cord at C1 level	Biconvex vertebral bodies; hooked-shaped vertebra at L2; kyphosis at L2
8	Synostosis of sagittal suture; sella not J shaped	No extradural compression of cervical spinal cord	Mild gibbus deformity at thoracolumbar area; beak-shaped bodies of L1–L3

*Axial abnormalities were detected by CT or MRI.
C1 = first cervical vertebra; AP = anteroposterior.

Patients 3 and 4

These two patients were sisters from a first-cousin marriage. The younger sister at the age of 4.5 years was referred with the diagnosis of MPS. Her height and weight were below the 2nd percentile, her head circumference was at the 25th percentile. She had hirsutism, stertorous breathing, coarse features (Figure 1E), bilateral corneal cloudiness, and nystagmus. She had thick skin but no ichthyosis. Liver was 6 cm, and spleen 4 cm, below costal margin. She was moderately retarded. She showed severe dysostosis and gibbus. There were Alder-Reilly granules in various types of leukocytes, and significant mucopolysaccharidiuria. Radiologic studies suggested Morquio's syndrome (Figure 2, Table 1).

At the same time, the older sister was referred for MPS work-up at age 6 years. While her height and weight were severely retarded (approximate 1-year level) (Figure 1H), her dolichocephalic head circumference measured at the 50th percentile. Skin was thick but without ichthyosis. She had coarse features, stertorous breathing, bilateral corneal cloudiness, and nystagmus. Liver was 3 cm, and spleen 2 cm, below costal margin. She had gibbus, multiple bone deformities, and joint contractures. She was moderately retarded. Alder-Reilly granules in various types of leukocytes and significant mucopolysaccharidiuria were found. Radiologic studies of the skeleton suggested Morquio disease (Table 1).

Patient 5

This 4.5-year-old girl was referred for work-up of MPS. The stertorous breathing was noticed at birth, gibbus at 2 years of age, and other deformities subsequently. Her height and weight were much more than 2 SD below normal. She had macrocephaly, with head circumference 53.5 cm, which was more than 2 SD above normal. Her skin was thick but without ichthyosis. She stood in a crouched position and had multiple joint contractures, mucoid rhinorrhea, hirsut-

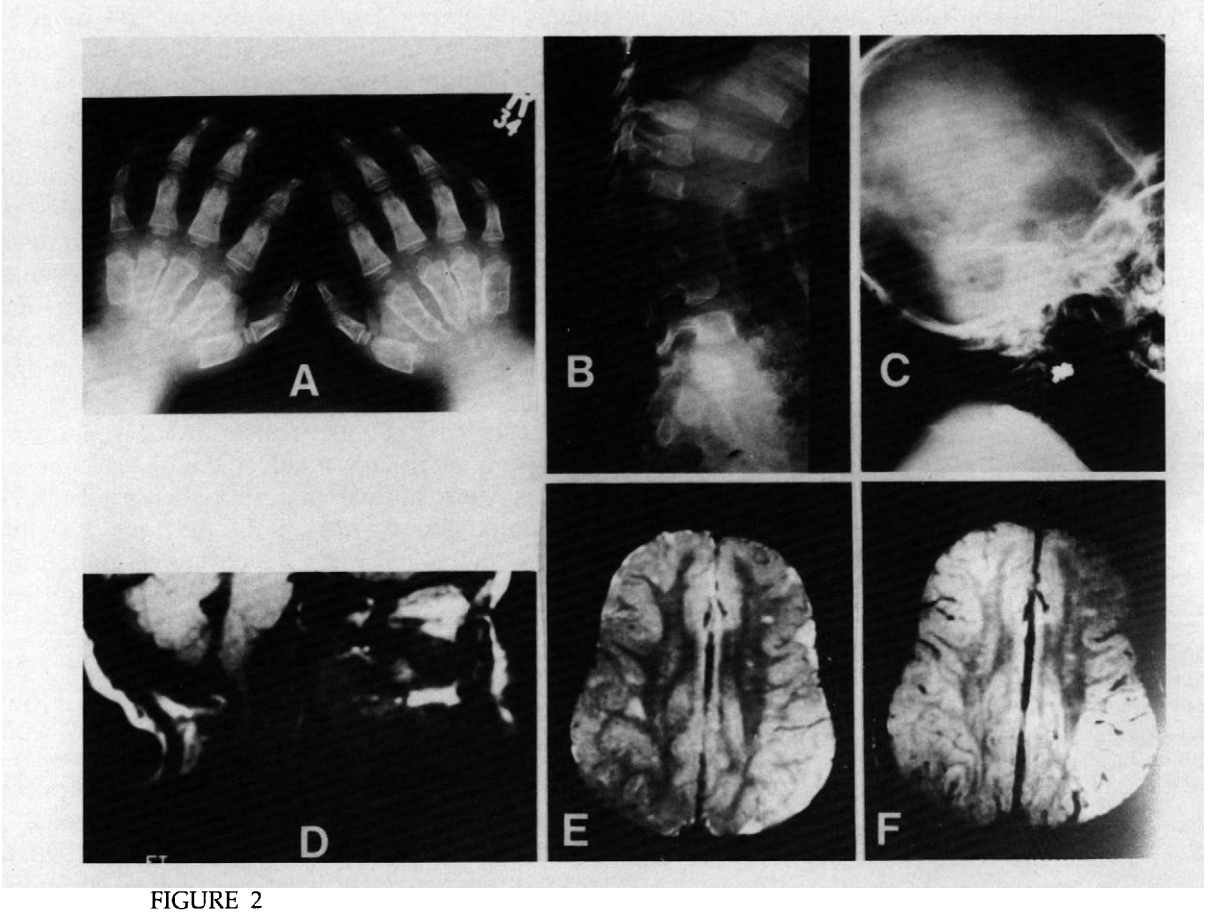

FIGURE 2
Radiologic findings in patient 3. **A.** Dysplastic V-shaped termination of radius and ulna; coarse and proximally tapered metacarpals, broad phalanges. **B.** Ovoid vertebral bodies, hook-shaped L2 and L3 with moderate gibbus formation. **C.** J-shaped sella, upper cervical spine abnormality with anterior location of the posterior arch of C1. **D.** MRI of cervical spinal cord (sagittal midline T_1-weighted slice) shows dislocation and compression of cord at C1 level. **E** and **F.** The T_2-weighted axial MRI sections of the brain demonstrate white-matter disease at trigonal regions bilaterally and multiple small high-intensity spots in the centrum ovale bilaterally.

ism, coarse facial features, umbilical hernia, skeletal anomalies of MPS, pectus carinatum, gibbus, thick gingiva, and macroglossia. Liver was 4 cm, and spleen 3 cm, below costal margins. Cornea were cloudy bilaterally; maculae, lens, and retina were normal. She showed severely exaggerated reflexes in both upper and lower extremities with bilateral sustained ankle clonus and bilateral Babinski signs. A child psychologist assessed her IQ at 91 to 105, despite her severe motor handicap. Radiologic studies showed severe dysostosis multiplex and maxillary sinusitis (Table 1).

Patient 6

This 17-month-old boy was referred for MPS. He had congenital dislocation of hip at birth. Motor development was mildly delayed. Coarse features and dorsolumbar scoliosis were noticed after he stood at 16 months. Growth parameters, including the skull, were at the 10th percentile. He had a coarse face with bushy eyebrows, flaring of costae, gibbus, and bilaterally cloudy cornea. He had a grade 3 systolic murmur over the left precordium and back. Neuropsychologic examination was within normal limits except for mildly delayed milestones. Cardiac work-up indicated right ventricular hypertrophy and pulmonary stenosis. Radiologic survey of skeleton was consistent with MPS (Table 1). At a visit 2 years later, his coarse features and hirsutism resembled more that of a Maroteaux-Lamy syndrome. The patients refused further work-up.

Patient 7

This 18-month-old boy was referred for sudden quadriparesis and possible MPS. Cranial deformity was noticed at birth. By 6 months of age, he had short neck and limbs and an abnormal thoracic cage. Parents did not worry, since his development remained normal. Six days before referral, he collapsed suddenly and lost the ability to move all extremities. His height and weight were at the 50th percentile. His forehead showed a crest, and he had mildly coarse features (Figure 1C, D, and G). His costae were flared. Cornea were clear. Liver was 3 cm, and spleen 2 cm, below costal margins. There was an inguinal herniotomy scar. Neurologic evaluation revealed slightly increased muscle tone, deep-tendon reflexes, and quadriparesis. His Bayley mental age was 13 months at 17 months of age. Metachromatic granules were observed in polymorphonuclear leukocytes. Radiologic survey detected the constriction of the spinal cord at the C1 level, and skeletal findings were suggestive of Maroteaux-Lamy syndrome (Table 1). The father refused emergency surgery for cervical cord decompression and C1 stabilization; he discharged the child against medical advice. We learned later that the child died at home.

Patient 8

This 26-month-old boy was referred for possible MPS. He had sepsis and seizures shortly after birth and had remained in intensive care for 45 days. His development had been slow; he gained head control at 3 to 4 months, sat at 1 year, and attempted to walk only recently, at which time his pes equinus was noticed. He had had recurrent chest infections and stertorous breathing since infancy. A 5-year-old sister has the same disease. Parents are first cousins. His height and weight were at the 10th percentile, and his head circumference was 2 SD below the mean. He had coarse facial features, hirsutism, and flexion contractures of elbows, fingers, and ankle (Figure 1I). Liver was 4 cm, and spleen 3 cm, below costal margins. He had umbilical and bilateral inguinal hernia. He had bilateral corneal cloudiness. His muscle tone and deep-tendon reflexes were increased, with positive Babinski on left and equivocal on right. He showed bilateral sustained ankle clonus. Mental development was approximately 10 months at age 26 months. His skeletal survey suggested MPS (Table 1). Although cervical MRI did not show cord compression, the child suddenly collapsed with quadriparesis at home and died during transport to the hospital.

Results

Our patients presented as MPS dwarfs (Figure 1). While some looked like patients with Maroteaux-Lamy syndrome, others appeared like Morquio syndrome patients. Consanguinity, as first or second cousins, was present in the parents of six patients. Corneal cloudiness was present in seven of eight patients. None had tapetoretinal degeneration or cherry red macula. None had clinically detectable deafness; one patient whose brain-stem auditory evoked response was available showed an abnormal result on one side. Seven had hepatosplenomegaly, and three of eight had cardiac valvular involvement. Hirsutism was present in seven of eight patients. None of the patients had ichthyosis. All children had the clinical appearance of dysostosis multiplex. Clinically or radiologically observed gibbus was present in all patients. The neurologic signs indicated pyramidal tract involvement. Electroencephalograms were normal in four patients tested. The psychometric assessment indicated four of eight to be moderately, and three of eight to be mildly, mentally retarded and one of eight to be normal. None of the patients showed progressive dementia.

Enzyme assays revealed the deficiencies of arylsulfatase A (metachromatic leukodystrophy), arylsulfatase B (Maroteaux-Lamy syndrome), *N*-acetylgalactosamine-6-sulfate sulfatase (Morquio syndrome), heparan sulfate sulfatase (San Filippo A), and sulfiduronate sulfatase (Hunter syndrome) activities. However, the activity of steroid sulfatase was normal, except in patient 1 (Tables 2 through 4).

Detailed radiologic survey of the skeleton confirmed the clinically observed skeletal abnormalities (Figure 2 and Table 1). The cranial vault, cervical spine, and vertebral findings are summarized in Table 2. All patients had premature synostosis of one or more of the cranial sutures, leading to cranial deformities as trigonocephaly, brachiocephaly, doli-

TABLE 2
Sulfatase Activity in Patients and Controls

Subjects	Total Sulfatase, μmol/g/h	Arylsulfatase A, μmol/g/h	Arylsulfatase B, μmol/g/h
Fibroblasts			
Controls (n = 54)	175 ± 17*	56 ± 7	119 ± 11
Pt 1	5.2	0.1	5.2
Pt 2	16.3	3.6	12.7
Pt 3	11.6	4.4	7.2
Pt 4	17.0	14.7	2.3
Pt 5	15.5	13.3	2.2
Pt 6	12.2	9.0	3.2
Pt 7	15.5	1.0	14.5
Pt 8	15.2	2.6	12.6
Patient Mean	13.6 ± 3.6	6.1 ± 5.2	7.5 ± 4.8
P	<.001	<.001	<.001
Lymphocytes			
Controls (n = 40)	90.8 ± 26.1	21.9 ± 6.8	69 ± 18
Pt 1	0.2	0.1	0.1
Pt 2	N.A.	N.A.	N.A.
Pt 3	8.0	1.8	7.2
Pt 4	3.1	1.4	1.7
Pt 5	2.5	1.1	1.4
Pt 6	1.1	0.1	1.0
Pt 7	3.6	0.2	3.4
Pt 8	8.2	0.1	8.1
Patient Mean	3.9 ± 2.9	0.7 ± 0.7	3.2 ± 2.9
P	<.001	<.001	<.001

*Mean ± SD.

chocephaly, macrocephaly, or microcephaly. The dense calvarial bones led to a smaller neurocranium than splanchnocranium. The six patients whose cervical spine could be studied showed various abnormalities of the odontoid process (Table 1, Figure 2). The abnormal axis led to cord impingement with subsequent narrowing. The clinical presentation of patient 7 was with sudden quadriparesis. Patient 8 initially showed no extradural compression of cervical cord. However, he collapsed at home suddenly, becoming quadriparalytic, and died with symptoms suggestive of sudden transection of the cervical cord. The abnormality of the odontoid process was the extension of the generally present vertebral dysostosis (Table 1).

TABLE 3
Steroid Sulfatase Activity in Patients and Controls

Subjects	Steroid Sulfatase, pmol/mg/h at 37° C
Controls (n = 15)	2.47 ± 1.23*
Range	1.16 ± 6.37
Index sex-linked ichthyosis	<0.01
Pt 1	0.69
Pt 2	2.15
Pt 3	4.07
Pt 4	4.44
Pt 5	2.44
Pt 6	4.12
Pt 7	NA
Pt 8	2.28
Patient mean†	3.25 ± 0.97
Range	2.15–4.44

*Mean ± SD.
†Patient 1 excluded.
NA = not applicable.

The brain CT or MRI showed the presence of white-matter changes (Table 5) in seven patients. This demyelination is shown in patient 3 (Figure 2). An arachnoid cyst was detected in patient 2, and hydrocephalus was seen in patient 1.

Discussion

A review of the clinical features of MSD indicates variability according to age of onset. The more commonly encountered early childhood form is that of a metachromatic leukodystrophy[4,5] with mild features of MPS.[11–14] This usual or classic form usually appears with ichthyosis,[4,15,16] severe deafness,[4,5] clear cornea,[4,5,17] microcephaly,[5,15,16] hepatosplenomegaly,[2,3,11,12,18] progressive encephalopathy, and eventual dementia.[4,5,15,17] The presumed initial diagnosis

TABLE 4
Sulfate and Sulfiduronate Sulfatase Activity in Patients and Controls

	N-Acetylgalactosamine-6-Sulfate Sulfatase, μmol/g/h at 37° C	Heparan Sulfate Sulfatase, μmol/g/h at 37° C	Sulfiduronate Sulfatase, μmol/g/h at 37° C
Controls*	2.8 ± 0.7†	8.5 ± 0.8	1.8 ± 0.4
Pt 1	0.57	**5.1**	0.35
Pt 2	0.28	**5.2**	0.51
Pt 3	0.18	**2.3**	**0.43**
Pt 4	0.17	**1.7**	0.32
Pt 5	0.36	**2.2**	0.23
Pt 6	0.26	**3.1**	**0.26**
Pt 7	0.20	**5.5**	**0.60**
Pt 8	0.48	NA	NA
Patient Mean	0.32 ± 0.15	3.6 ± 1.5	0.39 ± 0.13
P	<.001	<.001	<.001

*N = 27 for *N*-acetylgalactosamine-6-sulfate sulfatase, 46 for heparan sulfate sulfatase, and 32 for sulfiduronate sulfatase.
†Mean ± SD.
NA = not applicable.

TABLE 5
MRI and CT Findings in Brain and Cervical Spinal Cord

Patient	Findings*
1	CT: Marked (++) white-matter disease. Some prominence (+) of ventricular system. Normal sulci, fissures.
2	CT and MRI: Moderately dilated ventricles (++), normal sulci. Severe (+++) subcortical white-matter disease. Central and posterior fossa show normal myelination. Arachnoidal cyst anterior to right temporal lobe.
3	MRI: Normal-size ventricles and sulci. T_2-weighted sequences show a narrow zone of increased intensity surrounding the lateral ventricles and scattered small high-intensity spots in the subcortical white matter (+) and confluent high-intensity areas at the trigonal regions bilaterally.
4	MRI: The differentiation between gray and gray white matter less pronounced than expected for age. Some focal subcortical high T_2 intensity lesions (+). Slight prominence of the sulci (+). Ventricles normal. Some cord compression at C1 level.
5	MRI: Quite marked cord compression at the C1 level (to less than half the normal AP diameter). Very poor differentiation between gray and white matter (same intensity) and also quite pronounced subcortical focal white-matter disease (++). Ventricles and sulci normal width.
6	CT: Pronounced subcortical white-matter disease (++), sulci normal, ventricles small.
7	MRI: Slight prominence of the sulci over the frontal lobes (+), minimal prominence of the ventricles. The subcutaneous white matter is generally of the infantile type, consistent with delayed myelination. Some cord compression at the C1 level, in addition, high T_2 intensity within the cord at this level, indicating possible gliosis secondary to the compression.
8	MRI: Poor differentiation between white and gray matter, consistent with delayed myelination (+). In addition, scattered minute high T_2 intensity divisions within the subcortical white matter. Sulci normal appearing, ventricles slightly prominent (+). Cranial-cervical junction is normal without sign of cord compression.

*In none of the patients did CT or MRI demonstrate severe atrophic changes nor was there any suggestion of white-matter destruction.
MRI = magnetic resonance imaging; CT = computed tomography; AP = anteroposterior.

may be a type of Hunter or San Filippo syndrome.[4,17] A second phenotype presents at birth, the neonatal form, with severe features of MPS such as dysostosis multiplex, hydrocephalus, cloudy cornea, hepatosplenomegaly, and severe encephalopathy, with early death.[6,17,19] Lastly, a rare juvenile-onset type as reported by Tanaka et al[7] presents with short stature, ichthyosis, a slowly progressive quadriplegia, retinitis, and blindness.

The present report details yet another phenotype with early childhood onset appearing as either Maroteaux-Lamy or Morquio syndrome, with no ichthyosis, no deafness, mild to moderate mental retardation, symptoms and signs of cranial synostosis, cervical cord compression, or transection of the cord, with clinically absent, radiologically present evidence of central white-matter disease (Tables 1 and 5). These four different phenotypic expressions of MSD are summarized in Table 6.

Notable was the presence of mild to severe corneal cloudiness in seven of our patients, whereas this feature is almost always absent in the classic childhood presentation[4,15,17] (Table 6). Retinal involvement as pigmented degeneration[4,20] or cherry red maculae[12,21] described in classic childhood MSD were absent in our patients. Interestingly, our patient 2 had lenticular opacities, described as a rare occurrence.[4]

The steroid sulfatase deficiency and ichthyosis have been found in classic childhood MSD.[4,9,10,21–23] While our patients exhibited the thick and coarse skin of MPS, they did not have ichthyosis. Steroid sulfatase activity was normal in all (Table 3) except patient 1. The activities of arylsulfatases were 3% to 10%; of Hunter enzyme, 13% to 33%; of Morquio enzyme, 6% to 20%; and of San Filippo A enzyme, 20% to 61% of normal (Table 2). The sulfatase activities are absent in the severe neonatal form of the dis-

TABLE 6
Comparative Features of Multiple Sulfatase Deficiency

Feature	Classic Presentation*	Neonatal Form[6,19,25]	Juvenile Form[7,25]	Saudi Variant
Age of onset	1–2 yr	Birth	5 yr	Birth–1 yr
Age at death	10–18 yr	<1 yr	26 yr	<5 yr in half
Mucopolysaccharidosis features	Mild, resembles Hunter syndrome	Severe	Mild	Severe, resembles Maroteaux-Lamy or Morquio syndrome
Ichthyosis	Always present	Present	Present	Absent
Corneal cloudiness	Very rare	Present or absent	Absent	Present in 6 of 8
Lens involvement	Rare	NR	NR	Rare
Retinal degeneration	May be present	May be present	Present	Absent
Severe deafness	Present	NR	NR	Absent
Head circumference	Microcephaly	Macrocephaly	NR	Variable but macrocephaly in 5 of 8
Hydrocephalus	May be present	Present	NR	Present in 1 of 8
Abnormally shaped head	Absent	Present	NR	All had due to closed sutures
Cardiac valvular involvement	Rare	Present	NR	Present in 2 of 8
Hepatosplenomegaly	Present	Present	Only hepatomegaly	Present in 7 of 8
Dysostosis multiplex	Mild	Severe	Moderate	Severe
Gibbus	Rare	Present	NR	Present
Cervical vertebral anomalies	Absent	Absent	NR	Severe in 6 of 8
Cervical cord compression	Absent	Absent	NR	Present
Dementia	Severe progressive	Severe progressive	Severe	Absent
Main nervous system findings	Pyramidal tract signs	Dementia	Ataxia, dysarthria	Compression/transection of the cord
Mental retardation	Severe	Severe	Severe	Moderate to absent
Radiologic evidence of leukodystrophy	Severe	NR	NR	Quite severe
Sulfatase activities	Deficient	Absent	Reduced	Deficient

*From references 4, 5, 11, 12, 15–18, 20, 23, and 25.
NR = not reported.

ease[19,24,25] and severely deficient in the childhood form.[1,24,25] The activities of various sulfatases in lymphocytes and fibroblasts of the juvenile-onset patient reported by Tanaka et al[7] showed 20% to 60% of normal activity. The residual enzyme activities in our patients were higher than in the classic neonatal and childhood onset forms, but significantly lower than in the patient of Tanaka et al.[7]

The different phenotypic expressions of MSD may be due to different pathogenic mechanisms and not to the amount of residual activity.[7,24,25] The basic defect of MSD has not been yet identified, and the question of how a single genetic defect results in the deficiency of various sulfatases located on different chromosomes has not been answered.[1,7,24,25] The deficient sulfatase activity in fibroblasts is governed by the growth conditions. For example, in media buffered with N–2–hydroxyethylpiperasine–N–2–ethanulfonic acid rather than bicarbonate, sulfatase activity may reappear.[26] The rate of synthesis of various sulfatases may be normal in MSD, but their degradation may be rapid.[27] In fact if a thiol protease inhibitor, leupeptin, is added to the medium, arylsulfatase A activity will appear in MSD fibroblasts, and their capability to break down labeled sulfatides added to the medium will be restored.[25] The early complementation studies in cell hybrids indicated that the sulfatase structural genes were intact.[9] The presence of several complementation groups suggests involvement of different enzymes.[7] All studies with MSD cells are consistent with a defect in cellular regulatory processes for the expression of sulfatases.[24] One such mechanism may involve the cerebroside sulfatase activator proteins, of which three different molecules have been identified.[28,29] We postulate that the pathogenesis of the Saudi form of MSD may be different from those described previously. In particular, the prominence of the mucopolysaccharide disorder and the usual sparing of the steroid sulfatase component may account for the unique phenotype. Tissue studies may clarify how much of a sulfatide lipidosis accompanies the arylsulfatase A deficiency.

Acknowledgments

This project was realized through a private grant donated by Sheikh Al Hariri (85-0030) and by a King Faisal Specialist Hospital and Research Centre grant (85-0021). We are grateful for the administrative, monetary, and humanitarian support of Drs Fahad Al Abdul Jabbar, Chief Executive Director, and Abbass Al Marzouky, Executive director of the Research Centre.

References

1. Basner R, Von Figura K, Glossl J, et al: Multiple sulfatase deficiency of mucopolysaccharide sulfatases in mucosulfotidosis. *Pediatr Res* 1979;13:1316–1318.
2. Austin J, Armstrong D, Shearer L: Metachromatic form of diffuse cerebral sclerosis. V. The nature and significance of low sulfatase activity: A controlled study of brain, liver and kidney in four patients with metachromatic leukodystrophy (MLD). *Arch Neurol* 1965;13:593–614.
3. Austin JH: Studies in metachromatic leukodystrophy. XII. Multiple sulfatase deficiency. *Arch Neurol* 1972;28:258–264.
4. Bateman JB, Philippart M, Eisenberg SJ: Ocular features of multiple sulfatase deficiency and a new variant of metachromatic leukodystrophy. *J Pediatr Ophthalmol Strabismus* 1984;21:133–139.
5. Soong B-W, Casamassima AC, Fink JK, et al: Multiple sulfatase deficiency. *Neurology* 1988;38:1273–1275.
6. Burch M, Fensom AH, Jackson M, et al: Multiple sulfatase deficiency presenting at birth. *Clin Genet* 1986;30:409–415.
7. Tanaka A, Hirabayashi M, Ishii M, et al: Complementation studies with clinical and biochemical characterizations of a new variant of multiple sulfatase deficiency. *J Inherited Metab Dis* 1987;10:103–110.
8. Ozand PT, Gascon G, Al Aqeel A, et al: Prevalence of different types of lysosomal storage diseases in Saudi Arabia. *J Inherited Metab Dis* 1990;13:849–861.
9. Fedde K, Horwitz AL: Complementation of multiple sulfatase deficiency in somatic cell hybrids. *Am J Hum Genet* 1984;36:623–633.
10. Conary JT, Hasilik A, Von Figura K: Synthesis and stability of steroid sulfatase in fibroblasts from multiple sulfatase deficiency. *Biol Chem Hoppe Seyler* 1988;369:297–302.
11. Couchot J, Pluot M, Schmauch MA, et al: La mucosulfatidose. Etude de trois cas familiaux. *Arch Franc Pediatr* 1974;31:775–795.
12. Hogan K, Matalon R, Berlow S, et al: Multiple sulfatase deficiency: Clinical, radiologic, electrophysiologic, and biochemical features. *Neurology* 1983;33(Suppl 2):245.
13. Hug G, Soukup SW, Schubert WK, et al: Mucosulfatidosis: Biochemical and structural observations. *Pediatr Res* 1972;6:422.
14. Lansky LL, Hug G: Enzymatic and structural studies in mucosulfatidosis. *Pediatr Res* 1979;13:421.
15. Nevsimalova S, Elleder M, Smid F, Zemankova M: Multiple sulfatase deficiency in homozygotic twins. *J Inherited Metab Dis* 1984;7:38–40.
16. Bharucha BA, Naik G, Sawliwala AS, et al: Siblings with the Austin variant of metachromatic leukodystrophy multiple sulfatidosis. *Indian J Pediatr* 1984;51:477–480.
17. Burk RD, Valle D, Thomas GH, et al: Early manifestations of multiple sulfatase deficiency. *J Pediatr* 1984;104:574–578.
18. Rampini S, Isler W, Baerlocher K, et al: Die Kombination von metachromatischer Leukodystrophie und Mukosulfatidose als selbstandiges Kranheitsbild (Mukosulfatidose). *Helv Paediatr Acta* 1970;5:436–461.
19. Vamos E, Liebaers I, Bousard N, et al: Multiple sulfatase deficiency with early onset. *J Inherited Metab Dis* 1981;4:103–104.
20. Harbord M, Buncic JR, Chuang SA, et al: Multiple sulfatase deficiency with early severe retinal degeneration. *J Child Neurol* 1991;6:229–235.
21. Raynaud EJ, Escourolle R, Bauman N, et al: Metachromatic leukodystrophy. Ultrastructural and enzymatic study of a case of variant 0 form. *Arch Neurol* 1975;32:834–838.

22. Thieffry S, Lyon G, Maroteaux P: Encephalopathie metabolique associant une mucopolysaccharidose et une sulfatidose. *Arch Franc Pediatr* 1967;24:425–432.
23. Mossakowski M, Mathieson G, Cummings JN: On the relationship of metachromatic leukodystrophy and amaurotic idiocy. *Brain* 1961;84:585–604.
24. Guerra WF, Verity MA, Fluharty AV, et al: Multiple sulfatase deficiency: Clinical, neuropathological, ultrastructural and biochemical studies. *J Neuropathol Exp Neurol* 1990;49:406–423.
25. Eto Y, Gomibuchi I, Umezawa F, Tsuda T: Pathochemistry pathogenesis and enzyme replacement in multiple sulfatase deficiency. *Enzyme* 1987;38:273–279.
26. Fluharty AL, Stevens RL, Davis LL, et al: Presence of arylsulfatase A (ARSA) in multiple sulfatase deficiency disorder fibroblasts. *Am J Hum Genet* 1978;30:249–255.
27. Horwitz AL, Warshawsky L, King J, Burns G: Rapid degradation of steroid sulfatase in multiple sulfatase deficiency. *Biochem Biophys Res Commun* 1986;6:21–26.
28. Fischer G, Jatzkewitz H: The activator of cerebroside sulfatase. Purification from human liver and identification as a protein. *Hoppe Seylers Z Physiol Chem* 1975;356:605–613.
29. O'Brien JS, Ktretz KA, Dewji N, et al: Coding of two sphingolipid activator proteins (SAP-1 and SAP-2) by the same genetic locus. *Science* 1988;241:1098–1101.