Infantile Form of Sialic Acid Storage Disorder: Clinical, Ultrastructural, and Biochemical Studies in Two Siblings*


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Abstract. We describe two sibs with coarse facies, hepatosplenomegaly, prominent psychomotor retardation and unexpectedly fair complexion. Ultrastructural studies of conjunctival, skin, bone marrow and liver biopsies from these individuals showed generalized lysosomal storage of polysaccharide-like material, i.e., membrane bound inclusions containing sparse, fibrillo-granular material. Biochemical analyses of urine and cultured fibroblasts from these patients revealed increased levels of free (unbound) sialic acid.

The ultrastructural and biochemical findings in these sibs are similar to those previously found in Salla disease, however, the clinical course is much more severe. It is concluded that these children represent a new pathogenetic entity whose basic defect is still to be defined.

Key words: Lysosomal storage disease - Sialic acid - Muco-lipidosis

Case Reports

Patient 1 was the first male infant born to healthy unrelated Yugoslav parents after a 37-week gestation. Delivery was uneventful. Birth weight was 2,250 g and length 48 cm. Physical examination at birth was normal, except for an inguinal hernia which was surgically repaired at 1 week of age. No developmental abnormalities were noticed until 5 months of age. At this time, the infant was reported to be hypotonic; at 8 months of age he was unable to sit without support.

At the age of 10 months, physical examination revealed an underweight child (height 72 cm—25th percentile; weight 8,500 g—3rd percentile; head circumference 46 cm—3rd percentile), with pale complexion and fair hair, contrasting with the parents' Mediterranean pigmentation. Moderate, gargoyl.like, facial dysmorphism was noted, with a depressed nasal bridge and mongoloid palpebral fissures. Fundi and corneae were normal. The liver and spleen were enlarged, respectively 3 cm and 2 cm below the lower costal margin. There was marked axial hypotonia, contrasting with hypertonia of the lower limbs. The deep tendon reflexes were increased, range of motion restricted and a bilateral equino-varus deformity was evident with extension of the first toes. Psychomotor development as measured by the Gesell scale was markedly delayed (12-16 weeks for motor abilities and below 12 weeks for language and social abilities. Bone X-rays were unremarkable, including normal bone age. EEG, EMG, karyotype and nerve conduction velocities were normal.

Routine laboratory tests revealed a hypochromic anemia (Hb: 10.3 g%). Numerous vacuolated lymphocytes were seen in the peripheral blood smear. Serum acid phosphatase was increased (21.8 µ/ml—normal range 0-1 µ/ml). The urinary amino-acid pattern was normal. There was no increased excretion of free sialic acid and intralysosomal storage of “polysaccharide-like” material. Although the biochemical and pathological findings resemble those found in Salla patients, the clinical course is much more severe. We thus suggest that these patients represent yet another distinct disease entity.

Introduction

In 1970 Spranger and Wiedemann [12] suggested that the term “mucolipidosis” be utilized to describe a group of patients having features of both a chondrodystrophy, e.g., the type seen in some of the mucopolysaccharidoses and a sphingolipidosis. Subsequently, following the demonstration of specific alterations in oligosaccharide metabolism, Maroteaux and Humbel [11] suggested that the disorders fucosidosis, mannosidosis and aspartylglucosaminuria originally classified as mucolipidoses be reclassified as oligosaccharidoses. More recently another mucolipidosis, i.e., Type I, has been shown to be characterized by alterations in sialyl-oligosaccharides resulting from a sialidase deficiency. This disorder has now been reclassified as a sialidosis [5].

In 1979 Aula et al. [1] described a disorder, Salla disease, having the clinical features of mucolipidosis with a protracted course and increased urinary levels of free sialic acid. As all lysosomal enzymes analyzed to date have been normal, Salla disease is believed to represent a new mucolipidosis.

This report describes two siblings presenting with early neuromotor retardation, chondrodystrophy, increased excretion of free sialic acid and intralysosomal storage of “polysaccharide-like” material. Although the biochemical and pathological findings resemble those found in Salla patients, the clinical course is much more severe. We thus suggest that these patients represent yet another distinct disease entity.
The clinical status of the child deteriorated thereafter. Several episodes of bronchopneumonia were recorded and required prolonged hospitalization. At the age of 3, aneurysmal dilatations appeared in the capillaries of the bulbar conjunctiva. Since the age of 3½, he has been cachectic, bedridden and has lost social contact. The neurologic anomalies observed previously are even more prominent. Now aged 4½ he is in a terminal stage.

*Patient 2* is the youngest sister of Patient 1. She was born after a 37-week gestation. Acute fetal distress was detected at the time of delivery. Birth weight was 1,800 g, length 40 cm and cranial circumference 27.5 cm. Clinical examination showed combined signs of prematurity and dysmaturity. The Finnström index was 36 weeks. Fair skin and hair were noted. Otherwise, neither facial dysmorphism, hepatomegaly, nor neurologic abnormalities were noted. No abnormal cells were found in the peripheral blood nor in the bone marrow smears by light microscopic studies. Ultrastructural studies of the conjunctival biopsy at the age of 5 days, however, showed the same storage process previously noted in her older brother.

The child was readmitted at 4 months of age with pneumonia. Delayed somatic development was conspicuous (height 58 cm, weight 4,200 g). No facial dysmorphism was present. Very pale hair and complexion were noted. Both liver and spleen were enlarged. There were axial hypotonia and hypertonia of the lower extremities. Eye fundus were normal. Bone X-rays failed to show dysostosis multiplex but did demonstrate moderate signs of rickets. Laboratory tests revealed severe anemia (Hb: 6 g%) requiring blood transfusion. Several episodes of pneumonia required permanent hospitalization thereafter. Signs of psychomotor regression were noted from 10 months of age. Now aged two years, she has coarse facies, severe generalized hypotonia and is bedridden, reacting poorly to her environment (Fig. 1).

**Ultrastructural Studies**

Conjunctival, skin, bone marrow and liver biopsies from both patients were studied by electron microscopy (EM) after embedding and staining [9]. Silver proteinate and acid phosphatase staining procedures were also performed on these tissues. As no significant differences were noted between tissues from either patient, their findings are described together.

Clear membrane bound inclusions were numerous in almost all cell types. These inclusions contained sparse fibrillo-granular reticula and occasionally, small homogenous spheres resembling neutral lipid droplets. In the conjunctival biopsy, epithelial cells, fibroblasts, endothelial cells of the blood and lymphatic capillaries, as well as Schwann cells of the sensitive nerves showed evidence of the storage process (Fig. 2). The epidermal cells of the skin biopsy were spared, but...