Prenatal suggestion of Pena-Shokeir I syndrome postnatally confirmed

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Abstract
We describe foetus with arthrogryposis in which on the basis of additional structural anomalies detected by USG the Pena-Shokeir syndrome type I was suspected. Differential and final diagnosis was possible only in the newborn, based on the characteristics of dysmorphic features. Disease lead to death by mechanism of pulmonary dysplasia.

Key words: artrogryposis, Pena-Shokeir syndrom, prenatal detection

Introduction
Pena-Shokeir syndrome type I (PSS I) is rare autosomal recessive disease (OMIM 208150), often erroneously referred to as a sequence of defects with a fetal akinesia without oligohydramnions, rarely with polyhydramnions.

It is usually characterized by multiple congenital flexion contractures, pulmonary hypoplasia, often low birth weight (below 3SD), macrocephaly, dysmorphic features (micronathism, prominent nasal bridge with bent end, rear nostril atresia, multiple anomalies of ears, telecanthus, prominent eyes, cleft palate, short neck, camptodactyly) [1-3]. In type II PSS arthrogryposis and hypoplasia of the lungs are usually accompanied by a microcephaly, microphthalmia and cataract. Frequently observed malformations of the CNS are particularly localised within the cortex and cerebellum, as well as the number of cells in the front corners of the core are reduced and additionally, features of peripheral nemaline myopathy are frequently detected [4-7].

Two different genes have been identified so far, that may be responsible for various forms of syndrome: DOC 7 located in 4p16.2 and RAPSN located in 11p11; perhaps a third possibly candidate gene is located in 9q34. Family history of disease is usually corresponding to autosomal recessive lineage, however, sporadic cases are frequent. Lower than in overall autosomal recessive rate family row recursion rate suggests, that 15-20% of the cases are heterogeneous of both forms of the syndrome [8-10].

ERCC6-CSB gene, located in 10q11, responsible for aberrations repair, linked with Cockayne type II syndrome, has been associated with PSS II last time [4, 5].

Many possible features of the syndrome (fetal edema, cystic hygroma, CNS anomalies) can be observed prenatally, but differentiation and definitive diagnosis is usually possible after the birth [11-13].

The most important element, differentiating PSS I from the other akinesia syndromes is the presence and characteristics of fetal anomalies of the CNS [14, 15].

PSS syndrome is usually lethal during pregnancy, rarely postnatal.

Here we present the prenatal assessment of the fetus with the PSS I and postnatal findings: dysmorphology, clinical characteristics and ultrasound features of the child with the PSS syndrome.

Case report
23 year old primipara, not related with father of the child, referred to the clinic at 14th of the week of gestation. Three generational pedigree analysis, apart from simple trisomy 21 in the first degree cousin from the mother’s, family has not shown the burden of genetic or developmental defects.

In the first ultrasound examination, performed at 14th week of gestation, we found increase of nuchal translucency up to 4 mm, hyperechogenic bowels, fetal hypokinesia, flexion of hands. Joints of upper and lower limbs were unaffected.
Fig. 1. 14th week of gestation – hyperechogenic bowels

Other ultrasound markers of genetic deseases, including the ductus venosus flow and tricuspid valve flow were normal. Routine biochemical triple test showed no increased risk for trisomy 21, 13 and 18. During the next sonographic examination in the 15th week of gestation, further anomalies were exposed particular abnormal feet, in the form of "foot heel". Further invasive diagnostics was performed, followed by karyotyping in order to exclude trisomy 18, and FISH for a relatively frequent Prader-Willi Syndrome, which also includes hypokinesia of the fetus. Fetal karyotype was normal 46, XX and deletion 15q11.2q13 (PWS) was excluded.

Gravida decided to continue the pregnancy, which allowed further observation of fetal evolution. In the next ultrasound examination at 19.5th week of gestation, hypokinesia was noticed, also flexion of large joints, but without their deformation, flexion of hands, with correct number overlapping fingers. We detect both feet heel also show fingers and feet with unilateral heel foot and recession fingers 2 and 3 in that feet.

Level of bowel hyperechogenicity was diminished. Structure of the brain as well as chest size and lungs echogenicity was normal; similarly a normal heart view and intracardiac and umbilical cord flow, normal kidneys and amount of amniotic fluid were noted. Next five periodic sonographic examinations, showed additionally increasing retrognathia.
Fetal anomalies suggested at least a dozen of different syndromes with arthrogryposis. Defects in the hands and feet as well as retrognatia, suggested Pena-Shokeir syndrome, however, the final diagnosis could not be based on equivocal prenatal screening. During the pregnancy, neither the intraterinal growth nor infection, nor abnormal vascular flows nor anomalies of the placenta were observed. The course of pregnancy was normal and ended with a labor in the 41\textsuperscript{th} week of pregnancy.

Child's birth weight was 3200 g female, length 54 cm, head circumference 34 cm, Apgar 1, 3, 7. Postnatal evaluation revealed distinct facial deformation: microphthalmia, eminent nasal bridge with curved end, long labial groove with a thin red, large low-mounted ears, high palate, micro- and retrognatia resulting in inability of feeding.

Further deformations were: short neck and broad chest. Upper limbs were placed in flexible elbows and wrists flexed fingers closed. Hips abducted, knees with contractions, bilateral heel-feet, and the right site clawfoot with recession of the fingers 2 and 3.

Postnatal ultrasonographic examination of head, heart and abdomen were normal. In contrary to prenatal the increase of head circumference in next 4 months was minimal (0.5 cm/month). From the birth breathing disorders was found, continuously worsening, despite treatment followed by pulmonary hypertension which was the cause of death at 4 months of age. Suspected pulmonary dysplasia was confirmed by scintigraphic examination.

Discussion

Arthrogryposis is a condition, characterized by congenital contractures in one or more joints. Term is widely used for description of clinical symptoms, but not as a specific diagnosis. Arthrogryposis comprises heterogeneous group of disorders involving about 300 genetically well-defined syndromes, as well as many cases of non-specific defects. It may be a result of variety of teratogenic factors: prostaglandins, ergotamine, penicillamine, enzyme inhibitors and muscle tension lowering agents, hyperthermia, infection and acidosis. There is an increased risk of arthrogryposis after early amniocentesis and CVS\cite{16}. Many authors have linked all arthrogryposis in one group, which frequently result in erroneous conclusions\cite{16}. PSS is not a simple sequence of fetal akinesia, but the composed disturbances of this akinesia coexists with other symptoms.

Abnormalities observed in the fetus suggested the possible diagnosis of at least a dozen different sets of syndromes running with arthrogryposis. Defects in the
hands and feet and retrognathia narrowed the list of possible diagnoses, suggesting the PSS I syndrome, however, it could not be an unequivocal in prenatal diagnosis.

Pulmonary dysplasia is not observed in majority other of the syndromes with arthrogryposis, and thus it would focus prenatal differential diagnosis. The abnormal lung perfusion is typical for PSS I, distinguishing it from PSS II. Usually direct cause of death, similarly to the case described by us, is respiratory insufficiency, secondary to pulmonary perfusion disturbances. Ultrasonographic diagnosis of pulmonary dysplasia is difficult, therefore testing of MRI could be necessary [17]. Akinesis of the fetus is the result of a paralysis of muscles, including diaphragm. Abnormal amount of amniotic fluid often prevents the growth of the lungs and causes their hypoplasia [18-20].

The discovery of the fetus akinesia requires a long time usg examination, in order to verify the movable joints [11]. The diagnosis of phenotype of arthrogryposis can be put already in the first trimester of pregnancy, as occurred in this particular case.

The PSS I phenotype consist have juxta-articular contractures, muscle atrophy, camptodactyly, facial anomalies, and postnatal respiratory disorders as found in children described. Less commonly are detected: cleft palate and heart defects, which are not observed in our child. Possible other symptoms of the PSS II are also: microcephaly with extensive structural abnormalities of CNS, microphthalmia and cataracts, which are not found, both before and after birth [17, 21, 22, 23].

Absence of previously cases in family suggested autosomal recessive inheritance, as it usually takes place in the PSS. The patient was recommended of the next – planned pregnancy – in a center providing prenatal diagnosis. The patient was recommended for scientific purposes only [10].

Conclusion

This case demonstrate, that even the prenatal screening in I trimester of pregnancy may suggest a rare monogenic disease, but a definitive diagnosis can usually be carried out after the birth, if at all possible.

References

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