

Progressive development of sonographic features in prenatal diagnosis of Apert syndrome – case report and literature review

Zmieniające się cechy sonograficzne zespołu Aperta w diagnostyce prenatalnej – opis przypadku i przegląd literatury

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Abstract

Apert syndrome is characterized by craniosynostosis, midfacial malformations and symmetrical syndactyly of the hands and feet.

We report a case of prenatal sonographic diagnosis of Apert syndrome. Mild ventriculomegaly with normal head shape observed at 22 weeks gestation, followed by colpocephaly at 25 weeks gestation and bilateral syndactyly and subsequent craniosynostosis at 28 weeks, led to the prenatal diagnosis of Apert syndrome. The diagnosis was confirmed by physical examination and molecular study after birth.

Additionally, the authors present the review of literature on prenatal sonographic diagnosis of Apert syndrome.

Key words: **Apert syndrome / prenatal diagnosis / ultrasonography / echocardiography / ventriculomegaly / craniosynostosis / symmetrical syndactyly / FGFR2 gene mutation /**

Streszczenie

Zespół Aperta charakteryzuje się występowaniem kraniosynostozy, wad twarzoczaszki oraz symetrycznego palczostu u rąk i stóp. W pracy przedstawiono przypadek prenatalnego rozpoznania zespołu Aperta w badaniach ultrasonograficznych. Objawy ultrasonograficzne takie jak: powiększenie komór bocznych mózgu w 22 tygodniu ciąży przy prawidłowym kształcie głowy, następnie kolpocefalia w 25 tygodniu ciąży oraz obustronny palczost i kraniosynostoza w 28 tygodniu ciąży, doprowadziły do prenatalnego rozpoznania zespołu Aperta. Rozpoznanie zostało ostatecznie potwierdzone w badaniu molekularnym wykonanym po urodzeniu się dziecka.

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Słowa kluczowe: **zespół Aperta / diagnostyka prenatalna / ultrasonografia / echokardiografia / wentrikulomegalia / kraniosynostoza / symetryczna syndaktylia / mutacja genu FGFR2 /**

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Introduction

Apert syndrome (AS) is characterized by craniosynostosis, midfacial malformations and symmetrical syndactyly of hands and feet [1]. The prevalence of Apert syndrome in newborns is estimated as about 1 in 65,000 (15-16 cases per million) [2]. This syndrome is one of the most serious syndromes among the craniosynostoses and accounts for 4.5% of all cases.

Craniosynostoses, including Apert syndrome, are usually caused by mutations in *FGFR2* gene. Apert syndrome may be either caused by a new mutation (about 98% of cases), or inherited as an autosomal dominant trait, characterized by full penetrance and stable expression. Among several mutations discovered in *FGFR2* gene, the 755C-G, resulting in Ser252Trp, occurs most frequently (66% of all cases) [3]. The genotype-phenotype correlation has been described by Slaney (Slaney et al. 1996).

We report a case of Apert syndrome, diagnosed prenatally by sonography and confirmed postnatally by physical examination and molecular analysis of *FGFR2* gene.

Case report

31-year-old primipara and 33-year-old man, both healthy and non-consanguineous with unremarkable family history, were referred to Clinical Genetics Department for prenatal counseling. Ultrasound screenings were performed at 6, 12 (1.5mm NT) and 17 weeks gestation and the results were considered as normal, including serum level of maternal AFP. Mild ventriculomegaly was detected at 22 weeks gestation and the pregnant woman was referred for genetic sonography and fetal echocardiography. Symmetrical dilatation of the posterior horns was detected and colpocephaly was diagnosed, suggesting corpus callosum agenesis at 25 weeks gestation. The shape of the fetal head at that time was unremarkable. (Figure 1A).



Figure 1.

- A. Fetal head at 25hbd: normal fetal head shape, mild posterior horns dilatation suggesting partial or complete agenesis of corpus callosum
 B. Fetal head at 28hbd: abnormal fetal head shape, posterior horns up to 12mm.
 C. Biocular diameter at 28,1 weeks gestation suggesting mild hypertelorism, no midface hypoplasia was observed
 D. Biocular diameter at 34hbd suggesting hypertelorism (corresponding 37.4 wks), midface hypoplasia is present.

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However, symmetrical syndactyly of both hands and abnormal fetal feet were observed. All long bones (femur, tibia, fibula, humerus, ulna and radius) were within normal range. All other parameters were also normal (BPD, HC, cerebellum diameter, ocular diameter). Detailed fetal echocardiography revealed normal heart anatomy. The parents were informed about two major problems: the presence of skeletal anomaly with syndactyly and partial agenesis of the corpus callosum but they refused the opportunity of prenatal genetic studies and decided to continue with the pregnancy. At 28 weeks gestation an abnormal shape of the fetal skull was evident. (Figure 1B).

Ventriculomegaly at the level of the atrium was 12mm (10mm is considered the upper limit of normal). Progression of mild orbital hypertelorism was observed between 25 and 29 weeks gestation. (Figure 1c and 1d). Moreover, progression on midface hypoplasia became evident at that time as well. (Figure 1D).

As far as the changes in the fetal profile were concerned (depressed nasal bridge and nasal bone of 6 and 8mm respectively), not much was observed during the period between 25 and 28 weeks gestation. (Figure 2A and 2B).

The surface 3D ultrasonography clearly rendered the fetal face with prominent forehead, hands syndactyly and shape of the fetal feet (Figure 2C). 3D skeletal ultrasonography presented widely open metopic suture. (Figure 2D).



Figure 2.

- A. Fetal profile in 2D scan at 25th week of gestation, nasal bone 6mm.
 B. Fetal profile in 3D surface at 25th week of gestation, depressed nasal bridge.
 C. Syndactyly of the fetal hand in 3D surface US.
 D. Widely open metopic suture in 3D maximum mode (skeletal mode), prominent fetal forehead.

The child was born at term by elective cesarean section, with birth weight 2550g, OFC 34cm, Apgar scores 8 points at the first minute.

The newborn baby was referred to Genetics Department for genetic counseling. Typical facial appearance of Apert syndrome was observed, including broad forehead with horizontal supraorbital grooves, proptosis, hypertelorism, down-slanting palpebral fissures as well as midfacial hypoplasia, depressed nasal bridge with short, broad nose. Additionally, symmetrical, complex syndactyly of both hands was observed comprising 2nd, 3rd, 4th and 5th fingers. The thumbs were not involved in the fusion. Feet syndactyly affected all toes.

The chromosomal analysis performed according to standard procedures, revealed a normal, female karyotype. Molecular analysis of the *FGFR2* showed a mutation in exon 7 (S252W).

Discussion

Apert syndrome (AS) is a complex multisystem disorder. The clinical diagnosis is made on the bases of craniofacial dysmorphism, accompanied by hands and feet syndactyly [1]. However, the following other defects could also be present: cleft palate, bifid uvula and high arched palate (in 43% of cases), congenital heart defects and genitourinary anomalies (in about 10% of patients), and, in some cases, choanal stenosis and tracheal abnormalities, as well as central nervous system anomalies (including defect of corpus callosum and ventriculomegaly) [1, 4-6].

Craniosynostoses are inherited as autosomal dominant traits and result from mutations in either *FGFR1* or *FGFR2* (fibroblast growth factor receptors 1 and 2 genes, respectively). *FGFR1* maps to chromosome 8 (8p11.22-p12) while *FGFR2* maps to chromosome 10 (10q25-10q26).

Among variety of mutations observed in both, *FGFR1* or *FGFR2*, two of them are the most common in Apert syndrome patients: Ser252Trp (approximately two-third of the cases) and Pro253Arg (about one-third of cases) in *FGFR2* gene. S252W is associated with cleft palate and tends to be associated with more severe craniofacial phenotype when compared to Pro253Arg, which is more frequently found in cases with severe syndactyly. These correlations probably reflect a different impact of these mutations on the development during organogenesis [1, 3, 4].

The first report of sonographic prenatal diagnosis of Apert syndrome was published in 1986 by Kim et al. and since that time several other reports have been published, most of them based on 2nd and 3rd trimester studies [7]. Nevertheless, prenatal diagnosis of Apert syndrome remains to be challenging (Table I).

Craniosynostoses are usually sporadic, thus no family history may increase the concern of fetal deformities. Moreover, deformity of the skull may become visible relatively late in the course of pregnancy, just like in our case [8-10]. Also, only one fused suture (a feature characteristic for Apert syndrome) may not be evident until the second or the third trimester of pregnancy [8].

Table I. Prenatal diagnosis of Apert syndrome (AS) – review of literature [1-22, 24, 25].

Trimester and week of gestation	First author of report, publication year	Sonography result	ECHO result	TOP ¹
1 st trimester	Filkins 1997	NT not increased	-	-
	Chenoweth 1994	NT increased	-	-
	Souka 2001	NT increased	-	-
	Aleem 2005	NT increased	-	-
2 nd trimester				
16hbd ²	Narayan 1991	Mild ventriculomegaly,	-	-
16hbd	Quintero 2006	Partial agenesis corpus callosum	-	-
17hbd	Skidmore 2003	Cloverleaf skull, broad first toe	CoA	+
19hbd	Pooh 1999	Frontal bossing, changing over time	-	-
20hbd	Ferreira 1999	Depression of midface, syndactyly	-	+
20hbd	Lyu 2000	(Mother with AS), Fused digits	-	+
21hbd	Skidmore 2003	Cloverleaf skull, ventriculomegaly	HLHS	+
22hbd	Respondek 2009	Ventriculomegaly	-	-
24hbd	Boog 1999	Cloverleaf skull, mitten hand, syndactyly	-	+
25hbd	Benacerraf 2000	(Mother with AS),	-	+
25hbd	Chang 1998	Metopic suture (7 fetuses)	-	-
22-27hbd	Faro 2006	Ventriculomegaly + polyhydramnios	-	+
28hbd	Kaufmann 1997	Cleft palate, diaphragmatic hernia	-	-
29hbd	Quintero 2006		PS	-
3 rd trimester				
32hbd	Kim 1986	Craniosynostosis, Syndactyly Polyhydramnios	-	-
33hbd	Filkins 1997	Craniosynostosis, Syndactyly	-	-
31hbd	Mahieu-Caputo 2001		-	+

¹ TOP - termination of pregnancy

² hbd - week of gestation

The differential diagnosis of craniosynostoses appears to be difficult even postnatally, because of the complex pattern of deformities, as well as clinical outcome. Regardless, precise diagnosis is of vital importance, mainly because of very different clinical prognoses and genetic counseling of these syndromes: prognoses both for Pfeiffer and Crouzon are much more favorable when compared with Apert syndrome [6, 7, 11, 12].

In the present work we report our experience in prenatal sonographic diagnosis and monitoring of development of fetus with AS. Ventriculomegaly was observed at 22 weeks gestation, while abnormalities of fetal head became evident six weeks later.

In differential diagnosis a variety of syndromes, characterized by an unusual shape of the head, were taken into account, such as trisomy 18 ('strawberry-shaped' head), open neural tube defect ('lemon-shaped' head), Cornelia de Lange syndrome as well as trisomy 21 (brachycephalia), Wolf-Hirschhorn syndrome (skull asymmetry), thanatophoric dysplasia ('cloverleaf-shape' skull; however this syndrome is relatively easy to diagnose because of severe limb shortening) [7, 12-15].

Thus, we decided for careful evaluation of fetal hands and feet. The identification of symmetrical syndactyly allowed us to diagnose (with high probability) AS in the fetus. Despite the fact that heart defects are not an obligatory feature of AS, a variety of heart defects (such as hypoplastic left heart syndrome, aortal coarctation, pulmonary stenosis, dextrocardia) were observed [13-17] which may suggest that fetal echocardiography should also be taken into consideration in prenatal diagnosis of AS. In our case both heart anatomy and the functional heart studies appeared to be normal, suggesting a good short-term prognosis for fetal and neonatal survival.

In our case the gradual progression of the calvarian deformity was observed. To the best of our knowledge, similar observation has been reported only in one case [8]. In series of 5 cases of AS reported by Skidmore et al. four cases presented with normal NT, similarly to our case [18]. However, taking into consideration a few reports of an increased NT in fetuses, finally diagnosed with AS, it seems reasonable to include sonographic examination of fetal hands and feet into diagnostics algorithm in cases of NT enlargement [12, 19]. It seems also valuable, based on our experience, to look carefully at fetal hands and feet in case of 'mild ventriculomegaly'.

Conclusion

Summarizing, we would like to stress that in the prenatal life craniosynostoses might be a abnormality developing over time and may occur in fetuses with normal nuchal translucency, which is analyzed in the first trimester. Presence of mild ventriculomegaly, even accompanied by a normal shape of the skull, may be the first clue leading to detailed examination of fetal hands and feet, despite the fact that this analysis is difficult, time consuming and often limited due to fetal position [6, 20].

Thus, having the possibility of AS prenatal diagnosis at 22 weeks gestation (2nd trimester), both the 3rd trimester and postnatal AS diagnosis should be considered as "late diagnosis". Moreover, it should be also kept in mind that although some abnormalities observed in AS (e.g. diaphragmatic hernia) or heart defects are easily detectable in the second trimester sonography, it may not be the case in other defects, such as cleft palate for example [5, 21, 23].

Parents of our proband rejected the possibility of prenatal genetic diagnosis and option of possible termination of the pregnancy. They decided to continue their pregnancy regardless of the final outcome and postnatal prognosis. This is in the contrary to the majority of case reports from other European countries and may reflect the different cultural approach in Poland.

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