Prenatal diagnosis of Apert syndrome without craniosynostosis - case report

Diagnóstico pré-natal do síndrome de Apert sem craniossinostose – caso clínico

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ABSTRACT

Apert syndrome is a rare genetic disorder characterized by craniosynostosis, midfacial hypoplasia and severe symmetrical syndactyly (cutaneous and bony fusion) of the hands and feet. Despite being inherited in an autosomal dominant manner, most cases are sporadic, the result of a de novo mutation. The prevalence of this condition at birth is estimated as 15.5 per million (1:65 000). We report the prenatal diagnosis of Apert syndrome associated with increased nuchal translucency and with no ultrasonographic findings of craniosynostosis. An obstetrical ultrasound performed at 20 weeks of gestation showed ocular hypertelorism and bilateral syndactyly of the hands.

Examination of the remaining fetal structures revealed no further fetal anomalies, in particular no premature fusion of the cranial sutures. Genetic evaluation revealed a S252W mutation in fibroblast growth factor receptor 2, consistent with Apert syndrome.

Fetal autopsy performed at 24 weeks showed a male fetus with symmetric syndactyly of both hands and feet; the skull showed a mild frontal bossing, ocular hypertelorism, depressed nasal bridge and confirmed the absence of premature fusion of the cranial sutures. Prenatal diagnosis of Apert syndrome in sporadic cases can be difficult because the characteristic changes in cranial and orbital shape related to craniosynostosis may not be present until the third-trimester. Syndactyly and abnormalities of the skull shape should lead to the suspicion of Apert syndrome even in the absence of craniosynostosis. This case also suggests that increased nuchal translucency may be associated with this syndrome.

Keywords: Acrocephalosyndactylia; prenatal diagnosis

INTRODUCTION

Described by Wheaton in 1894 and later in 1906 by the French physician Apert, acrocephalosyndactyly type I or

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Apert syndrome is a rare genetic disorder characterized by craniosynostosis (i.e. premature fusion of one or more cranial sutures), craniofacial anomalies, and severe symmetrical syndactyly (cutaneous and bony fusion) of the hands and feet. Despite being inherited in an autosomal dominant manner, most cases are sporadic, the result of a de novo mutation. The birth prevalence of this condition is estimated as 15.5 per million (1:65 000), the male to female ratio is 1:1.
Prenatal detection of the syndrome became possible with the routine prenatal ultrasound screening of fetal anomalies. Once suspected, the diagnosis can be confirmed by DNA analysis of mutations in the fibroblast growth factor receptor 2 gene (FGFR2)\(^3\). Prenatal diagnosis of Apert syndrome is established precociously when there is a suggestive familiar history but rather late in the majority of cases because facial and skull abnormalities due to craniosynostosis are often third-trimester ultrasonographic findings.

CASE REPORT

A 34-year-old woman in her first pregnancy, with a 35-year-old partner, was referred to our unit for prenatal routine care. In the first trimester scan, performed at 12 weeks, the fetal crown–rump length and nuchal translucency were 59 mm and 3.7 mm, respectively and nasal bone was present. The estimated risk for Down syndrome, after the prenatal biochemical screening (measurement of free β subunit of chorionic gonadotrophin (FβhCG) and pregnancy-associated plasma protein A (PAPP-A)), was 1/62. An amniocentesis was performed and cytogenetic analysis demonstrated a normal male karyotype. A fetal ultrasound performed at 20 weeks of gestation showed ocular hypertelorism (fig. 1) and syndactyly of the hands (fig. 2, 3). Examination of remaining fetal structures, especially intracranial, revealed no other fetal anomalies. Although there were no signs of craniosynostosis the couple were informed that the findings were suggestive of Apert syndrome. Molecular analysis of the FGFR2 gene, performed on DNA extracted from the amniocytes, showed a S252W mutation consistent with Apert syndrome. After being informed of the prognosis, including the probability of low intellectual function and the likely need for multiple cranial and limb surgeries, they...
elected to terminate the pregnancy. This was performed at 24 weeks of gestation.

The fetal autopsy showed a male fetus, with symmetric syndactyly of both hands (fig. 4, 5) and feet (fig. 6). The skull showed a mild frontal bossing, ocular hypertelorism, depressed nasal bridge, the exam didn’t show fusion of cranial sutures (fig. 7).

DISCUSSION

Prenatal diagnosis of Apert syndrome in sporadic cases is challenging because the characteristic sonographic features of craniosynostosis may not be present during the second-trimester, changes in cranial and orbital shape are often not marked until late in the second-trimester and become more obvious during the third. The other major features are bilateral symmetric syndactyly and midfacial hypoplasia. In our case, the ultrasound performed at 20 weeks has not shown any signs of craniosynostosis and the fetal autopsy, at 24 weeks, complemented by radiologic examination postmortem, confirmed that there was no premature fusion of cranial sutures.

Apert syndrome accounts for 4.5% of all patients with craniosynostotic syndromes. All newborns with Apert syndrome have coronal synostosis and the midline of the calvaria has a gaping defect, extending from the glabellar area to the posterior fontanelle via the metopic suture area, anterior fontanelle, and sagittal suture area. The gestational age when craniosynostosis appears is unclear. Apert syndrome was reported at 20 weeks of gestation with skull deformity and no premature fusion of cranial sutures confirmed on fetopathological examination and our case confirm that craniosynostosis and syndactyly may develop asynchronously up to 24 weeks.

Syndactyly is an invariable characteristic present in fetus affected with Apert syndrome. The characteristic “mitten-like” hand can be detected as early as in the first trimester scan.

In this case we have been able to identify another important characteristic of this syndrome, midfacial hypopla-
sia, inferring it by the presence of hypertelorism.

This is the third case of Apert syndrome reported associated with increased NT, the accumulation of nuchal fluid may be caused by the altered composition of the extracellular matrix, as a consequence of altered conformation of the FGFR2 protein.\(^8\)\(^9\)

Although there were no cerebral anomalies detected, central nervous system anomalies have been frequently reported: non-progressive ventriculomegaly, hydrocephalus, partial absence of septum pellucidum and partial or complete agenesis of the corpus callosum.\(^10\)

Several other syndromes that include craniosynostosis can lead to a similar appearance of the face and head, but do not include the severe hand and foot problems of Apert syndrome. These similar syndromes include: Carpenter syndrome (kleeblattschadel, cloverleaf skull deformity), Crouzon disease (craniofacial dysostosis), Pfeiffer syndrome and Saethre-Chotzen syndrome.\(^11\)

When Apert syndrome was suspected the diagnosis was confirmed by DNA analysis for the S252W and P253R mutations in the FGFR2 gene, which together account for 98% of this type of craniosynostosis.\(^12\) The other mutations involved the insertion of Alu-element mutations in or near exon 9 of FGFR2. DNA extracted from the amniocytes showed a S252W mutation. This is the most common mutation, occurring in 67% of patients and is associated with more severe craniofacial anomalies.\(^13\) The majority of cases are due to de novo mutations which are increased exponentially with paternal age. In this case, the father was 35 years-old and in a population-based study almost half of fathers were older than 35 years when the child was born.\(^14\)

It's important to give accurate information about the prognosis of the affected individuals. An important question that should be considered in prenatal counseling is the possibility of mental retardation. Although patients of normal intelligence have been reported approximately one half of the affected individuals are mentally retarded.\(^15\)\(^16\) The majority will require multiple surgeries, like craniofacial disjunction or shunting to reduce intracranial pressure, and to correct syndactyly.\(^9\)\(^11\) Despite multiple reconstructive procedures will be necessary, they will play an important role in enhancing the psychosocial condition of the patient.\(^17\)

Considering the vast majority of the cases are sporadic (>98%), the parents should be informed that the risk of recurrence is minimal but autosomal dominant inheritance and germinal mosaicism have been reported and should also be taken into consideration in genetic counseling.\(^13\)

Apert syndrome is being diagnosed at early gestational ages using ultrasound and DNA analysis. This case demonstrates the feasibility of the prenatal diagnosis of Apert syndrome and demonstrates that syndactyly and abnormalities of skull shape should lead to the suspicion of Apert syndrome even in the absence of craniosynostosis.

**REFERENCES**