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Medical Journal of Obstetrics and Gynecology

Case Report

Selective Fetal Reduction in a Monochorionic Diamniotic Twin Pregnancy with a Discordance in Pena-Shokeir Type I Phenotype

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Submitted: 17 May 2016

Accepted: 25 May 2016

Published: 26 May 2016

ISSN: 2333-6439

Keywords

- Pena-Shokeir syndrome
- Prenatal diagnosis
- Monochorionic diamniotic twins
- Fibrous fatty replacement
- Cryptorchidism

Abstract

We here report the first case of discordant Pena-Shokeir phenotype observed in monochorionic diamniotic twins. A 41-year-old woman, pregnant with twins, was referrend at 12 weeks' gestation because the combined test was altered. Serial ultrasonographic examination suggested that twin A may have had arthrogryposis, micrognathia, kyphoscoliosis, fixed flexion of the limbs, polyhydramnios, myocardial ventricular hypertrophy, lack of visualization of the stomach, pulmonary hypoplasia, decreased movements, low-set ear, hypertelorism and rocker-bottom feet with a 10% restriction of growth. Twin B showed normal growth, no structural abnormalities, but a severe oligohydramnios. At 31 weeks of gestation a selective reduction of twin A was performed. At 32 weeks of gestation, the twins were delivered by cesarean section. Autopsy findings of twin A were consistent with the diagnosis of Pena-Shokeir phenotype. We suggest that cerebral injury during early gestation is a possible cause for the occurrence of Pena-Shokeir phenotype through an anoxic-ischemic mechanism.

ABBREVIATIONS

FADS: Fetal Akinesia Deformation Sequence; **IUGR:** Intrauterine Growth Restriction; **PSP:** Pena-Shokeir Phenotype; **NT:** Nuchal Translucency; **PAPP-A:** Pregnancy Associated Plasma Protein; **COFS-1:** Cerebro Oculo Facio Skeletal syndrome 1; **LCCS:** Lethal Congenital Contracture Syndrome; **PS:** Pena-Shokeir

INTRODUCTION

Fetal akinesia deformation sequence (FADS; OMIM 208150) is a clinically and genetically heterogeneous disorder characterized by a variable combination of arthrogryposis, fetal akinesia, intrauterine growth restriction (IUGR), developmental abnormalities such as cystic hygroma, pulmonary hypoplasia, cleft palate, cryptorchidism, cardiac defects and intestinal malrotation, and occasional pterygia of the limbs [1-3]. Bayat et al [4] reported that the incidence of FADS was 1:15,000; it was originally reported by Pena and Shokeir [1] and Lindhout et al [5] to describe a disorder called Pena-Shokeir syndrome consisting of the symptoms of IUGR, polyhydramnios, facial dysmorphism, pulmonary hypoplasia, a short umbilical cord, and supplementary symptoms of cleft or high-arched palate and bell-shaped chest. In 1986, it was possible to suggest that reports of Pena-Shokeir syndrome represented a phenotype produced by decreased in utero movement, and then to subdivide the reported cases into six possible subgroupings [6]. Remarkable progress has been made since then in further defining the etiologies and features that are associated with lack of embryonic and fetal movement, as well as in recognizing specific familial subtypes and in identifying responsible genes and environmental factors. Although there have been six previous reports describing monochorionic twins affected with PSP/FADS [7-10], this is the first demonstrated report of discordance in the Pena–Shokeir phenotype in monochorionic diamniotic twins.

CASE PRESENTATION

A 41-year-old woman, gravida 3, para 0, spontaneously

pregnant with monochorionic diamniotic twins and a bicornuate uterus, was referred to our institution at 12 weeks' gestation because the combined test (Nuchal translucency with Bi-test) was abnormal: free β-hCG 181.0 UI/l (1.066 MoM), PAPP-A 0.300 UI/l (0.132 MoM), NT twin A 1.6 mm, NT twin B 1.2 mm, with a consequent high risk of foetal genetic anomalies (Trisomy 21=1:7, Trisomy 18=1:28, Trisomy 13=1:6); foetal anatomy, evaluated by ultrasound, was apparently regular shaped. In gestational week 13, chorionic villous sampling was performed for kariotyping and genetic analyses; the chromosomal analysis of chorionic villous revealed a 46, XY kariotype, negative for cystic fibrosis, congenital deafness, Duchenne muscular dystrophy and fragile X syndrome; during the diagnostic procedure the sonographer described regular movements of both fetuses. At 23 weeks' gestation, during the second trimester morphology ultrasound, arthrogryposis, micrognathia, kyphoscoliosis, fixed flexion of the upper and lower limbs, polyhydramnios, ventricular hypertrophy of the myocardium, lack of visualization of the stomach were observed in the twin A with a 10% restriction of growth. Ultrasound scans were repeated every 2 weeks since the suspicion of Twin to Twin Transfusion Syndrome. The finding of serial ultrasonographic examination also indicated that twin A may have had many others abnormalities, including pulmonary hypoplasia and decreased movements at 25 weeks of gestation, low-set ear, hypertelorism and rocker-bottom feet at 27 weeks of gestation. All of these abnormalities are compatible with the Pena-Shokeir phenotype. In contrast, twin B showed normal growth, no structural abnormalities, but a severe oligohydramnios. For this reason at 31 weeks of gestation a fetoscopy with fetal cord clamping (selective reduction of twin A) and drainage of polyhydramnios were performed. At 32 weeks of gestation, the twins were delivered by cesarean section; twin A was a boy weighing 1240 g with Apgar scores of 0; he exhibited craniofacial anomalies, low-set ear, micrognathia, cleft palate, multiple contractures, short umbilical cord, arthrogryposis, ulnar deviation of the hands, camptodactyly, facies amimica, rocker bottom foot oedematus head and severe thanatological alterations (Figure 1). Twin B weighed 1550 g at birth and had no abnormalities, with Apgar scores of 7 at 1 min, and 9 at 5 min. An autopsy of twin A revealed pulmonary hypoplasia, cardiac ventricular hypertrophy and cryptorchidism. Because colliquative necrosis of brain, was impossible to examine the brain and look for possible causes of the disease. Microscopically scalp appeared edematous, iliopsoas muscle was characterized by fibrosis with fatty infiltration and moderate variability in diameter of muscle fibers (Figure 2), lungs showed borderline hypoplasia and testis showed atrophy of testicular tubules, fibrosis and hypertrophy of Leydig-cells (Figure 3), suggesting a chronic ischemia. It was not carried out an X-ray of the whole fetal body. The normal 46, XY karyotype, without chromosomal alterations, allows to exclude differential diagnoses like Cerebro Oculo Facio Skeletal syndrome 1 (COFS1- Pena-Shokeir syndrome, Type II), Trisomy 18 and Lethal Congenital Contracture Syndrome (LCCS). The macroscopic and microscopic features, the medical history, the course of the disease and the phenotype of the twin A suggest the diagnosis of Pena-Shokeir syndrome, Type I.

DISCUSSION

In 1974, Pena and Shokeir first described this lethal autosomal recessive syndrome characterized by arthrogryposis,

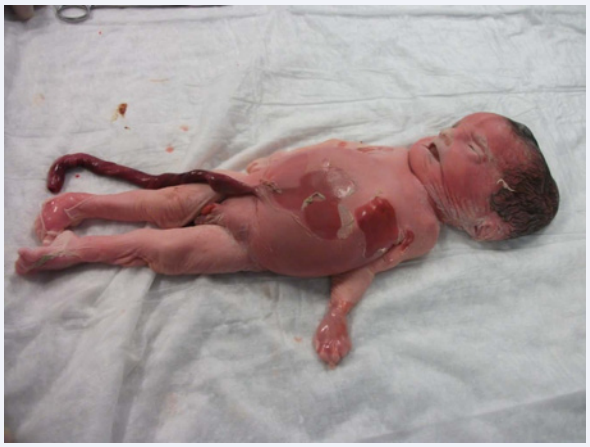

Figure 1 Fetus A affected by Pena-Shokeir syndrome, Type I. Notice the craniofacial anomalies, low-set ear, micrognathia multiple contractures, short umbilical cord, arthrogryposis, ulnar deviation of the hands, camptodactyly, facies amimica, oedematus head and severe thanatological alterations.

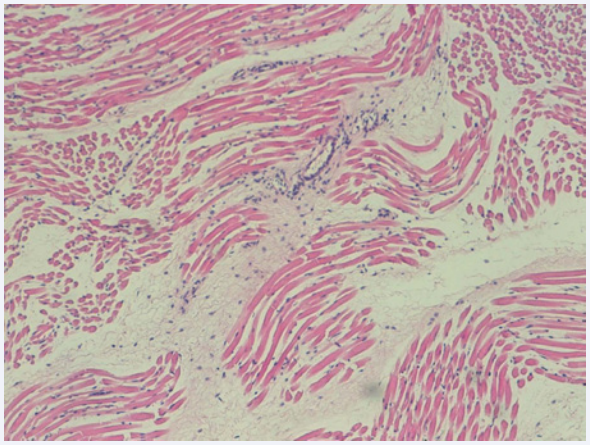

Figure 2 Microscopy: iliopsoas muscle is characterized by fibrosis with fatty infiltration and moderate variability in diameter of muscle fibers (10X).

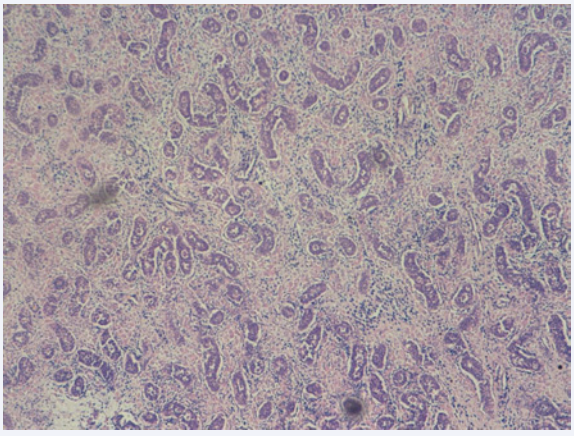

Figure 3 Microscopy: testis show atrophy of testicular tubules, fibrosis and hypertrophy of Leydig-cells (10X).

camptodactyly, facial anomalies and pulmonary hypoplasia in two siblings [1].

The pathogenesis of PSP/FADS is attributable to familial muscle dystrophy or anoxic-ischemic etiology [7]. In the present case, prenatal ultrasonographic findings consistent with PSP/FADS were observed as early as 23 weeks of gestation, but a biochemical alteration had already been found at 12 weeks (altered PAPP-A) during the combined test.

In utero continuous fetal movement is essential for development of normal respiratory and limb function. If movements stop, the joints become stiff and muscle mass decreases. The earlier starting and longer standing the lack of movement, the worse the deformations will be. Fetal lack of movement leads to a recognizable set of abnormalities that has come to be known as the Pena-Shokeir phenotype, or fetal akinesia deformation sequence. Lack of in utero movement leads to a variety of secondary deformations. The polyhydramnios and pulmonary hypoplasia are related to depressed swallowing and absence of normal fetal breathing. Prenatal diagnosis of reduced or absent fetal movements in association with abnormal fetal posture should include a differential diagnosis of spina bifida, trisomy 18, trisomy 13, arthrogryposis, FADS, fetal constraint, body stalk anomaly, caudal regression sequence, fetal hypoxia/severe hypotonia, amniotic bands, fetal neck masses, joint dislocations, vertebral segmentation abnormalities, iniencephaly, multiple pterygium syndrome, Cerebro Oculo Facio Skeletal syndrome, Lethal Congenital Contracture Syndrome, Freeman Sheldon syndrome, Potter syndrome, Neu-Laxova syndrome, restrictive dermopathy and Larsen syndrome. Among these, pulmonary hypoplasia is only found with Potter syndrome; however, the presence of severe oligohydramnios in this condition differentiates it from PS syndrome [11]. Fetal akinesia/arthrogryposis can result from primary defects of brain, spinal cord, peripheral nerves, neuromuscular junction, skeletal musculature and connective tissues, vascular compromise, restricted intrauterine space, teratogenic exposures, ischemia, maternal illness, and circulating maternal antibodies to neurotransmitters, myelin, and muscle proteins. Prenatal ultrasound findings of fetal akinesia/arthrogryposis include lack of extremity motions, persistent abnormal posture of the limbs, lack of facial movements, polyhydramnios due to decreased fetal swallowing, pulmonary hypoplasia, a short umbilical cord due to decreased fetal movements, IUGR, increased nuchal translucency, nuchal edema or cystic hygroma in the first trimester, and hydrops fetalis.

Families with apparent increase in monozygotic twinning have been described by Chen et al. (1983); Lindhout et al. (1985), and Ho (2000) [7]. Affected twins and affected singletons occur in the same families. The relationships between monozygotic twinning and this type of PSP/FADS is unclear. Potentially they are cases of classic Pena-Shokeir syndrome. Due to the discordance of PSP/FADS in monozygotic twins, it is unlikely in the present case that the cause of PSP/FADS is hereditary. We therefore hypothesize that an hypoxic accident during early gestation may have resulted in the development of PSP/FADS of ischemic origin in only one twin in this case. Six case reports of monochorionic twins with PSP/FADS have previously been published [10]. In three cases the PSP/FADS was determined to have occurred in response to intrauterine anoxic-ischemic damage. Similarly, as only one of the monoamniotic twins in our study was affected by PSP/FADS, we have attributed the cause to anoxic-ischemic damage. Twins, particularly monozygotic, seem at increased risk for this type of change because of their vascular connections [7]. Quinn et al. (1991) [12] suggested that in utero ischemic changes are much more common than earlier recognized. All large series of lethal multiple congenital contractures include sporadic cases related to intrauterine ischemia [13]. Most cases are sporadic, but familial recurrence is also described. If the primary mechanism in these families is a Central Nervous System vascular accident. These cases and families strongly suggest in utero vascular accidents, going all the way back into the early second trimester leading to FADS. Establishing the exact timing is difficult but in this particular case, at 12 weeks of gestation, PAPP-A was altered, indicating an initial vascular suffering. Overall, recurrence risk in this group is probably small in the range of 2 to 3%. Ischemic changes during embryonic/fetal development being recognized in as many as one third of neonatal deaths caused by PSP/FADS. These ischemic disturbances can be predisposed by developmental vascular abnormalities, trauma, hypotension, drugs, infections, and maternal illness or thrombophilia. They tend to be sporadic, but the occasional familial form can recur.

In 1983, Moessinger [14] performed an experimental study in which rat fetuses were paralysed by daily transuterine injection of curare from day 18 until term. At the time of delivery multiple joint contractures, pulmonary hypoplasia, micrognathia, fetal growth retardation, short umbilical cord, and polyhydramnios were noted, bearing a striking similarity to the PS syndrome phenotype. He postulated that this phenotype is not specific, but rather represents a fetal akinesia deformation sequence that results from fetal immobilization or akinesia. The basis for this theory is that use and motion are necessary for normal fetal development. Muscle atrophy, and abnormal shape and position of the limbs are due to lack of normal motion [11]. Depressed swallowing is probably responsible for polyhydramnios and an empty stomach. Lack of muscle pull at sites of normal attachment may lead to craniofacial anomalies.

In this clinical case, the histological examination of the affected fetus revealed an edematous scalp, while iliopsoas muscle was characterized by fibrosis with fatty infiltration and moderate variability in diameter of muscle fibers; the observation of fatty change in chronically denervated muscles suggests an irreversible process [15]; lungs showed borderline hypoplasia and testis showed atrophy of testicular tubules, fibrosis and hypertrophy of Leydig-cells, suggesting a chronic ischemia. This case, which is the first involving the discordant prenatal diagnosis of PSP/FADS in monochorionic diamniotic twins, has led us to advocate a novel cause for this pathology, whereby an anoxic-ischemic event can lead to PSP/FADS in one diamniotic twin, forewarned by an altered value of PAPP-A in the first trimester of pregnancy.

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Cite this article

Di Luigi G, D'Alfonso A, Patacchiola F, Sollima L, Leocata P, et al. (2016) Selective Fetal Reduction in a Monochorionic Diamniotic Twin Pregnancy with a Discordance in Pena-Shokeir Type I Phenotype. Med J Obstet Gynecol 4(2): 1079.