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Case Report

Zellweger syndrome: an older child with progressive foot deformity

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Abstract. Zellweger spectrum disorders result from defects in the assembly of the peroxisome and are sometimes referred to as peroxisome biogenesis disorders. Orthopedic manifestations of this condition are variable. This case report illustrates an ambulatory child with Zellweger syndrome and progressive foot deformity. The course of treatment consisted of initial soft tissue surgery, early recurrence of the deformity, followed by successful arthrodesis.

Keywords: Zellweger, peroxisomal biogenesis disorder

1. Introduction

Zellweger spectrum disorders result from defects in the assembly of the peroxisome and are referred to as peroxisome biogenesis disorders (PBD). PBD refer to disorders in the Zellweger spectrum, which include: infantile Refsum disease, neonatal adrenoleukodystrophy, and Zellweger syndrome [1,2]. PBD are rare conditions affecting all major systems of the body. Common manifestations include abnormalities of the facies and skull, vision difficulties secondary to cataract or glaucoma, hypotonia, seizure disorders, cognitive impairment, hepatic and renal dysfunction. Atypical presentations of this condition have been reported [3]. Because of the rarity of the disorder and atypical presentations, orthopedic manifestations and treatments are largely unknown. Previous reports have included deformities of the upper extremities (camptodactyly, cubitus valgus), hip dysplasia, and deformities of the feet (rocker bottom, equinovarus). Chondrodysplasia punctata, especially in the patella and hips, has been described [3,4].

This report is of an older child with PBD who presented with progressive foot deformity.

2. Case report

2.1. Genetic and biochemical testing

The patient was diagnosed with PBD in the Zellweger syndrome spectrum at age 18 mo. At the time, he was hospitalized for failure to thrive, global developmental delay, poor weight gain, and hepatomegaly. Biochemical and genetic testing was performed and was consistent with peroxisomal disorder. Initially, testing was consistent with a single enzyme deficiency. However, subsequent genetic testing revealed that he was a compound heterozygote with two sequence variations in the PEX1 gene. He has one mutation, Nt2098insT,

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which results in an extra T nucleotide inserted into the normal sequence at position 2098. This causes a shift in the open reading frame and introduces a premature stop codon several amino acids downstream. The second mutation, G2528A, results in the normal G nucleotide being replaced by an A nucleotide at position 2528. This causes the substitution of aspartic acid for glycine in the amino acid 843 (G843D). Subsequently, his parents were tested and each found to be a carrier of one PEX1 gene mutation.

In laboratory studies, pristanic acid oxidation in cultured cells demonstrated a mean level of 45.0 pmol/48 h/mg protein (range for Zellweger syndrome = 23.1 ± 35.5 pmol/48 h/mg protein, normal control = 463.8 ± 146.2 pmol/48 h/mg protein). In addition, recent biochemical results from 2012 are as follows: C22:0 27.3 nmol/L (normal ≤ 96.3 nmol/L), C24:0 - 37.4 nmol/L (normal ≤ 91.4 nmol/L), C26:0 2.03 nmol/L *high (normal 1.30 nmol/L), C24/C22 ratio 1.37 (normal ≤ 1.39), C26/C22 ratio 0.074 *high (normal ≤ 0.023), pristanic acid 1.56 nmol/L (normal ≤ 2.98 nmol/L), phytanic acid 4.85 nmol/L (normal ≤ 9.88 nmol/L), and pristanic/phytanic ratio 0.32 (normal ≤ 0.39).

2.2. Clinical history

He has significant cognitive delays, currently functioning at a level of 6–24 mo of age. Systemic manifestations of his condition include vitamin K deficiency secondary to hepatic dysfunction, complex partial epilepsy and tonic seizures controlled with antiepileptic agents, gastroesophageal reflux, hepatomegaly, mental retardation, hearing impairment, vision impairment, asthma, and severe oral and tactile sensory defensiveness.

2.3. Orthopedic management

He initially presented to an outside institution at 10 years old, with progressive bilateral foot deformities (equinocavovarus) that led to problems with balance, ambulation, and frequent falls. The family noted that 3 years prior to presentation at age 7, his ambulatory ability began to decline. During this time, the patient received aggressive physical therapy for muscle strengthening and gait training. Ankle foot orthoses (AFO's) were prescribed to improve positioning of the feet and provide stability with standing and walking. Initially, his balance and ambulatory ability stabilized. However, over the ensuing months, he became intolerant of bracing secondary to progression of the foot deformity. Because of his age and the severity of his deformities, surgical correction was offered.

Initial treatment consisted of attempts to rebalance the soft tissues around the foot and ankle. The surgery included bilateral plantar fascia release, split posterior tibial tendon transfer, extensor hallucis longus tendon transfer to the metatarsal head (Jones procedure), and percutaneous Achilles tendon lengthening. Postoperatively, the patient was placed into short leg non-weight bearing casts for 4 weeks, followed by solid AFO's.

Initially, his foot position notably improved. However, over the ensuing months, recurrent deformity in both feet led to difficulty with brace wear. During his initial evaluation at our facility, he was able to ambulate with moderate assistance. After the recurrence, his balance was poor secondary to improper foot position and abnormal loading of his feet. He presented with increased callus along the lateral border of both feet, absence of heel strike during the stance phase of gait, and poor selective muscle control of his feet and ankles (Fig. 1). Clinically, the deformities were noted to be rigid with limited mobility of the hindfoot and midfoot.

Radiographs revealed significant cavovarus deformities, slightly worse on the left as compared with the right (Fig. 2). Dynamic pedobarography showed increased loading and excessive pressure along the lateral midfoot. Because of the failed attempt at soft tissue balancing, an arthrodesis strategy was offered.

At age 11, he presented for a second surgery, which included bilateral triple arthrodesis. Three joints of the hindfoot (subtalar, talonavicular, and calcaneocuboid) were removed and fused with the foot in a plantigrade position. A standard Ollier's incision allowed access to the hindfoot and midfoot. The cartilage was denuded and the joints realigned correcting the cavovarus deformity. Local autograft was utilized to supplement the fusions. Three large Steinmann pins secured the position of the foot during the postoperative period. Short leg non-weight bearing casts were used to maintain the correction for 6 weeks. A cast change with pin removal and molding for AFO's was performed in the operating room under general anesthesia at 6 weeks post-surgery. Casts were then replaced for an additional 4 weeks after which ambulation with AFO's was begun. The patient resumed physical therapy with focus on gait training and mobilization.

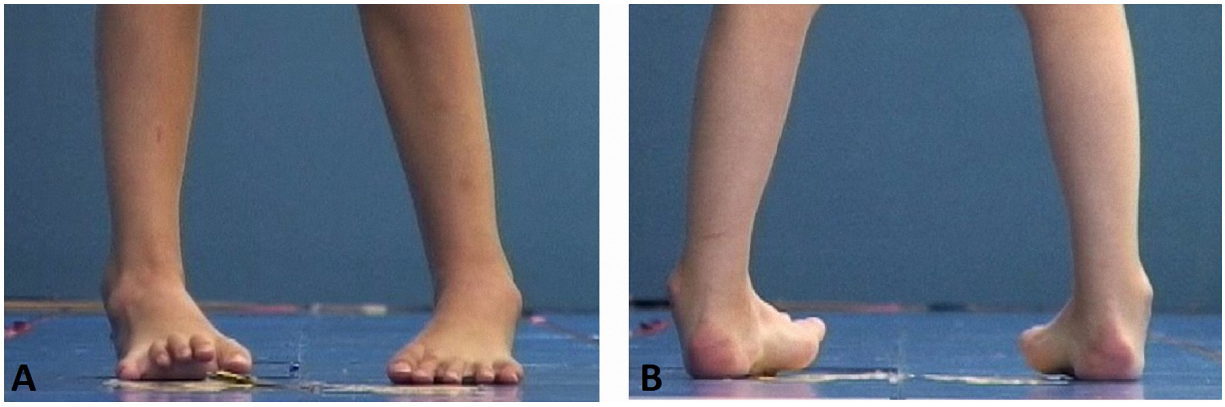

Fig. 1. Preoperative standing clinical photos of feet. (A) Frontal view, (B) Posterior view.

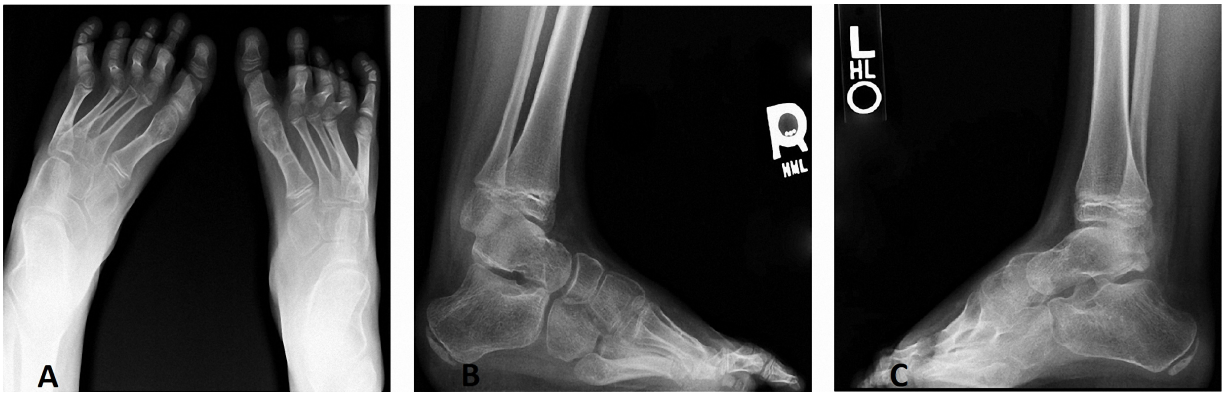

Fig. 2. Preoperative standing radiographs of feet. (A) Anterio-posterior view. (B) Lateral right foot. (C) Lateral left foot.

At his most recent follow up, the foot position is stable. Current radiographs demonstrate maintenance of alignment and stable plantigrade position of the foot and ankle (Figs 3 and 4). He is now 2 years post triple arthrodesis and no longer requires the use of AFO's. According to the family, he is now running and walking without assistance.

3. Discussion

Zellweger syndrome is a rare condition with a wide spectrum of musculoskeletal manifestations. In a series of 12 patients described by Poznanski et al. [4] nine were reported to have various foot abnormalities. Clubfoot was the most prevalent deformity in this group. Metatarsus adductus and rocker bottom foot deformities were also included. In addition, hand abnormalities were also appreciated in this series with camptodactyly most frequently noted.

Poll-The et al. [5] reported the natural history of patients with PBD. Orthopedic manifestations were variable in this cohort of 31 patients. Four patients experienced non-traumatic fractures. One patient was treated for congenital hip dislocation. Syndactyly of the toes was identified in one patient. One-third of the patients presented with valgus foot deformity.

The etiology of musculoskeletal deformity in conditions such as PBD is poorly understood. Clinical and experimental evidence suggests that fatty acids may have an effect on calcium metabolism. Fatty acid deficiency in animals can lead to a loss of bone calcium and matrix, resulting in significant bone demineralization. Fatty acids might be involved in calcium metabolism influencing cellular calcium ion transport directly, as second messengers, or generating, through the

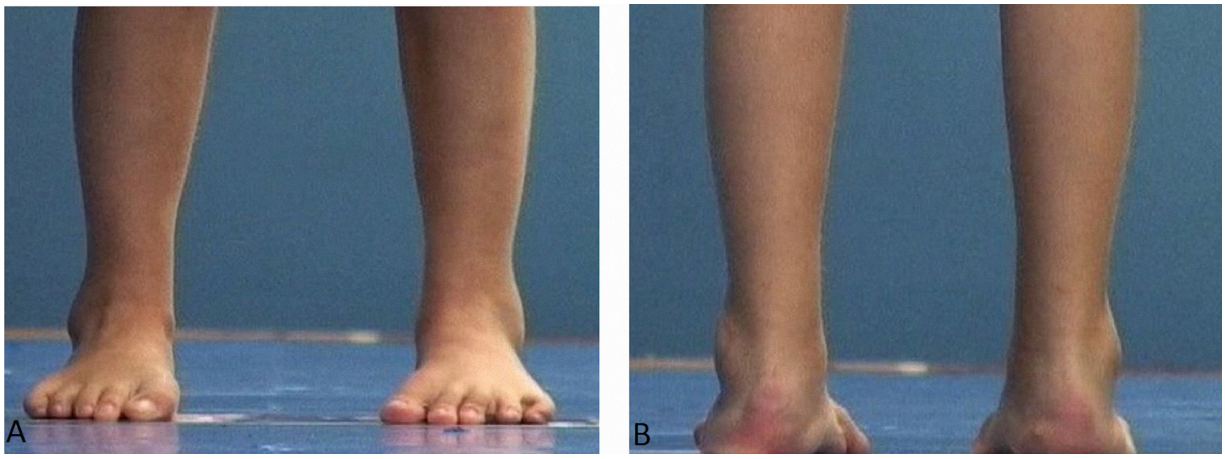

Fig. 3. Postoperative standing clinical photos of feet. (A) Frontal view. (B) Posterior view.

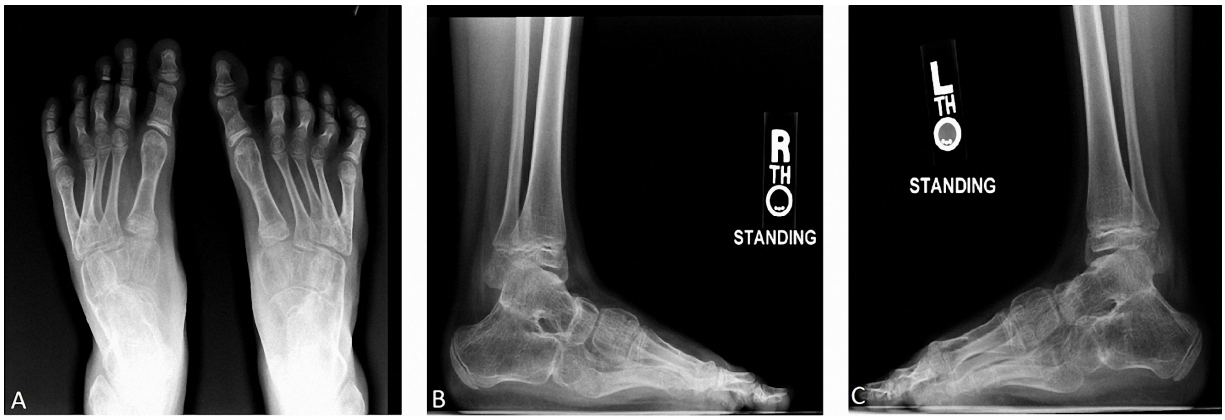

Fig. 4. Postoperative standing radiographs of feet: (A) Anterio-posterior view. (B) Lateral right foot. (C) Lateral left foot.

cyclooxygenase pathway, potential biological mediators which have complex effects on bone remodeling [6]. Poorly mineralized bone can be more susceptible to deformity, especially in the setting of diminished selective control and strength of the muscles about the extremities.

Due to the rarity of this condition, an algorithm for management of musculoskeletal pathology in PBD is not readily available. The progressive cavovarus deformity in this case report is similar to that seen in other neurologic conditions such as Charcot-Marie-Tooth disease and the hereditary motor sensory neuropathies. Soft tissue balancing performed in the younger growing child is often complicated by recurrence with growth and the need for osteotomy or arthrodesis strategies. Staged procedures are not uncommon in progressive neurologic conditions. In some cases, variables such as age of the child, nature of the neurologic impairment, and degree of deformity might influence the choice of surgical correction. In most cases, soft tissue balancing with necessary osteotomies are preferred over arthrodesis to maintain motion and preserve nearby articulations. Although there are inherent disadvantages to arthrodesis in a young individual, it may be the only option to provide lasting correction and stability of the deformity [7].

In the ambulatory child with PBD, the development of foot deformities can be managed with standard corrective procedures that address segmental malalignment of the foot and ankle. In this particular case, a stable foot position was achieved only with arthrodesis.

References

[1] FitzPatrick DR. Zellweger syndrome and associated phenotypes. J Med Genet 1996;33(10):863–8.

[2] Poll-The BT, Gärtner J. Clinical diagnosis, biochemical findings and MRI spectrum of peroxisomal disorders. Biochim Biophys Acta 2012;1822(9):1421–9.

[3] Braverman NE, D'Agostino MD, Maclean GE. Peroxisome biogenesis disorders: Biological, clinical and pathophysiological perspectives. Dev Disabil Res Rev 2013;17(3):187–96.

[4] Poznanski AK, Nosanchuk JS, Baublis J, Holt JF. The cerebro-hepato-renal syndrome (CHRS) (Zellweger's syndrome). Am J Roentgenol Radium Ther Nucl Med 1970;109(2): 313–22.

[5] Poll-The BT, Gootjes J, Duran M, De Klerk JB, Wenniger-Prick LJ, Admiraal RJ, et al. Peroxisome biogenesis disorders with prolonged survival: phenotypic expression in a cohort of 31 patients. Am J Med Genet A 2004;126A(4): 333–8.

[6] Baggio B. Fatty acids, calcium and bone metabolism. J Nephrol 2002;15(6):601–4.

[7] Wetmore RS, Drennan JC. Long-term results of triple arthrodesis in Charcot-Marie-Tooth disease. J Bone Joint Surg Am 1989;71(3):417–22.