Combined Tarsal and Carpal Tunnel Syndrome in Mucolipidosis Type III : A Case Study and Review

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Abstract

Mucolipidosis type III (MLIII) (MIM# 252600) is an uncommon autosomal recessive disorder that results from uridine 5'-diphosphate-*N*-acetylglucosamine: lysosomal hydrolase *N*-acetyl-1-phosphotransferase or UDP-GlcNAc 1-phophotransferase deficiency. Clinical manifestations include developmental delay, short stature and other structural abnormalities. Less common clinical features, such as carpal tunnel syndrome, claw hand deformities, trigger fingers, and claw toes have previously been reported, but no specific association with tarsal tunnel syndrome has been reported in the literature. Tarsal tunnel syndrome is caused by entrapment of the posterior tibialis nerve in the tunnel formed by the medial malleolus of the ankle and the flexor retinaculum. It causes pain in the heel and sole of the foot as well as abnormal sensation in the distribution area of nervus tibialis posterior. In adults, the most common cause described is a ganglion. The phenomenon is rare in children and the published series are small. This case report portrays the presentation of a young girl with breath-holding spells secondary to painful bilateral tarsal tunnel syndrome and trigger fingers subsequently diagnosed with MLIII.

Introduction

Tarsal tunnel syndrome (TTS) is caused by the entrapment of the posterior tibialis nerve in the tunnel formed by the flexor retinaculum, which runs from the medial malleolus to the calcaneus.[1–3] This dense, fibrous structure covers the contents of the tarsal tunnel, which consists of the long flexors (flexor digitorum longus (FDL) and flexor hallucis longus (FHL) of the toes, the posterior tibial neurovascular bundle, and the tendon of the posterior tibial muscle. Any swelling of structures in or adjacent to the tunnel, e.g., inflammatory

tenosynovitis or edema secondary to trauma, ganglia of adjacent joints or tendon sheaths, varicosities or other masses, can be the cause of the signs and symptoms of TTS. In adults the most common cause described is a ganglion.[3] It causes pain in the heel and sole of the foot as well as abnormal sensation in the distribution area of tibialis posterior. The phenomenon is rare in children and the series are small.[3,4] The association of tarsal tunnel syndrome and mucolipidoses has not been described previously.

Carpal tunnel syndrome is a rare cause of neuropathy in children, but contrary to tarsal tunnel syndrome, it has previously been described in association with mucopolysaccharidoses and mucolipidoses (ML).[5] The patients may present with clawed hands. Additional clinical signs indicative of median nerve compression include impaired thumb function, pulp atrophy, thenar wasting, and decreased sweating. These clinical signs are associated with significant abnormalities of nerve conduction.[6] Haddad also found an association between triggering and carpal tunnel syndrome in 6/48 patients in their cohort, including patients with mucopolysaccharidoses and mucolipidoses.[6] In this case study we report on a patient diagnosed with mucolipidosis type III who presented with tarsal and carpal tunnel syndrome with trigger fingers. In view of this unusual case study and recently proposed nomenclature by Cathey and colleagues, we present a short review of the classification of ML to position the unusual case presented here.[7]

Case Report

A 4-year old girl was referred to the pediatric neurology clinic for the assessment of possible epilepsy. According to the history she daily experienced several episodes of seizure like events preceded by crying, followed by peri-oral cyanosis, and subsequent loss of consciousness. The episodes lasted for approximately two minutes. The parents reported that she had puffiness of the hands and feet that seemed worse in the early morning. Her hands and feet were increasingly sensitive to touch and at presentation she refused to bear weight on her feet. Her fingers had restricted range of movement. She was unable to straighten or flex them adequately and it was impossible for her to hold a cup. Night pain and episodes of enuresis were prominent features.

The previous medical history included several episodes of hospitalizations for apnea and suspected epilepsy or cardiac failure. The mother experienced an uncomplicated pregnancy. She was born at term with a caesarean section, but she was small for gestational age. The neonatal period was uncomplicated. Her gross motor development was within normal limits, but the speech and language development was of great concern as she was still stuttering and had unclear speech. There was no family history of neuromuscular or metabolic disorders.

On physical examination, she appeared chronically ill and in extreme discomfort. The most prominent clinical features were that of coarse facial features and swollen hands and feet with indurated, dry skin overlying the hands, wrists, feet, and ankles. She exhibited pronounced sensitivity to any form of touch to her hands and feet. Movements of the fingers were limited, with clinical impression of clawing of the hands (Fig. 1). Closer inspection revealed limited metacarpophalangeal (MP) joint flexion combined with limited proximal and distal interphalangeal (PIP and DIP) joint extension. There was palpable thickening of the flexor tendons with trigger finger deformities.

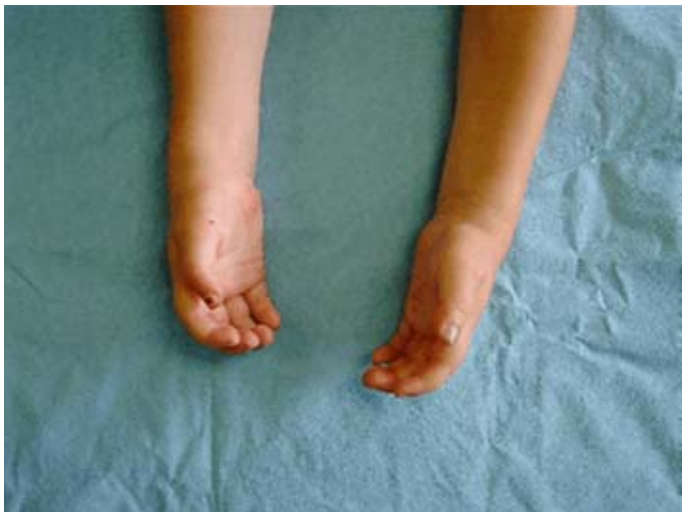

Figure 1. Soft tissue induration of the hands and wrists with the appearance of claw hand deformities.

The shoulder girdle muscle demonstrated moderate generalized wasting. No proximal muscle weakness was noted, however. A mild thoracolumbar kyphosis was present (Fig. 2).

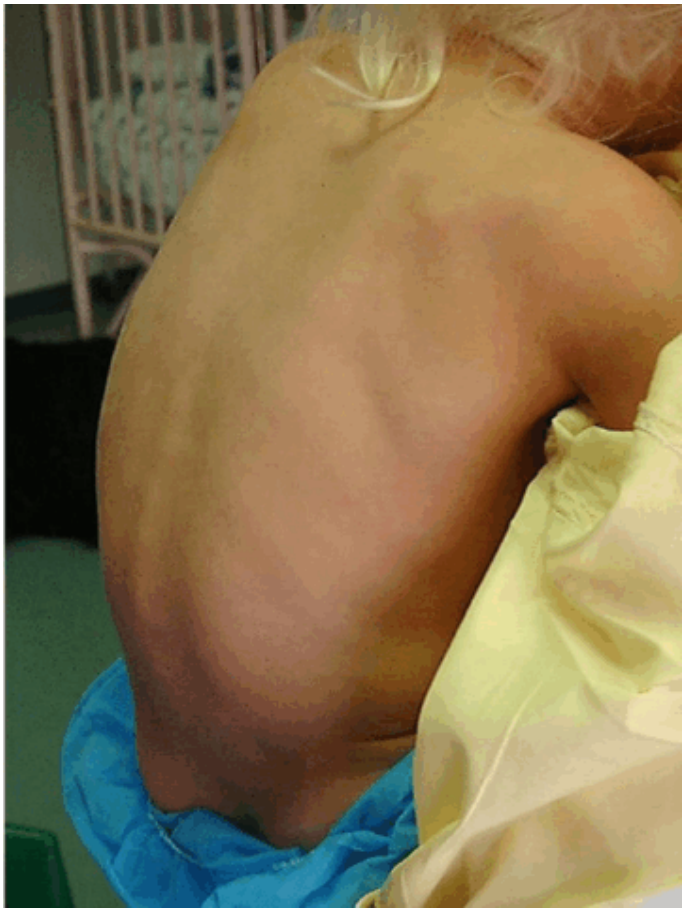

Figure 2. The patient had muscle wasting around the shoulder girdle and a mild thoracolumbar kyphosis.

There was no evidence of cardiomegaly or heart murmurs and hepato-splenomegaly was absent. Her eyes were normal and she had normal vision.

Special Investigations and Results

Special investigations included X-rays that revealed extensive soft tissue swelling around all the joints, but no bony involvement of the hands and feet. The child had hypoplasia of the second lumbar vertebra (L2) and inferior beaking of the vertebrae. The PR-time of the electrocardiogram was 0.16 s and a QTc was 0.43 s. The cardiac sonar demonstrated a mild mitral valve prolapse. The EEG was normal. The full blood count was normal. The ESR was 4 mm/h. The rheumatoid factor and auto-immune screen was negative. The mucopolysaccharides tested negative in the urine, but oligosaccharides were detected. Activities of the lysosomal enzymes, arylsulfatase B, β-galactosidase, β-hexosaminidase, and acid phosphatase were analyzed in cultured skin fibroblasts. Fibroblasts of the patient and controls were cultured under 5% CO2 at 37°C using Ham's F10 medium supplemented with 10% fetal calf serum and antibiotics. The enzyme activities were measured as described by Hall and colleagues using acid phosphatase as the reference enzyme.[8] Lysosomal enzyme activities in fibroblasts (Table 1) indicated a marked deficiency in β-galactosidase (13%) and β-hexosaminidase (21%), with arylsulfatase B activity (90%) falling into the lower levels of control values.[8]

TABLE 1. Lysosomal Enzyme Activities in Fibroblasts

	Arylsulfatase B µmol/hr/mg*	**β-Galactosidase µmol/hr/mg***	**β-Hexosaminidase µmol/hr/mg***	**Acid phosphatase µmol/hr/mg***
Patient	0.47 ± 0.17	0.06 ± 0.01	0.72 ± 0.14	1.97 ± 0.08
Controls average	0.52 ± 0.20	0.47 ± 0.20	3.50 ± 1.30	1.87 ± 0.20
Controls range	0.30–0.84	0.28–0.66	1.96–4.73	1.63–2.06
Literature reference range*	0.20–0.8	0.18–0.45	1.50–5.3	1.00–2.0

*Values are mean (*n*= 3) ± standard deviation.[8]

A diagnosis of mucolipidosis type III was made. It was complicated by carpal and tarsal tunnel syndrome, with trigger fingers and breath-holding spells secondary to the severe pain.

Treatment

As the diagnosis of TTS remains a clinical one and because of the severity of her symptoms, surgical releases of bilateral carpal and tunnels were performed within 5 days of referral to the pediatric orthopedic clinic. Simultaneous release of the A1 and A3 pulleys of the fingers (thumbs excluded) of both hands were performed. Both median nerves were found to be visibly bruised and the tendons of the flexor digitorum profundus were thickened with diffuse nodular changes.

The tarsal tunnel releases were performed through standard medial longitudinal incisions of the feet, extending 3 cm above the medial malleoli proximally and distally up to the level of the necks of the first metatarsals. Extensive release of the tarsal tunnels were preformed, including the flexor retinaculum, the superficial and deep fascia of the abductor hallucis muscle, and a meticulous release of the medial and lateral plantar nerve branches of the

posterior tibial nerves, especially at the musculotendinous junctions of the abductor hallucis muscle. Proximally, the deep fascia of the leg was released along the line of the skin incision, freeing the neurovascular structures to a level well above the ankle joints. The sheaths of the long flexors of the toes (FHL and FDL) were released along their entire course in the feet and around the ankles. As was the finding in the hands, the flexor tendons were found to be similarly thickened in the feet with nodular changes (Fig. 3).

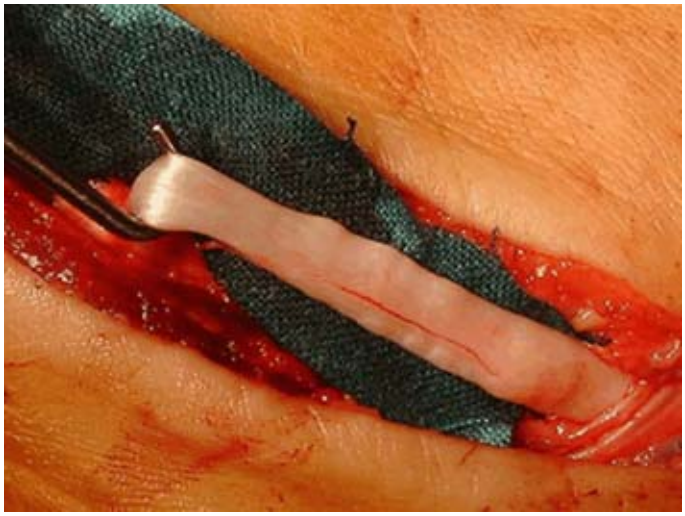

Figure 3. Nodular changes and thickening are visible in the flexor tendons on release of the tarsal tunnel.

Postoperative, the patient demonstrated immediate pain relief and was able to walk with her splints within days. Touch was allowed and the breath-holding spells resolved completely with immediate effect. At 2 weeks follow-up the parents reported that no episodes of enuresis had occurred since surgery.

Discussion

The lysosomal storage disorders are a group of different clinical entities due to incomplete degradation of macromolecules and subsequent accumulation in different predominant tissue types. The classification is based upon the specific substrates stored. Well-known groups of disorders include the sphingolipidoses, mucopolysaccharidoses, glycogen storage disorders, glycoproteinoses; or oligosaccharidoses, and disorders of lipid, amino acids, peptide, and S-acylated protein storage disorders. A group, including mucolipidosis II and III, has functional deficiencies of multiple enzymes due to impaired posttranslational modification.[9,10]

Mucolipidosis was first recognized by Spranger and Wiedemann in 1970 as resembling mucopolysaccharidoses without urinary excretion of glycosaminoglycans.[9,11] It is a group of disorders that is traditionally classified into four subtypes. The classification can be confusing because of the different biochemical and clinical manifestations that exist between the subtypes. As understanding of the molecular basis has expanded, the borders have become less clear and, although the term "mucolipidoses" is still used, the different subtypes are further classified into subgroups and may also be classified amongst other lysosomal storage disorders.

Mucolipidosis type I (MLI) (MIM# 256550), which is also called sialidosis type II, is a

glycoproteinosis with sialyloligosaccharides secreted in the urine and decreased activity of α-neuraminidase (sialidase).[9] More than 40 mutations in the sialidase gene *NEU1* have been described in patients with sialidosis.[12] In the mutation update by Seyrantepe and colleagues 20 mutations specifically associated with sialidosis type II are mentioned.[10] Different clinical variants are described according to the age of onset. The prenatal onset or congenital form presents with nonimmune hydrops fetalis, hepatomegaly, dysmorphisms, skeletal abnormalities, and vacuolated lymphocytes.[13] Nine different mutations are associated with early onset.[10] The early infantile form presents with hepato-splenomegaly, ascites, cherry-red spots with possible lenticular opacities, and severe developmental delay.[9] If patients survive beyond the second year of life, renal impairment and significant developmental delay become evident.[14,15] The phenotypes of infantile, juvenile or even adult MLI resemble that of galactosidoses, but the latter has a combined deficiency of neuraminidase and ß-galactosidase in contrast to MLI. These patients have myoclonus, dysostosis multiplex, mental retardation, coarse facial features, cherry-red spots, and vacuolated lymphocytes.[16] In the mutation update by Seyrantepe no mention of a specific mutation associated with sialidosis type II with a pure adult onset is made, but there are three different reports on a single missense mutation G227R: The age of onset in two of these reports is in the infantile group and only one is in the juvenile group.[10,17,18]
Mucolipidosis type II (MLII) (MIM# 252500) is also known as I-cell disease, whilst mucolipidosis type III (MLIII) (MIM# 252600) is subdivided into Pseudo-Hurler (MLIIIA) and MLIII variants (MLIIIC). The nomenclature of mucolipidosis types MLII, MLIIIA, and MLIIIC resulted from *in vitro* complementation studies, as recently reviewed by Cathey and colleagues[7] MLII and MLIII A are rare allelic disorders, and 15 different mutations with 5 common mutations are known. This is important knowledge with regard to screening, genetic counseling (including carrier and prenatal testing), and for prognostication.[19,20] Bargal found 10 unique mutations in the *GNPTA* gene in their cohort of 24 patients. Seven of these mutations were newly described.[21]

Both MLII and MLIII are caused by impaired activity of uridine 5'-diphosphate-*N*-acetylglucosamine: lysosomal hydrolase *N*-acetyl-1-phosphotransferase referred to as UDP-GlcNAc 1-phosphotransferase (Glc- NAc-PT).[22,23] GlcNAc-PT is a hexamere ($2\alpha2\beta2\gamma$) with the α/β units encoded by the *GNPTAB* gene and the γ subunit by the *GNPTG* gene.[24–26] This enzyme is crucial in the synthesis of the mannose-6-phosphate (M6P) recognition marker. This marker is responsible for the binding of the lysosomal enzymes to the M6P receptors. Thus, if GlcNAc-PT is deficient, lysosomal enzymes (being acid hydrolases), accumulate in intercellular spaces and body fluids. The lysosomes are filled with undigested macromolecules and oligosaccharides are secreted in the urine.[7]
The GlcNAc-PT activity is absent in MLII, decreased in MLIII A and altered in MLIIIC.[22,23,27]

Bargal and colleagues (2006) suggested that the basis for the classification should rest upon the clinical features, age of onset, and disease severity. The common clinical manifestations include developmental delay, short stature, coarse facial features, stiff skin, enlarged joints with contractures, hepato-splenomegaly, mitral valve prolapse, kyphosis, and skeletal abnormalities, including beaking of vertebrae and gingival hypertrophy.[21] Claw hand deformities can be complicated by carpal tunnel syndrome. MLIII is often mistaken for a rheumatological disorder because such deformities present with progressive stiffness of the hands and shoulders and musculoskeletal changes.[29,30]

The diagnosis of mucolipidosis was previously based upon mainly clinical and biochemical

analyses of the enzymes.8,28 Chen and colleagues (2004) described the use of sonography, Doppler studies, and MRI to distinguish between thickening of the tendon sheaths and inflammation as found in other rheumatological conditions of hands and wrists. They found hypo echoic lesions over the tendons in the wrists and fingers with normal vascularity. MRI supported the sonar findings and specifically extensor tendons sheaths were thickened, in contrast to increased vascularity associated with tenosynovitis in rheumatoid arthritis, which was also demonstrated with MRI. The T1 weighted and proton density images revealed low to intermediate signals, and T2 weighted images had low signal intensities without contrast enhancement.[31]

The recently revised nomenclature by Cathey and colleagues (2008) is more descriptive and is based on the current molecular and biochemical knowledge. It is proposed that MLII as well as MLIIIA be subdivided into MLII alpha/beta and MLIII alpha/beta, respectively, and MLIIIC be renamed as MLIII gamma. MLII alpha/beta and MLIII alpha/beta are both associated with mutations in the *GNPTAB* gene on chromosome 12q23.3, and MLIII gamma results from mutations in the *GNPTG* gene on chromosome 16p13.3.[7,26,32]

Mucolipidosis type IV (MLIV) (MIM# 252650) is a developmental as well as degenerative disorder; Altarescu and colleagues (2002) eloquently described the genotype and phenotype in their cohort of patients. The important features present in all the patients were corneal clouding, progressive optic atrophy, and changes in the retina as well as elevated gastrin levels implicating achlorhydria. The other prominent features were EEG changes and severe motor and mental impairment. The motor manifestations deteriorated in 11% of patients and the muscle tone changed during the course of the disease form hypotonia to hypertonicity. The majority of patients had a static neurological picture and if the systemic involvement was limited, it might lead to the misdiagnosis of cerebral palsy. Problems with speech and swallowing were also found. Changes in the corpus callosum included dysmyelination, and cerebellar atrophy was found in older patients. In contrast to other storage disorder, patients with MLIV did not reveal dysmorphic signs, skeletal abnormalities and organomegaly. Genetic homogeneity was found, as all the patients had *MCOLN1* mutations, and it was postulated that the MLIV gene not only plays an important role in the development of the central nervous system but also contributes to the maintenance of neuronal integrity in the cerebellum and retina.[33]

MLIV is unique in the sense that the lysosomal hydrolytic activity is not affected, and that the heterogeneous lysosomal storage of the macromolecules are due to abnormal endocytosis.[34] Bach highlighted in his review the role of the *MCOLN1* or MLIV gene. It lies on chromosome 19 and encodes for mucolipin 1, a membrane protein with six transmembrane domains, a serine lipase motif, and a nuclear localization signal.[35] It is also depicted as a cation channel of the transient receptor potential (TRP) family.[35,36] Bach also foresaw that MLIV and Nieman Pick type C might be classified separately in the lysosomal storage disorders as membrane endocytosis defects as soon as the proteins in these disorders have been better characterized.[35]

In a thorough review of the literature on carpal tunnel syndrome in children by Van Meir and De Smet in 2005, it was found that mucopolysaccharidoses and mucolipidoses were the two most common causes of carpal tunnel syndrome in children. They also advised that clinical screening or nerve conduction studies should be considered in children with storage disorders, before signs become present.[37] Furthermore, Haddad advocated early surgery to minimize damage.[6]

Summary

The patient described presented primarily with both bilateral carpal and tarsal tunnel syndrome. The symptoms were so significant that she was not able to bear weight on her feet, experienced breath-holding spells, and enuresis secondary to the pain. In view of this case, mucolipidosis should be considered in patients with tarsal tunnel syndrome.

Conflicts of Interest

The authors declare no conflicts of interest.

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