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Mucolipidosis I

Roentgenographic Follow-up

C.R. Staalman, M.D.[1], and H.D. Bakker, M.D.[2]
Departments of [1] Radiology and [2] Metabolic Disorders, Emma Children's Hospital, Amsterdam, The Netherlands

Abstract. A patient with mucolipidosis I (ML I) is presented. The roentgenographic findings in the skull, hands, ribs, vertebral column, pelvis, and tubular bones are described. Special emphasis is laid on the evaluation of the skeletal alterations during a 13-years follow-up. The similarities to and the differences from the so-called dysostosis multiplex (DM) are outlined. Some peculiarities which may be specific to ML I are discussed. Attention is given to an exceptional feature in our case of this very rare condition, namely, the marked thickening which developed on the frontal portions of the base of the skull, including the sellar region.

Key words: Mucolipidosis I, skeletal findings – Dysostosis multiplex – Thickening of the skull base – Lysosomal storage diseases – Sialidosis – Oligosaccharidosis

Mucolipidosis I (ML I) is a very rare condition belonging to the group of lysosomal storage diseases. Disorders of lysosomal storage are relatively rare, being caused by a genetically determined enzyme defect. Depending on the storage product different types are distinguished, including mucopolysaccharidosis, sphingolipidosis, and mucolipidosis. The term "mucolipidosis" was introduced in 1970 [15] to name a group of conditions in which features of both the mucopolysaccharidoses and the sphingolipidoses are combined. This term is still in use to describe patients with clinical and radiographic manifestations of a mucopolysaccharidosis, but which cannot be so classified, since most of them excrete normal amounts of acid mucopolysaccharides in the urine. Since sialyl-oligosaccharides are commonly stored and excreted, these conditions are also called "oligosaccharidoses"; the term "sialidosis" is employed to describe patients with primary neuraminidase deficiency [6, 10].

ML I is a neurodegenerative disorder in which neuraminidase deficiency is the only defect so far demonstrated. The activity of B-galactosidase in patients suffering from this disease is normal [17]. During recent years several patients have been described with a "cherry-red spot" myoclonus syndrome [10, 11, 14, 18]. In these young adults an isolated neuraminidase deficiency has been found. So a group of patients, classified as a sialidosis, is characterised by a deficiency of a lysosomal neuraminidase specific for glycoproteins and oligosaccharides with terminal sialic acid [4]. This group includes disorders previously described as mucolipidosis I and "cherry-red spot" myoclonus syndrome [3–5, 10, 11].

Spranger et al. [16] and Bérard et al. [2] described ML I as a nosological entity combining clinical and radiographic features of a mucopolysaccharidosis with signs of a neurodegenerative process affecting gray and white matter. Clinical history and physical examination are not specific, only giving rise to suspicion about the diagnosis. To establish the diagnosis, apart from thin layer chromatography, urine and fibroblast sialic acid measurements are required. A few cases have been published since with only a brief description of the roentgenographic findings [8, 9, 17][1].

In The Netherlands, Bakker et al. [1] and Verheijen et al. [19] reported a patient in whom mucolipidosis I was diagnosed with the aid of the one-

Address reprint requests to: C.R. Staalman, M.D., Department of Diagnostic Radiology, Emma Children's Hospital, Spinozastraat 51, 1018 HJ Amsterdam, The Netherlands

1 Recently, Cibis et al. reported the ophthalmologic and skeletal follow-up of Kelly's Case 2 [9] who died at 2 years of age [Cibis GW, Harris DJ, Chapman AL, Tripathi RC (1983) Mucolipidosis I. Arch Ophthalmol 101:933]

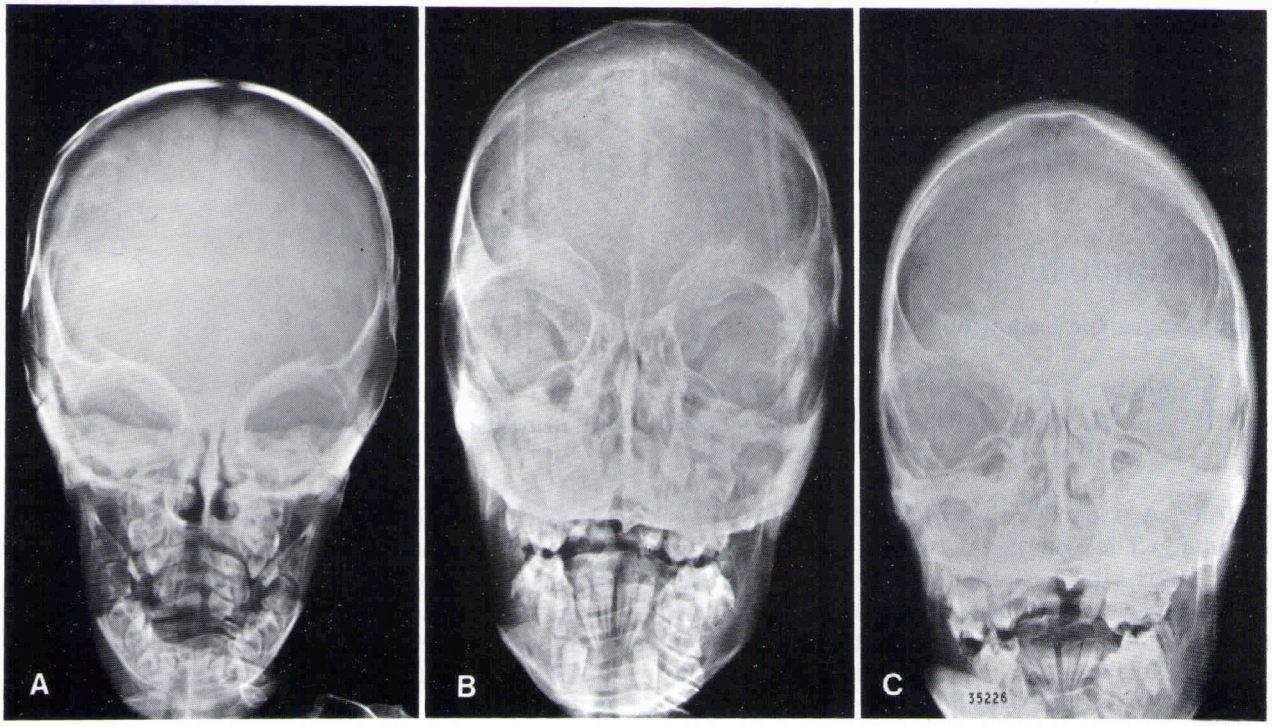


Fig. 1 A–C. Skull, anteroposterior view. **A** at $1^{2}/_{12}$ year. Normal findings. **B** at $9^{10}/_{12}$ years. Thickening of the floor of the anterior fossa. **C** at $13^{11}/_{12}$ years. Same findings as in **B**. In addition thickening of calvaria is evident

dimensional thin layer chromatography method for screening oligosaccharides and glycopeptides in urine and by studies of the enzyme activity in cultured fibroblasts. We present this patient again in order to describe the initial and follow-up radiographic examinations, and to evaluate their contribution to the differential diagnosis of other mucolipidoses and mucopolysaccharidoses.

Material and Case Presentation

E.V., a girl born in 1968, is the third child of clinically normal parents who are full cousins. Three other children in the family, two girls and a boy, are physically and mentally normal. Retarded development was noted from the age of 6 months. At 10 months the patient had converging strabismus and nystagmus. Because of mental retardation the patient was admitted to hospital at the ages of one and two years. The most striking abnormalities then were gargoyle-like facies, dolichocephalic skull, prominent eyes, short stature, and general hypotonia. Subsequently the girl deteriorated progressively and required admission to an institution, incidentally developing a severe scoliosis. The diagnosis of mucolipidosis I has been established. Currently the patient is unable to walk. Her face shows a superciliary arch, hypertelorism, epicanthus, exophthalmus, and maxillary protrusion. Gingival hyperplasia, a big tongue, central deafness, and macular cherry-red spots are also present.

The roentgenographic images obtained during the first and subsequent admissions include films of the thorax and other portions of the skeleton at the ages of $1^{2}/_{12}$, $2^{2}/_{12}$, $9^{10}/_{12}$, $11^{9}/_{12}$, and $13^{11}/_{12}$ years. The findings in the skull, hands, ribs, vertebral column, pelvis, and tubular bones are analysed below.

Radiographic Findings

Skull (Figs. 1 and 2)

Calvaria	Dolichocephaly. Thickening, gradually increasing during life, especially in the frontal region. Disappearance of the margins of inner and outer table at $9^{10}/_{12}$ years.
Skull base	Diffuse thickening and broadening especially of the frontal portion. The thickening is fully developed at $9^{10}/_{12}$ years, and subsequently continues to increase.
Sellar region	The sella is relatively small at all ages except the first year of life. Diffuse thickening of the anterior clinoid processes is evident. The dorsum sellae is broad, as is normal during the first years of life, but fails later to become slender.
Paranasal sinuses	Normal pneumatisation of maxillary antrum and ethmoidal sinuses at $9^{10}/_{12}$ years. Absent pneumatisation of sphenoid and frontal bones.
Mastoids	Only poor pneumatisation visible.
Mandible	Short rami, deformed condyles.

Hands (Fig. 3)

Skeletal age	Retardation at all ages, initially more in the carpals than in the phalanges; at $9^{10}/_{12}$ the phalanges are more retarded than the carpals. After the 10th year the retardation decreases.

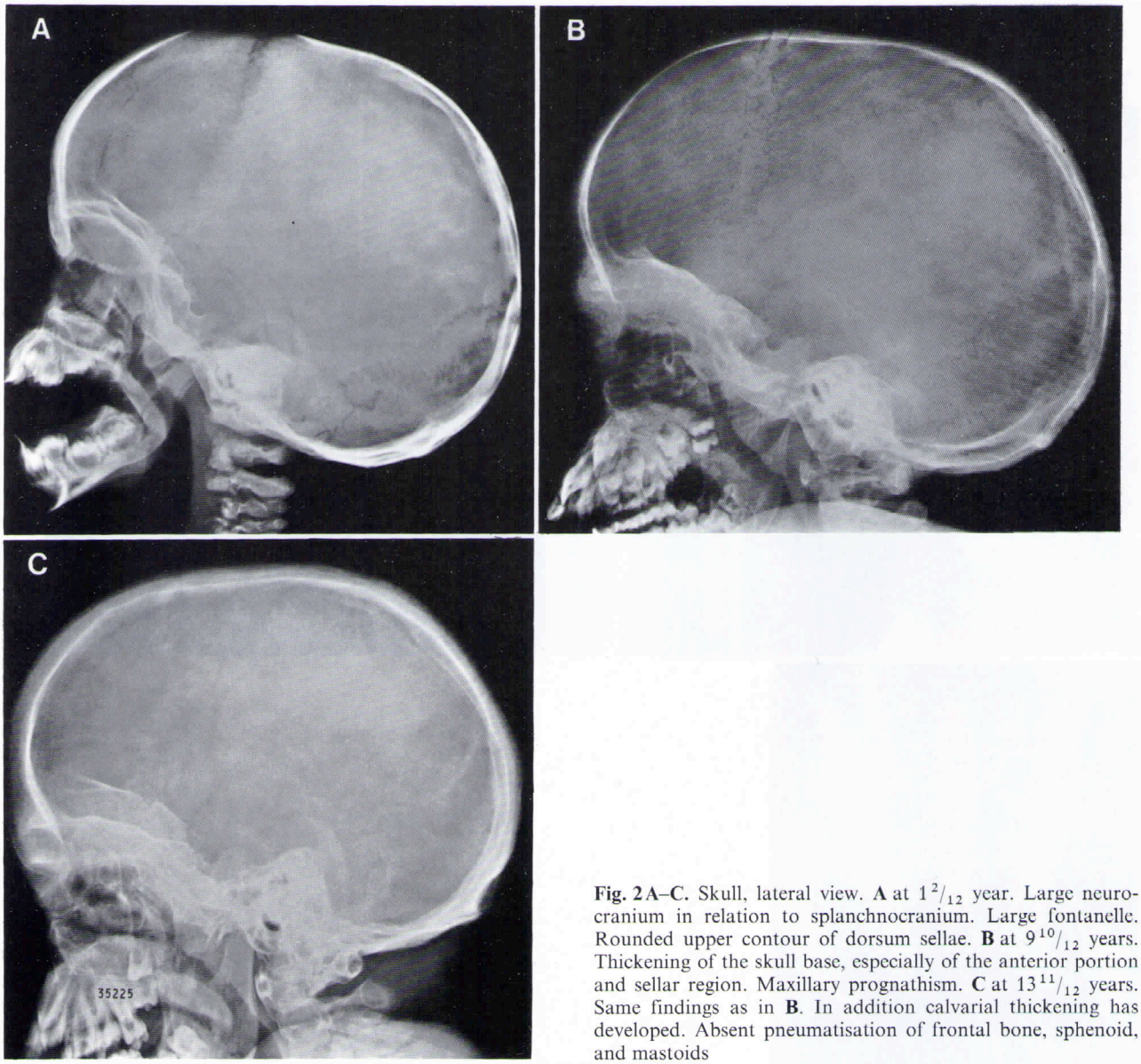


Fig. 2A–C. Skull, lateral view. **A** at $1\,^{2}/_{12}$ year. Large neurocranium in relation to splanchnocranium. Large fontanelle. Rounded upper contour of dorsum sellae. **B** at $9\,^{10}/_{12}$ years. Thickening of the skull base, especially of the anterior portion and sellar region. Maxillary prognathism. **C** at $13\,^{11}/_{12}$ years. Same findings as in **B**. In addition calvarial thickening has developed. Absent pneumatisation of frontal bone, sphenoid, and mastoids

Bone structure	General osteoporosis increasing with age until the age of $11\,^{9}/_{12}$, then slightly decreasing.
Slenderness	At $1\,^{2}/_{12}$ year the fifth metacarpal is somewhat broad. At $2\,^{2}/_{12}$ (not illustrated) the other metacarpals also are somewhat broad; the metacarpal index is 5.1 (N 5.84, SD 0.43). After the age of $9\,^{10}/_{12}$ remodelling and proximal pointing of the first metacarpal is noted. The other metacarpals become increasingly slender in later years; the metacarpal index is 5.9 at $9\,^{10}/_{12}$ and 8.1 at $13\,^{11}/_{12}$ (The Index lies between 6.5 and 7.9 in 96% of normal individuals of unstated age [12]). The proximal and middle phalanges also become increasingly slender.
Position	At $9\,^{10}/_{12}$ subluxation of the first metacarpal with lateral displacement of the trapezium, gradually increasing with age. Flexion contracture of the fifth left distal interphalangeal joint. Positive metacarpal sign.
Length	The lengths of individual bones are compared with normal values for skeletal age. Each bone length is expressed in standard deviation units (Z scores). These Z scores are plotted in graphic representation. (Pattern profile analysis according to Poznanski [12], Fig. 4). The first and second metacarpals are short, as to a lesser degree, are also the second and fifth middle phalanges.
Ribs (Fig. 5)	Broadening of the ribs already is recognisable at the age of one year and two months. At $9\,^{2}/_{12}$ years the ribs are widened and osteoporotic with coarse trabeculae. At $1\,^{9}/_{12}$ years osteoporosis is somewhat diminished.

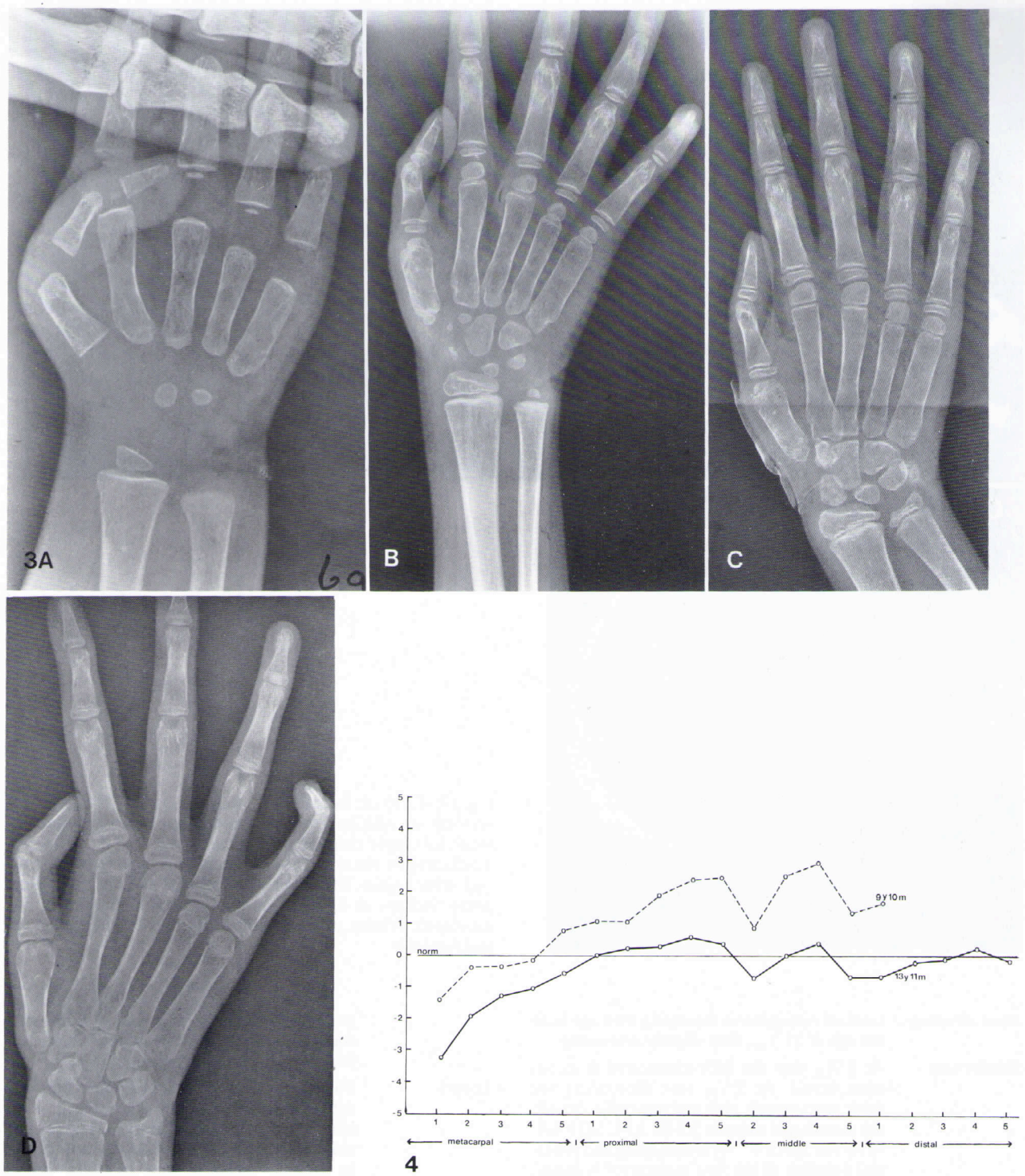
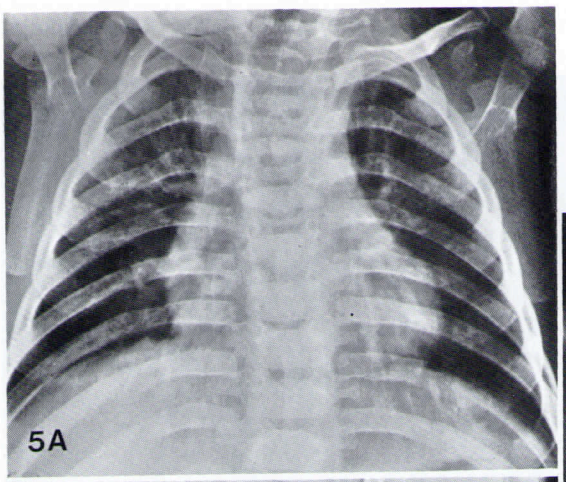
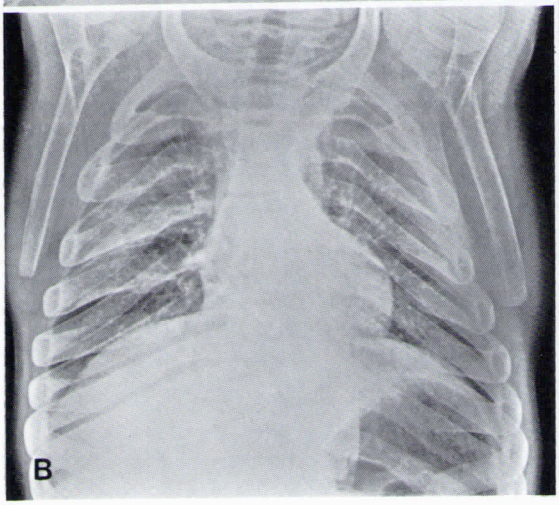
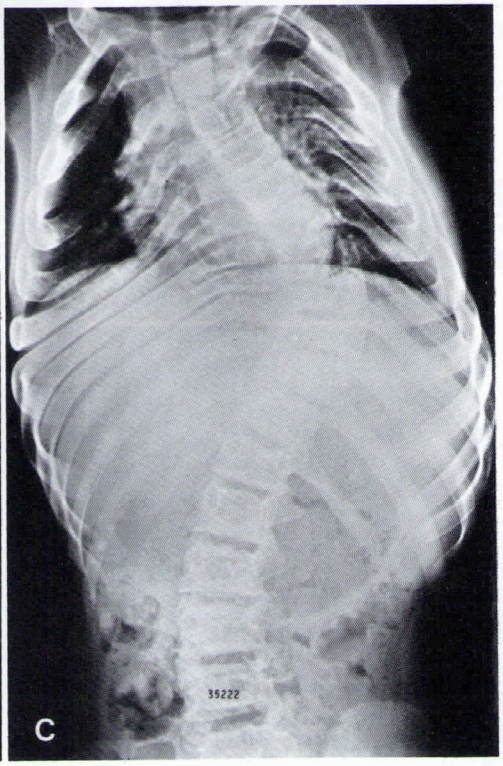


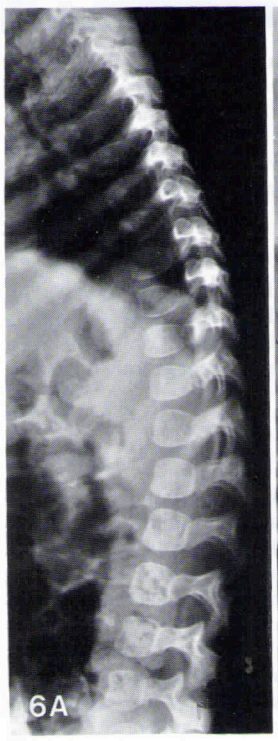
Fig. 3A–D. Right hand. **A** at $1^{2}/_{12}$ year. Broad fifth metacarpal. Otherwise normal findings. **B** at $9^{10}/_{12}$ years. Osteoporosis with thin cortices, especially metacarpals. Broad fifth metacarpal. Positive metacarpal sign. **C** at $11^{9}/_{12}$ years. Obvious increase in skeletal age. Slight metaphyseal irregularities. Proximal pointing and subluxation of first metacarpal. Slenderness of other bones. **D** at 15 years. Decrease of osteoporosis. Increase of modelling of metacarpals. Subluxation of first metacarpal

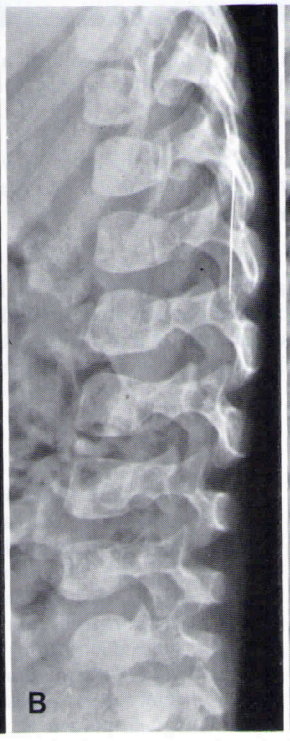
Fig. 4. Pattern profile analysis of patient with mucolipidosis I. The upper curve responds to $9^{10}/_{12}$ years, skeletal age 5 years. The lower curve corresponds to $13^{11}/_{12}$ years, skeletal age 11 years. There is shortening of the first and second metacarpals and, to a lesser degree, of the second and fifth middle phalanges

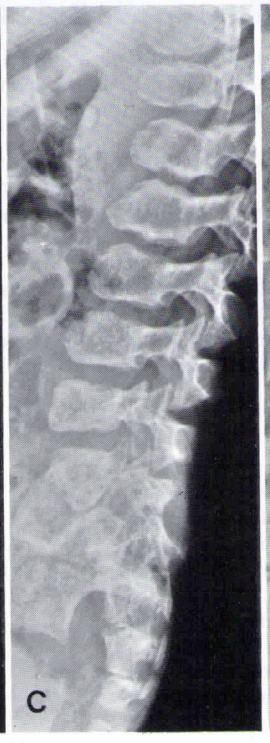


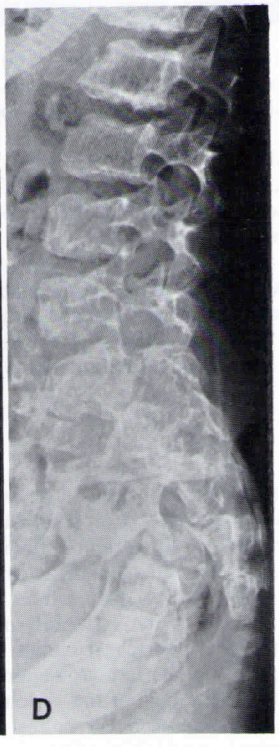












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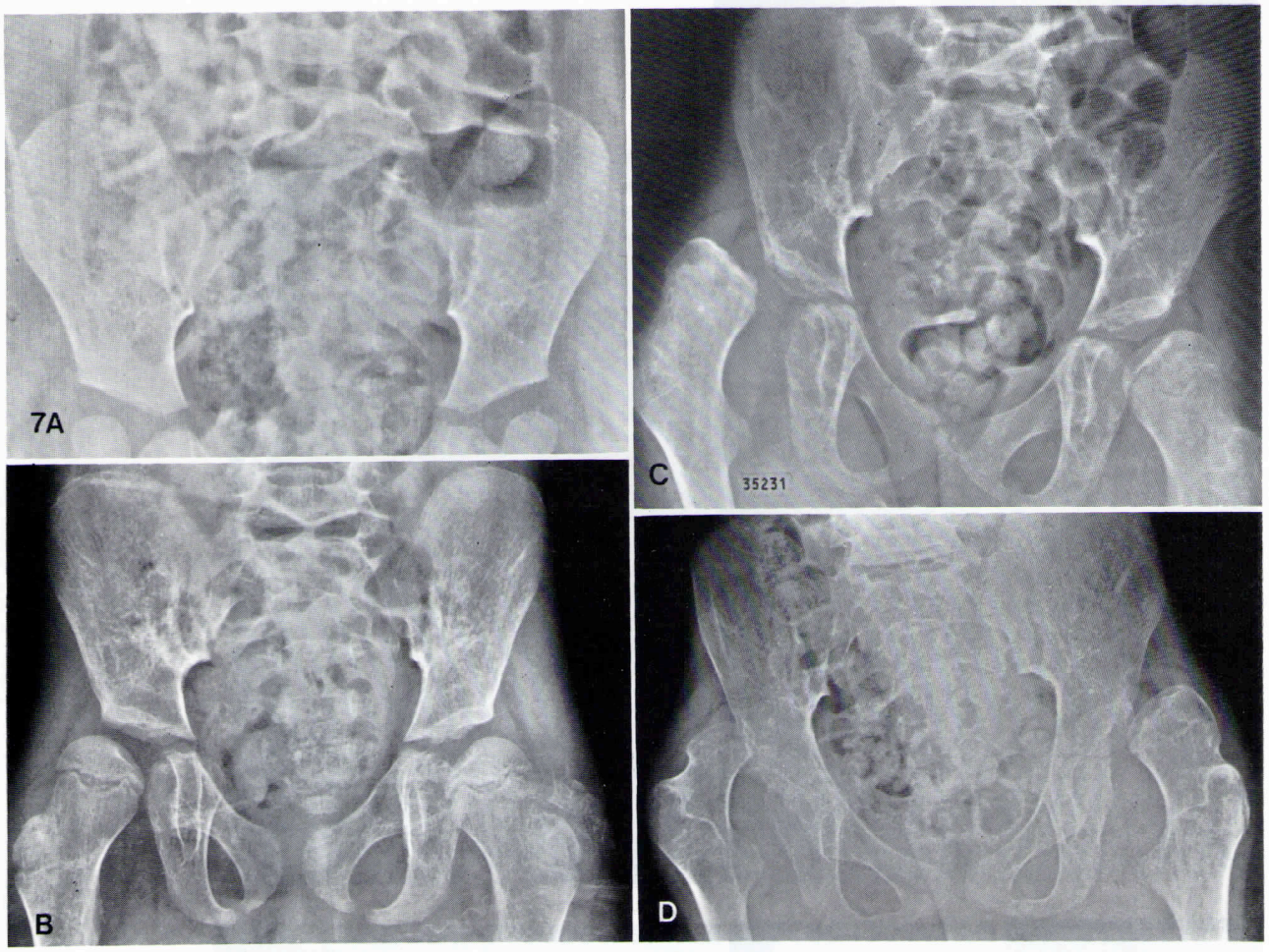

Fig. 5A–C. Thorax. **A** at $1^{2}/_{12}$ year. Heart and lungs show no abnormalities. A minimal scoliosis and very slight widening of ribs already are recognisable. **B** at $10^{3}/_{12}$ years. Scoliosis. Severe widening of ribs. Osteoporosis. **C** at $11^{9}/_{12}$ years. Increasing scoliosis. Osteoporosis somewhat diminished. Appearance of ribs otherwise unchanged

Fig. 6A–D. Vertebral column. **A** at $1^{2}/_{12}$ year. Slight genuine kyphosis with short ap-diameter of vertebral bodies. **B** at $2^{1}/_{12}$ years. Same changes. Slight anterior beaking L2. **C** at $9^{10}/_{12}$ years. Relatively long ap-diameter and diminished height of vertebral bodies. Severe osteochondritic changes of vertebral end plates, especially of L2. **D** at $11^{9}/_{12}$ years. Slight improvement of the changes of the vertebral end plates

Fig. 7A–D. Pelvis. **A** at $2^{1}/_{12}$ years. Small iliac bones and shallow acetabula. Normal position of femoral heads. **B** at $9^{10}/_{12}$ years. Osteoporosis with coarse trabeculae. Retarded ossification of ischio-pubic synchondroses. Tendency to lateral subluxation of both hips. **C** at $11^{9}/_{12}$ years. The ossification of the ischio-pubic synchondroses is still incomplete. Dislocation of the right hip with hypoplastic and deformed femoral head. **D** at $13^{11}/_{12}$ years. Small pelvis. Both hips are dislocated from grossly dysplastic acetabula

Vertebral column (Fig. 6)

At $1^{2}/_{12}$ and $2^{2}/_{12}$ years a very slight thoracolumbar kyphosis is present with a short ap-diameter of the vertebral bodies. At $9^{10}/_{12}$ years, severe osteochondritic changes are visible, with growth disturbances and retarded ossification of the vertebral end plates. The height of the vertebral bodies is diminished, especially in the lumbar region. In the later years some repair of the vertebral end plates becomes evident, but a scoliosis of increasing severity is noted (Fig. 5C).

Pelvis (Fig. 7)

At $2^{2}/_{12}$ years the iliac bones are small and the acetabular roofs are shallow. At $9^{10}/_{12}$ years the pelvis is osteoporotic with coarse trabeculae; the sacrosciatic notches are normal; both femoral heads are displaced laterally, with actual subluxation of that on the right; ossification of the ischio-pubic synchondrosis is retarded. At $11^{9}/_{12}$ years complete dislocation of the right hip is evident with corresponding growth disturbance of the femoral head; ossification of the ischio-pubic synchondrosis is still incomplete. At $13^{11}/_{12}$ years both hips are dislocated from grossly dysplastic acetabula. The iliac bones are small and osteoporotic.

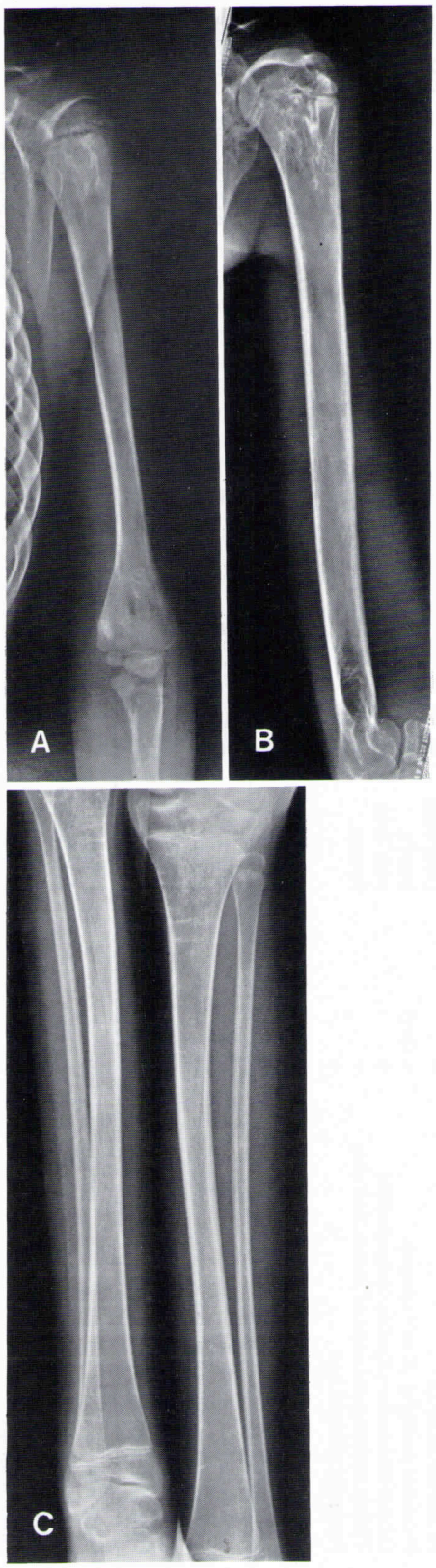

Fig. 8A–C. Tubular bones. **A** the left humerus at $9^{10}/_{12}$ years is slender and osteoporotic with metaphyseal irregularities. **B** at $13^{11}/_{12}$ years the same bone shows the metaphyseal changes more clearly, but no disturbance of modelling or longitudinal growth have developed. **C** Both tibiae and fibulae at $13^{11}/_{12}$ years are slender and osteoporotic

Tubular bones (Fig. 8)	Gradually become slender and osteoporotic. At $9^{10}/_{12}$ years some metaphyseal irregularities are visible, especially in the left humerus. These changes subsequently become more pronounced, but without disturbances of modelling and longitudinal growth.

Discussion

The three cases of mucolipidosis I of Spranger et al. [16, 17], the case of Bérard [2], and the three cases of Kelly et al. [9] all were described as presenting with gargoyle-like clinical features and radiographic changes resembling dysostosis multiplex. Dysostosis multiplex (DM) [13] generally is accepted as a brief description for a combination of skeletal abnormalities. This pattern should lead the radiologist to suspect a disorder of complex carbohydrate metabolism. It is found typically in mucopolysaccharidosis I (Hurler) [7] and includes the following changes:

Skull	Scaphocephaly/dolichocephaly; ω-shaped sella; poor or absent pneumatisation of paranasal sinuses and mastoids; deformed mandibular heads; thick, dense calvaria (not present in MPS I, but typically found in MPS III).
Vertebral column	Short ap-diameter of vertebral bodies; "anterior beaking" with lumbar kyphosis.
Pelvis	Flaring of iliac bones with hypoplasia of their inferior portions; "tilting" acetabula; small flat femoral epiphyses; coxae valgae.
Hands	Broad metacarpals with "proximal pointing"; coarse trabecular structure; "tilting" of metaphyseal ends of radius and ulna; retarded skeletal age.
Tubular bones	Widened; coarse trabecular structure.
Thorax	Wide, osteoporotic ribs; short, broad clavicles.

Dysostosis multiplex (DM) in its most severe form is found in MPS I (Hurler), MPS II (Hunter), MPS VI (Maroteaux-Lamy), Gm_1 Gangliosidosis I (Landing), and ML II (I-cell disease). Severe but more specific skeletal changes are found in MPS IV (Morquio) and ML III. Moderate to mild DM is present in MPS III (San Filippo), MPS V (Ullrich-Scheie), Gm_1 Gangliosidosis II, fucosidosis, mannosidosis, and infantile sulfatidosis (Austin).

Our patient demonstrates a basic pattern of dysostosis multiplex to be present, comparable to the cases of ML I quoted above from the literature (Table 1). In addition, however, our case demonstrates some abnormalities which may be specific for ML I and which were evident to some extent

Table 1

	Dysostosis multiplex Rampini [13]	Mucolipidosis I							
		Staalman and Bakker present case	Bérard et al. (1968) [2]	Spranger et al. (1968) [16]		Spranger et al. (1977) [17]	Kelly et al. (1981) [8]		
				Case 1	Case 2		Case 1	Case 2	Case 3
Skull	Scapho-/dolichocephaly	+		Brachy-cephaly	Brachy-cephaly				Pro-gres-sion of DM
	Thick, dense calvarium	+		−	+	+	−		
	ω-shaped sella	−	+	wide	−	−	−		
	Poor/absent pneumatisation sinuses/mastoids	±/+		+/+	+/+		/+		
	Other findings	Thick, dense base of skull		"Basis-sklerose"	"Basis-sklerose"	Prognathism, hypoplastic odontoid	Hypo-plastic odontoid		
Vertebral column	Short ap-diameter	+							DM-like
	Anterior beaking/hypoplasia T10-L2	+		+	+	+	+	+	
	Lumbar kyphosis	+	+	+	−	+	+	+	
	Other findings	Osteochondrosis, scoliosis				Osteo-chondrosis	Platy-spondyly, scoliosis		
Pelvis	Flaring iliac bones	−		+	−	+	Asymmetric development of distal iliac bones	Changes consistent with DM	DM-like
	Hypoplasia inferior portions	−		−	±	+			
	Small, flat femoral epiphyses	±		−	−	±			
	Coxae valgae	+		+	+	+			
	Other findings	Luxation of both hips; retarded ossification of ischio-pubic synchondrosis				Tendency to hip subluxation			
Hand	Broad metacarpals	−	Deformed hands with long fingers	−		±			DM-like
	Proximal pointing of metacarpals	+ (1st)		±	±	−			
	Coarse trabecular structure/osteoporosis	+		−		+	+		
	Tilting metaphyseal ends of radius and ulna	−		−		−			
	Retarded skeletal age	+		−(!)		+	+		
	Other findings	Subluxation first metacarpal					Bifid calcaneus	Phalanges cystic	
Tubular bones	Broadened	−	Short major bones	−	+	−		Remodeling of the distal femurs	DM-like
	Coarse trabecular structure/osteoporosis	+		+		+			
	Other findings	Slender		Slender		Slender			
Thorax	Wide ribs	+	Chest deformities		+		+	+	+
	Osteoporotic ribs	+			−	+	+		
	Short, broad clavicles	+			−		+		
	Other findings							Cardiome-galy	

also in the cases already reported in the literature. These changes include: (a) slender fingers, metacarpals, and long tubular bones (with the exception of Bérard's case), with the absence of tilting of the metaphyseal ends of radius and ulna; (b) a small sella, as was also found in two cases of Spranger et al. [16, 17] and in Case 1 of Kelly [8]; (c) sclerosis of the base of the skull, as mentioned by Spranger et al. [16] in his two cases.

Furthermore, other unusual features were detected in our patient: (1) The very marked thickening of the frontal bone and skull base is striking. It differs in distribution and extent from the thick calvaria in MPS III and also from the roentgenographic images illustrated in Spranger's publication [16]. (2) The dislocations of the hips are possibly due to the neurological element of the disorder, being attributable to the hypoplastic femoral epiphyses and the dysplastic acetabula. From the other authors, only Spranger et al. [17] mentioned a tendency to hip subluxation. (3) A severe thoracolumbar scoliosis, crippling our patient, was possibly also due to her neurological deterioration. From the cases of ML I reported in the literature, only Kelly's first patient developed a scoliosis [9].

These findings at present appear to be unique, since we have been unable to find any description of such a combination of abnormalities in the literature.

Summary

A patient with mucolipidosis I is described. The diagnosis was made with the aid of one-dimensional chromatography and fibroblast cultures. A follow-up study of the roentgenographic skeletal changes was undertaken. The results are compared with the available data of the main cases from the literature. In our and other cases of ML I a basic pattern of dysostosis multiplex is present. In addition, some findings may be specific to ML I, including slender fingers and tubular bones, a small sella, and less frequently, sclerosis of the base of the skull. Peculiar findings in our patient with ML I, but not features of the pattern of dysostosis multiplex and not mentioned in the literature on ML I, are: (a) thickening of the frontal parts of the skull base including the sellar region, (b) dislocation of both hips and subluxation of the first metacarpals, and (c) severe thoracolumbar scoliosis.

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