

Prenatal diagnosis of Pena-Shokeir syndrome as a rare lethal disorder influencing fetal neuromuscular system: A case report

Fetal nöromuskuler sistemi etkileyen nadir öldürücü bir bozukluk olarak Pena-Shokeir sendromunun prenatal tanısı: Bir vaka sunumu

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Abstract

Pena-Shokeir syndrome type I (fetal akinesia deformation sequence, FADS) is a mostly autosomal recessive lethal disorder characterised by combination of abnormal limb position, restrictive fetal movement with reduced or absent response to acoustic stimulation, growth restriction, polyhydramnios, and pulmonary hypoplasia. Limb defects like camptodactyly, rocker bottom feet and clubfoot are other prominents of the syndrome. Obstetric ultrasonographic examination of a 24-year-old pregnant woman, consanguineous with her husband, revealed a single male fetus with contractures of the upper and the lower limbs and polyhydramnios due to the absence of swallowing, persistent flexion of the bilateral wrist, elbow joints and the knee joints consistent with Pena Shokeir syndrome phenotype. The parents were informed about the diagnosis and its poor prognosis. Fetus had no viability, therefore the termination of the pregnancy was offered to the parents and they accepted. We report the prenatal and postnatal sonographic, pathologic and genetic diagnostic features of a Pena-Shokeir syndrome case.

Keywords: Pena-Shokeir syndrome, prenatal diagnosis, lethal, neuromuscular disorder

Özet

Pena-Shokeir sendromu tip 1 (fetal akinezi deformasyon sekansı, FADS); anormal ekstremitte pozisyonu, akustik stimülasyonla azalmış veya kısıtlanmış fetal hareket, büyüme geriliği, polihidramniyos ve pulmoner hipoplazi bulgularının kombinasyonu ile karakterize sıklıkla otozomal resesif olan öldürücü bir bozukluktur. Kamptodaktili, hokey sopası şekilli ayaklar ve ayaklarda içe dönüklük gibi ekstremitte problemleri sendromun diğer bulgularıdır. Eşi ile akraba evliliği yapan 24 yaşında gebe bir kadının obstetrik ultrasonografik muayenesinde; Pena-Shokeir sendromu fenotipi ile uyumlu olacak şekilde, üst ve alt ekstremitelerde kontraktürler, yutma eksikliğine bağlı polihidramniyos, bilateral el bileği, dirsek ve diz eklemlerinde persistan fleksiyon deformitesi olan tek erkek fetus tespit edildi. Aile tanı ve kötü prognoz hakkında bilgilendirildi. Fetusün viyabilite ihtimali yoktu ve gebelik terminasyonu önerilen aile bunu kabul etti. Bir Pena-Shokeir sendromu vakasının prenatal ve postnatal, sonografik, patolojik ve genetik tanısal özelliklerini sunuyoruz.

Anahtar sözcükler: Pena-Shokeir sendromu, prenatal tanı, öldürücü, nöromuskuler bozukluk

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Introduction

Pena-Shokeir syndrome type I (fetal akinesia deformation sequence, FADS) is a mostly autosomal recessive disorder characterized by intrauterine growth restriction, polyhydramnios, multiple joint contractures, arthrogryposis, camptodactyly, facial anomalies like micrognathia, and lung hypoplasia. It was first described by Pena and Shokeir (1974) as an early lethal disorder characterized by neurogenic arthrogryposis, facial anomalies, pulmonary hypoplasia and dysmorphic features resulting from fetal akinesia [1]. It is a rare, mostly autosomal-recessive transmitted syndrome with a frequency of 1 in 12.000 live births. Heterogenic etiology of this syndrome results with unusual presentations. Pena-Shokeir syndrome may result from truncating mutations in RAPSN or DOK7. Prenatal exposure to circulating maternal neurogenic antibodies to the acetylcholine receptor is another cause of the syndrome [2]. The protein encoded by DOK7 induces autophosphorylation of the skeletal muscle receptor-like tyrosine kinase, a key protein involved in postsynaptic differentiation. The protein rapsyn acts as a link connecting the acetylcholine receptor to the cytoskeleton-anchored dystrophin-glycoprotein complex at the neuromuscular junction. Contractures of multiple joints including wrists, ankles, elbows, knees, and hips are main phenotypic characteristic features. Limb defects like camptodactyly, rocker bottom feet and clubfoot are other prominents of the syndrome. Apparently short neck, posteriorly rotated ears, hypertelorism, proptosis, epicanthal folds, micrognathia, small mouth, and highly arched palate are craniofacial anomalies of the syndrome [1]. Trisomy 18 may present with features that overlap with Pena-Shokeir syndrome; particularly craniofacial, limb, and intrathoracic abnormalities. Karyotype analysis clarifies the differential diagnosis. Prenatal ultrasonography is an useful adjunct for diagnosing Pena-Shokeir syndrome phenotype in addition to demonstrating reduced fetal movements or akinesia. The combination of abnormal limb position, restrictive fetal movement with reduced or absent response to acoustic stimulation, growth restriction, polyhydramnios, and pulmonary hypoplasia are the main signs for establishment of the diagnosis [3]. Low-set malformed ears, hypertelorism, short neck, cleft palate, scalp edema, thoracic deformities, camptodactyly, and micrognathia may also be found. Diaphragmatic hernia, gastroschisis, and microcephaly are anomalies less frequently described in Pena-Shokeir syndrome. Other findings at birth include a short umbilical cord and small placenta. We report the prenatal sonographic diagnosis of Pena-Shokeir phenotype in our case [4].

Case report

A 24-year-old pregnant woman, (gravida 3 and parity 2), referred to our department for level 2 obstetric ultrasonography at 23 weeks of gestation according to the last menstrual period. She had no history of familial disease, drug abuse, or systemic illness. The parents were relatives (cousins) and via the anamnesis, we learned that her previous pregnancy had resulted with in-utero fetal demise demonstrating multipl joint contractures at about 20 weeks of gestation. Ultrasonographic examination was performed for screening fetal anomalies. A single male fetus with contractures of the upper and the lower limbs and polyhydramnios due to the absence of swallowing, persistent flexion of the bilateral wrist, the elbow joints and the knee joints was viewed on the sonography. Fetal posture was fixed and there was no fetal movement during the examination. Fetal mouth was fixed opened, no breathing and swallowing was visualised during sonographic examination [5]. When vibroacoustic stimulation was applied through the maternal abdominal wall, no fetal movement was seen [3]. On the ultrasonography, the biparietal diameter (41 mm), the femur length (27 mm) and the abdominal circumference (133 mm) were consistent with the gestational date of 18 weeks and revealed symmetric growth restriction. On the examination of the thorax, cardiomegaly, pulmonary hypoplasia, approximately 2 mm of pleural and pericardial effusion were also detected. Gastric fluid was not visible revealing depressed swallowing reflex of the fetus. The lateral ventricle width at atrium was 7 mm and the fetus had also microcephaly, micrognathia and gastroschisis as major abnormalities (Figure 1, 2).



Figure 1. Fetal ultrasonographic view of fixed flexion of the lower limbs, knee and ankle.



Figure 2. Fetal ultrasonographic view of fixed opened mouth, small thoracic cage and absence of gastric fluid.

These findings were consistent with the Pena Shokeir syndrome phenotype. The parents were informed about the diagnosis and its poor prognosis. Fetus had no viability, therefore, the termination of pregnancy was offered to the parents and they accepted.

Posttermination macroscopic findings confirmed the prenatal sonographic diagnostic features of the syndrome (Figure 3, 4). The muscle biopsy specimen including epidermis and subcutaneous tissue was examined with Haematoxylen-Eozine staining. Thickened subcutaneous tissue under the epidermis, patchy replacement of native muscle tissue areas with fatty tissue and scattered muscle tissue areas were the prominent findings (Figure 5, 6) [6]. Karyotype analysis was normal (46, XY).



Figure 3. Posttermination macroscopic view of the fetus demonstrating gastroschisis, contractures of the elbow, wrist, knee and the ankle joints.

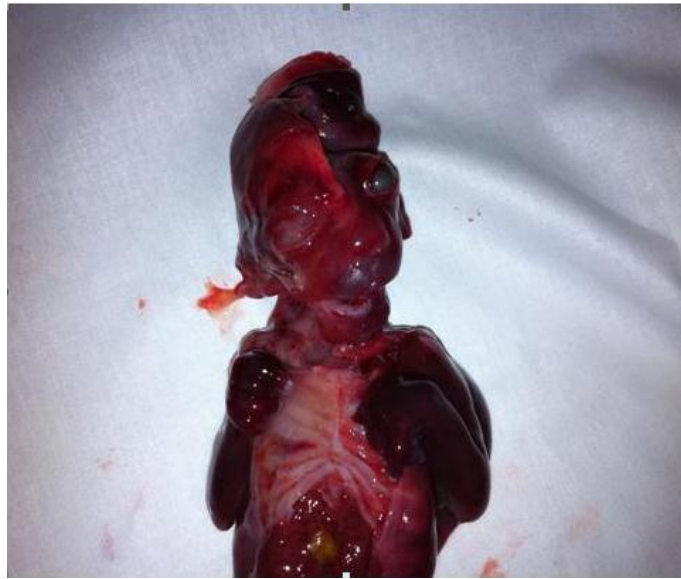


Figure 4. Posttermination macroscopic view of the fetus demonstrating fixed opened mouth, micrognathia, hypertelorism, proptosis, short neck, posteriorly rotated ears, skin anomalies, chest hypoplasia and multipl joint contractures.

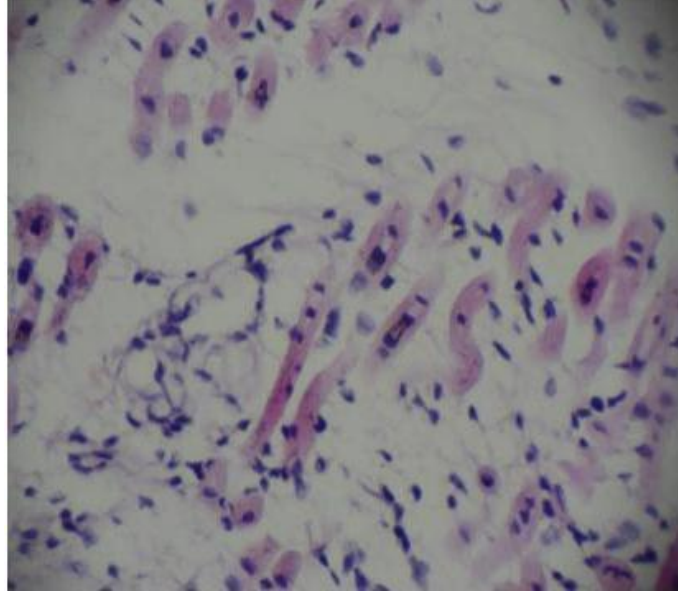


Figure 5. Pathological examination with Haematoxylin-Eosin staining of the fetal quadriceps muscle biopsy specimen demonstrating thickened subcutaneous tissue under the epidermis (HEX40).

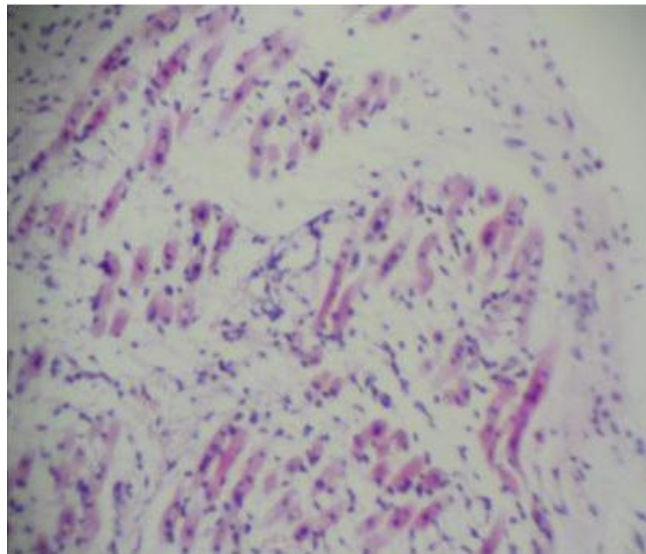


Figure 6. Pathological examination on Haematoxylin-Eosin staining of the fetal quadriceps muscle biopsy specimen demonstrating patchy replacement of native muscle tissue areas with fatty tissue and scattered muscle tissue areas (HEX10).

Discussion

Pena-Shokeir syndrome is a lethal, autosomal recessively inherited syndrome characterized by arthrogryposis, facial dysmorphic abnormalities and pulmonary hypoplasia, first described by Pena and Shokeir in 1974. Based on ultrasonographic major abnormalities of the syndrome like fetal growth restriction, lung hypoplasia, polyhydramnios, fetal akinesia, absence of swallowing, persistent flexion of bilateral wrist, elbow and knee joints, we diagnosed Pena-Shokeir syndrome prenatally. The differential diagnosis includes Freeman-Sheldon syndrome, multiple pterygium syndrome, trisomy 18, and Potter syndrome. Pena-Shokeir syndrome differentiates from those syndromes by lung hypoplasia and differentiates from trisomy 18 by karyotype

analysis. Potter syndrome also results from lung hypoplasia but differentiates from Pena Shokeir syndrome by severe oligohydramnios [7]. In our case, the parents were relatives with a history of major fetal abnormality in their previous pregnancy (multipl joint contractures) which resulted in in-utero death that supports autosomal recessive inheritance of the syndrome [8]. It is a rare syndrome with an incidence of approximately 1 in 12,000 births. The prognosis is very poor with 30% of cases being stillborn, and another 40% not surviving beyond the first few weeks and the remainder not surviving beyond a few months due to the complications of pulmonary hypoplasia. Failure of swallowing causes polyhydramnios, and neuromuscular deficiency in the function of the diaphragm and intercostal muscles causes lung hypoplasia. There may be a recurrence rate of 10-15% for future pregnancies. It is a lethal syndrome, so parents should be informed about the diagnosis and its poor prognosis and termination of pregnancy should be offered.

Pena-Shokeir syndrome shows many heterogeneous phenotypes. Gastroschisis, pericardial effusion and ventriculomegaly are rare sonographic findings of the syndrome. In our case, we diagnosed gastroschisis prenatally and macroscopic examination of the fetus confirmed our prenatal diagnosis after termination of the pregnancy. The fetus also had elbow, wrist and ankle joint contractures, fixed opened mouth, chest hypoplasia and micrognathia, ear and skin abnormalities as we prenatally diagnosed by ultrasonographic scan (Figure 4).

Posttermination pathological examination of the muscle biopsy specimen confirmed our diagnosis by demonstrating muscle atrophy due to fetal akinesia [6].

This case suggests that prenatal ultrasonography plays a very important role for the diagnosis of Pena-Shokeir syndrome and its heterogeneous phenotypes. As an autosomal recessively inherited syndrome, prenatal genetic consultation should especially be offered to the consanguineous couples with a previous history of this syndrome because of the risk of recurrence. Because Pena-Shokeir syndrome is a lethal syndrome with major malformations resulting in bilateral lung hypoplasia, these pregnancies complicate with in-utero death or children born with this syndrome mostly die during neonatal period. Until discovery of the prenatal or postnatal treatment of Pena Shokeir syndrome, termination of the pregnancies with this syndrome prenatally diagnosed by ultrasonographic examination should be offered to the couples.

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