

Clinical Report

Plantar Lipomatosis, Unusual Facies, and Developmental Delay: Confirmation of Pierpont Syndrome

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In 1998, Pierpont et al. reported on two unrelated boys with plantar lipomatosis, unusual facial phenotype, and developmental delay as a possible new MR/MCA syndrome. Here we report on a 2-year-old boy with similar manifestations: axial hypotonia in the first few months, prolonged feeding problems, moderate developmental delay, no speech development, deep palmar and plantar grooves, fat pads at the anteromedial aspect of the heels, and a distinct facial phenotype (high forehead, high anterior hairline, mild midfacial hypoplasia, remarkably narrow and upward slanted palpebral fissures, broad nasal ridge and tip, broad philtrum, bowed upper lip, "pouting" lower lip, full cheeks, and flat occiput). Brain MRI and MR spectroscopy studies showed relatively small frontal lobes, some widening of the lateral and third ventricles, and increased choline levels in the frontal white matter. Cytogenetic studies in lymphocytes and skin fibroblasts and whole genome micro-array CGH failed to show abnormalities. The present patient has a phenotype almost identical to that of the earlier reported children (Pierpont et al. [1998]: *Am J Med Genet* 75:18–21), which thereby validates this as a separate MR/MCA syndrome, appropriately designated Pierpont syndrome. The cause of the entity remains uncertain, the most likely etiologies being X-linked recessive or autosomal dominant genes.

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KEY WORDS: plantar lipomatosis; developmental delay; Pierpont syndrome; autosomal dominant inheritance; X-linked recessive inheritance

INTRODUCTION

In 1998, Pierpont et al. described two boys with global developmental delay, mild microcephaly, high forehead, midface hypoplasia, broad nasal tip with anteverted nares, widely spaced teeth and central palatal ridge, plantar fat pads, fetal

finger and toe pads, and increased internipple distance [Pierpont et al., 1998]. As they were unable to retrieve earlier reports of similar individuals, they postulated this as a 'new' MR/MCA syndrome.

Recently we had the opportunity to study a boy with identical findings. We believe that this phenotype and that of the patients described by Pierpont et al. [1998] constitute a unique entity.

CLINICAL REPORT

The proband was the second child of healthy, non-consanguineous parents. He had one brother with normal mental and physical development. There was no family history of mental retardation or other birth defects. Maternal age was 32 and paternal age 37 years, respectively. Pregnancy was unremarkable, delivery was spontaneous at 37 weeks. Weight at birth was 2,690 g (25th centile). Head circumference (OFC) at birth was not recorded but at 21 days, OFC was 33.8 cm (10th centile). Immediately after birth he was hypotonic, and had bradycardia and respiratory problems, possibly due to amniotic fluid aspiration. He had feeding difficulties, consisting of swallowing difficulties and frequent vomiting, necessitating tube feeding. By supportive strategies, he was gradually able to drink independently, but feeding problems remained present.

Re-evaluation at 7 months showed slightly delayed motor development. He was still unable to roll over. His weight was 7,455 g (16th centile), and OFC was 42.8 cm (10th centile). He had a remarkable facial appearance (Fig. 1A): high forehead, high anterior hair line, mild midfacial hypoplasia, unusually narrow and upward slanted palpebral fissures, in part explained by full periorbital tissues, broad nasal bridge and ridge, bulbous nasal tip, broad philtrum, bowed upper lip, "pouting" and hypotonic lower lip, full cheeks, and flat occiput. He had curly blond hair. His neck was short, the internipple distance was large, and the areolas were small. He had a small penis and slightly underdeveloped scrotum. There was excessive skin over hands and feet, causing them to have a puffy appearance. On the palms and soles, the grooves were deeper than normal with pillowing of the areas between the grooves (Fig. 2A). Fat pads were located on the medial border of both feet just anterior to the calcaneus. Otherwise hands and feet had a normal shape.

Chromosomal analysis in blood revealed a normal male karyotype (46,XY). Chromosomal analysis of 30 metaphase spreads from cultured skin fibroblasts showed no evidence of chromosomal mosaicism. Whole genome micro-array CGH gave normal results.

On radiographs of skull, thorax, hands, and feet no abnormalities were seen. Urinary metabolic screening (including oligosaccharides, sialic acid, lactate, amino acids, and mucopolysaccharides) and plasma screenings (including creatine kinase, lactate, amino acids, sialotransferrins, phytanic

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Fig. 1. Face of the present patient at 18 months (A) and 2½ years (B, C). Note the high forehead, narrow and upslanted palpebral fissures, broad nasal tip, and midfacial hypoplasia.

acid, pipercolic acid, long-chain fatty acids, acylcarnitine) showed no abnormalities. Ophthalmologic examination showed small palpebral fissures, alternating strabismus, and hyperopia (S + 6). A brain MRI scan showed relatively small frontal lobes, widening of lateral and third ventricles and of the subarachnoid space, a relatively large cerebellum, and delayed myelination.

At 18 months of age, he underwent repair of bilateral inguinal hernia and a left hydrocele. He still manifested feeding difficulties (mainly vomiting). Gastroscopy failed to show an anatomical or acquired anomaly. His length, weight, and OFC were between the 10th and 25th centile. He was able to roll over, but could not sit or stand independently.

Neurological examination showed axial hypotonia and hypertonia of the arms and legs with brisk tendon reflexes. A repeated brain MRI scan at 21 months showed the frontal lobes, cerebellum, ventricles, and subarachnoid space to be less abnormal. The degree of myelination had become normal for age, although the border between white and gray matter was still unsharp in especially the frontal and temporal lobes. Multivoxel MR spectroscopy (chemical shift imaging) was performed. In general, N-acetyl aspartate is a marker of neuron content and integrity, choline of myelin content, and total creatine of cell density. Under the given conditions (TR/TE = 1,500/135 msec), at this age, and taking the width of the peaks into account as well the N-acetyl aspartate peak area normally exceeds the choline and creatine peak integrals by more than 50% in the entire supraventricular volume of interest examined. The absolute level of choline

in this patient appeared to be very high, especially in the frontal region (Fig. 3A–C). Electroencephalography was unremarkable, apart from slight slowing of background activity for age.

At 2½ years, he had no speech development, was able to roll over and sit independently. He was not able to crawl but moved around by shuffling along on his back. Usually he was a happy child, but sometimes he had behavior problems, mainly biting himself or others and sleeping difficulties. He suffered from constipation. His facial features had not changed much (Fig. 1B,C), although it had now become clear that his teeth were widely spaced, the right upper medial incisor was broad, and all incisors had an irregular edge. His weight and OFC were between the 10th and 25th, his length at the 3rd centile. The plantar lipomatosis had decreased but still was remarkable (Fig. 2B). The grooves and excessive skin on the palms and soles had become less obvious.

DISCUSSION

The phenotype of the present patient and the previously reported patients is remarkably similar [Pierpont et al., 1998]. They all had a high forehead, high anterior hairline, narrow and upslanted palpebral fissures, midfacial hypoplasia, broad nasal tip, flat and broad philtrum, and widely spaced teeth. The feet are especially distinctive because of the large fatty pads anteromedial to the heel; but also the deep palmar and plantar grooves with pillowing of the areas between the grooves are a hallmark. Growth of both body length and skull were at the lower border of normal. They had all a moderate to severe developmental delay, and especially the delay in speech development was distinct. The first patient described in Pierpont et al. [1998] had a seizure disorder starting at 5 years. At follow-up he still had seizures, and was severely retarded; the plantar lipomatosis had decreased with time [R.J. Gorlin, 2004; personal communication]. The second patient in the original paper had no seizures at age 2½ years. Follow-up showed him to have very delayed development (no speech and unsteady walking at 8 years), behavior problems, constipation, strabismus, scoliosis, and unilateral hearing loss [F.J. Stewart, 2004; personal communication]. The present patient has had no seizures until now. Multivoxel MR spectroscopy in this patient showed a high level of choline, especially in the frontal region. The spectral pattern resembled that of normal subjects younger than six months old and fits with the patient's global developmental delay. However, it should be noted that development is always slower in the frontal region than the posterior brain. In a previous study hypomyelination was not associated with increased brain choline level [Van der Knaap et al., 2002].

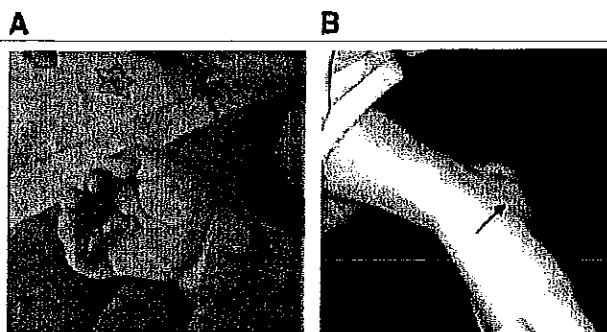


Fig. 2. Palm of the present patient at 18 months (A). Note deep palmar grooves with pillowing of the areas between the grooves. Right foot of the present patient at age 2½ years (B). Fat pads were evident on the medial border of both feet, just anterior to the calcaneus.

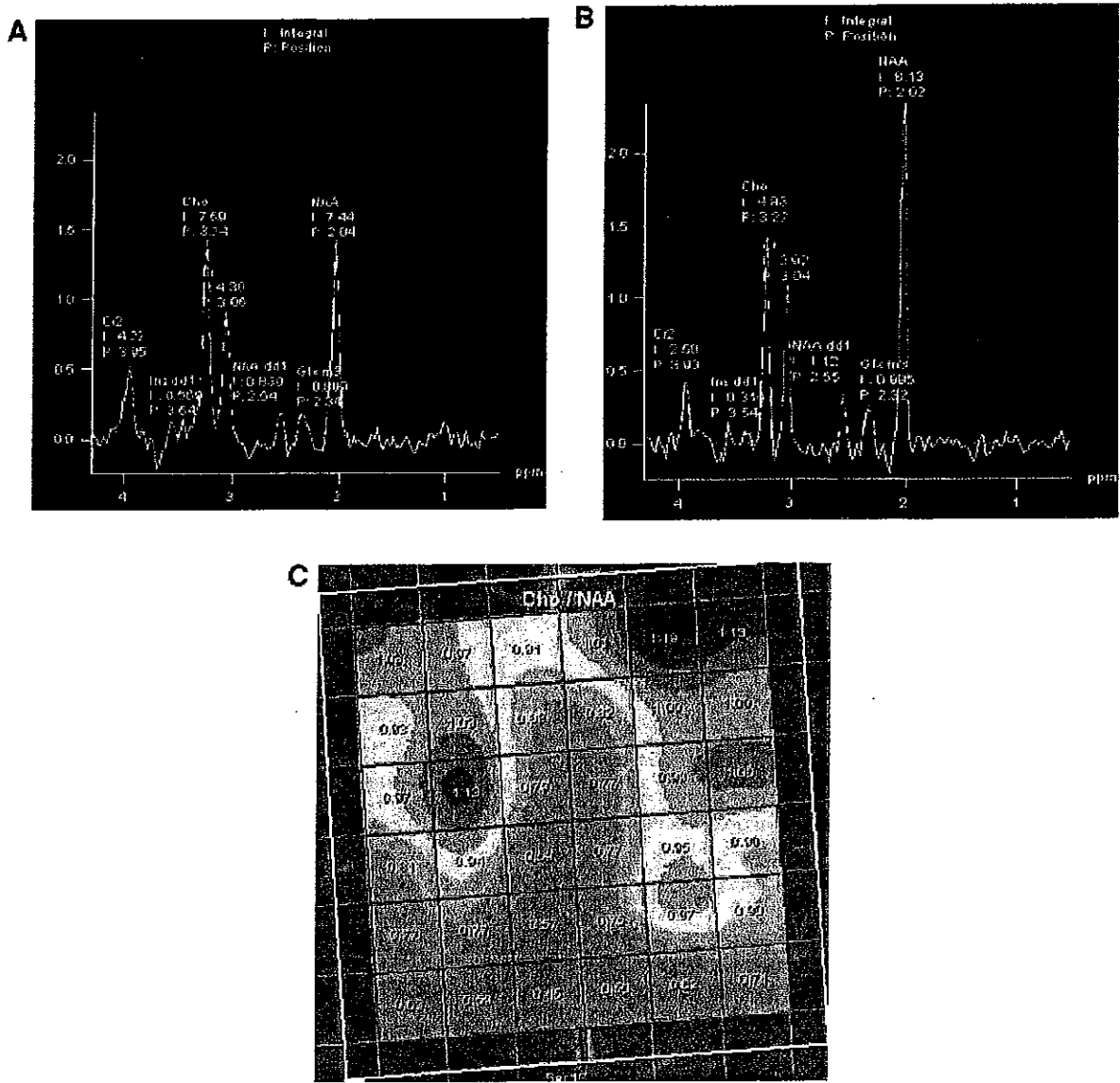


Fig. 3. Multivoxel MR spectroscopy showing chemical shift imaging of a supraventricular volume of interest reveals posterior region spectra that are normal for the age of the patient (A) and frontal spectra with clearly increased choline peak areas (position 3.2 ppm) combined with normal creatine (3.0 ppm) and N-acetylaspartate levels (2.0 ppm) (B). The spectral map shows most abnormality (red) in the voxels containing frontal white matter (C).

The facial appearance and the thickened palms and soles resemble findings in Costello syndrome to some extent [Hennekam, 2003]. Costello syndrome is characterized by an increased weight at birth, postnatal growth retardation, macrocephaly, facial abnormalities, perioral papillomata, loose skin, non-progressive cardiomyopathy, developmental delay, and a friendly behavior. The palms and soles show deep creases and redundant skin, and also inguinal hernia are often seen in Costello syndrome, probably due to the abnormal connective tissue in this disorder [Hinek et al., 2000]. However, the present patient has no macrocephaly, papillomata, or cardiac disorder. The typical large fatty pads anteromedial to the heels have not been reported in Costello syndrome. Some patients with Costello syndrome were initially suspected to have Hurler syndrome or another mucopolysaccharidosis [Hennekam, 2003], but extensive metabolic studies in the present patient failed to show clues for a storage disease.

The grooves on the palms and soles can also be found in patients with (mosaic) trisomy 8 [Schinzel, 2001]. Full trisomy 8 is usually a lethal disorder early in life, but mosaic trisomy 8 is a well-known entity, about 120 cases being reported. Findings often include normal or advanced growth, moderate mental retardation, slender body build, expressionless face, limitation of motion in multiple joints with contractures, radiologic abnormalities of spine, ribs, iliac wings, patellae, and brain (absence of the corpus callosum). Cardiomyopathy, additional nipples, and proximal syndactyly of the toes occur occasionally. Our patient was not slender and did not have skeletal anomalies or cardiomyopathy. Cytogenetic studies in lymphocytes from the original patients of Pierpont et al. [1998], and in skin fibroblasts of the present patient showed a normal male karyotype. Furthermore a whole genome micro-array CGH study in the patient presented here has given normal results.

We suggest that this condition be called Pierpont syndrome. The etiology of Pierpont syndrome remains uncertain. All cases have been isolated until now. There has been no clue for a teratogenic cause in either patient. A chromosomal cause (microdeletion or microduplication) was made unlikely in the present patient but still cannot be completely excluded. None of parents have been consanguineous, pleading against autosomal recessive inheritance. The advanced paternal age in the first patient from Pierpont et al. [1998] is in favor of an autosomal dominant, spontaneous mutation. Presently reported patients are boys, this may be in keeping with X-linked (recessive) inheritance. Future reports of other similar patients with this phenotype may hopefully make the type of inheritance pattern clearer.

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