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Apert Syndrome: The Importance of Prenatal Diagnosis and Maternal-Fetal Medicine Management

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Abstract

Apert syndrome is a rare congenital disorder whose diagnosis remains challenging because of its variable phenotypic expression. Craniosynostosis and symmetric syndactyly are two of the most commonly seen characteristics of this syndrome. We present the case of a 44-year-old multigravida (G5A3P1) who received regular prenatal visits and whose first-trimester ultrasound showed only one umbilical artery. Noninvasive prenatal testing (NIPT) indicated a low risk of common aneuploidies. During subsequent follow-up ultrasound studies, an abnormal cranial morphology was noted, and bilateral syndactyly was evident. After performing amniocentesis at 28 weeks of gestation, whole exome sequencing confirmed a pathogenic variant in the fibroblast growth factor receptor 2 (*FGFR2*) gene, thus establishing the diagnosis of Apert syndrome. At 32.5 weeks of gestation, the patient presented with reduced fetal movements, and a subsequent ultrasonographic assessment confirmed intrauterine fetal demise. At delivery, the stillborn fetus exhibited phenotypic findings consistent with Apert syndrome. An evaluation of the umbilical cord revealed a true knot. The present case highlights the importance of detailed fetal anatomical assessment by maternal-fetal medicine specialists, enabling appropriate parental counseling, as well as facilitating the development of a multidisciplinary perinatal plan.

Categories: Obstetrics/Gynecology, Radiology, Genetics
Keywords: apert syndrome, craniosynostosis, fetal ultrasonography, fgfr2, maternal-fetal medicine

Introduction

Genetic disorders cover a wide range of conditions, and they can involve whole chromosomes or single genes. In either case, the impact on the family can be substantial, which is exactly why early, accurate identification is important. Early identification enables genetic counseling, allows clinicians to design an individualized diagnostic and therapeutic plan, and provides families with guidance on prognosis, reproductive options, and available interventions.

Prenatal diagnosis plays a central role here. Obstetric ultrasound, especially the detailed fetal structural scan, is one of the main tools for detecting congenital abnormalities and genetic syndromes, and it often provides the first indication of a specific condition, which can then be confirmed with whole exome sequencing when appropriate [1,2].

This report focuses on Apert syndrome, also known as acrocephalosyndactyly type I, a rare genetic disorder defined mainly by syndromic craniosynostosis, craniofacial abnormalities, and complex syndactyly of the hands and feet [3,4]. Hand involvement is variable, ranging from less severe to severe complex syndactyly. It follows an autosomal dominant inheritance pattern, though in practice most cases arise from de novo variants rather than being inherited [3].

French pediatrician Eugène Apert first described the condition in 1906, based on nine patients who shared a similar set of clinical findings [5].

Apert syndrome is closely associated with specific pathogenic variants in fibroblast growth factor receptor 2 (*FGFR2*), a gene located on the long arm of chromosome 10 at 10q26 [3,6]. *FGFR2* encodes a transmembrane receptor that belongs to the fibroblast growth factor (FGF) receptor family, and it plays a key role in embryonic development (cell proliferation, differentiation, and migration) as well as in bone formation and remodeling. Once fibroblast growth factor (FGF) binds and activates *FGFR2*, this triggers intracellular signaling pathways that regulate how tissues develop and differentiate [7,8].

In Apert syndrome specifically, gain-of-function variants in *FGFR2*, most commonly p.Ser252Trp and

p.Pro253Arg, cause abnormal receptor activation and disrupt that signaling in bone development [6-8]. The result is premature differentiation and maturation of the cranial sutures, which is what leads to craniosynostosis while also contributing to abnormal limb development and the syndactyly that is characteristic of this disorder [3,6,8]. In a study of Mexican patients with Apert syndrome, four of six carried the p.Ser252Trp variant, and the other two had p.Pro253Arg, supporting how relevant these two recurrent *FGFR2* variants are in the Mexican population [9]. It illustrates how a single molecular change in *FGFR2* can translate into such a complex congenital phenotype.

Apert syndrome is rare, occurring in roughly one in 65,000-200,000 live births, and it affects both sexes equally [10]. A link between de novo *FGFR2* variants and advanced paternal age has also been documented [10].

From a prenatal standpoint, Apert syndrome is usually first suspected on ultrasound when craniofacial abnormalities, particularly craniosynostosis and abnormal skull shape, are present together with limb findings such as syndactyly. That said, some of these findings can be subtle or not fully apparent yet at the time of the scan, so ultrasound suspicion should be confirmed with molecular genetic testing, such as targeted *FGFR2* analysis or exome sequencing, whenever it is warranted [1-3].

We report a pregnant woman under routine prenatal care whose structural ultrasound identified findings suggestive of Apert syndrome: craniosynostosis together with fetal syndactyly. Whole exome sequencing of the amniotic fluid sample identified a heterozygous *FGFR2* variant, NM_000141.5:c.755C>G (p.Ser252Trp), classified as pathogenic and associated with autosomal dominant Apert syndrome [2,3].

Case Presentation

A 44-year-old multigravida (G5A3P1) received routine prenatal care early in pregnancy. Her partner, aged 48 years, was apparently healthy. Her obstetric history included three previous pregnancy losses, the cause of which was not investigated, and one previous delivery of a healthy daughter, now seven years old, with no known comorbidities. No family history of craniosynostosis, syndactyly, or other congenital anomalies was recorded in the clinical record.

During the first-trimester structural assessment, the only abnormal finding identified was a single umbilical artery (Figure *1*). As part of routine prenatal care, noninvasive prenatal testing (NIPT) using cell-free fetal DNA was performed, with a low-risk result for common aneuploidies.



FIGURE 1: First-trimester ultrasound axial view at the level of the fetal bladder showing a single umbilical artery (arrow).

During the second-trimester structural assessment, an axial view of the fetal skull showed the non-visualization of the coronal suture and a prominent forehead, findings suggestive of craniosynostosis (Figures *2*, *3*). At 28 weeks of gestation, abnormal cranial morphology with persistent frontal prominence was again observed.

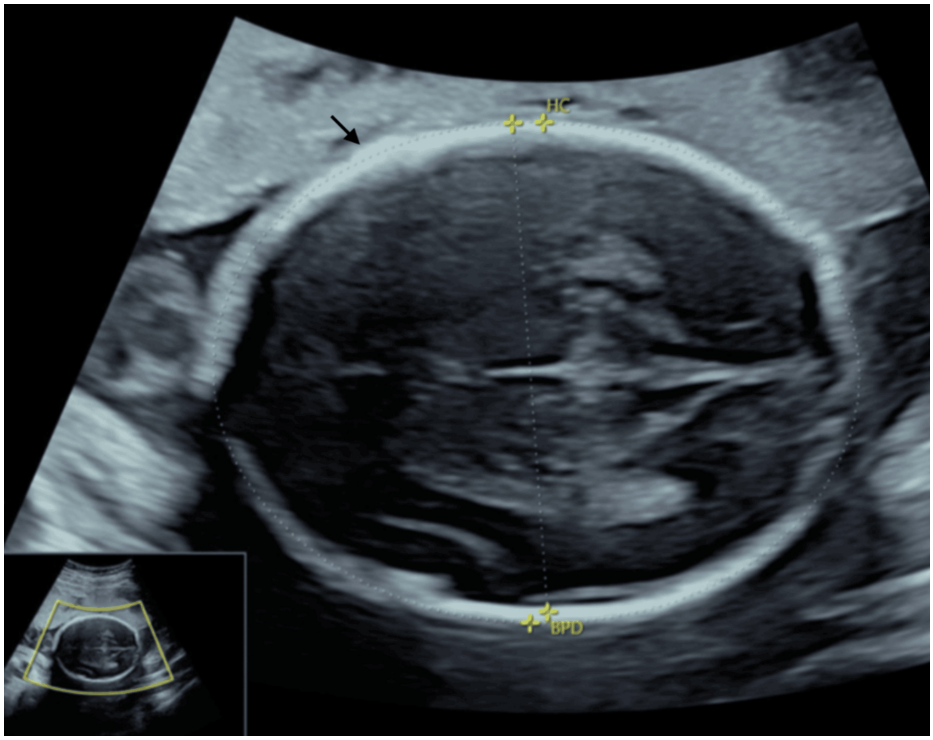


FIGURE 2: Second-trimester ultrasound at 21 weeks of gestation. Axial view of the fetal head at the transthalamic level showing the non-visualization of the coronal suture (arrow).

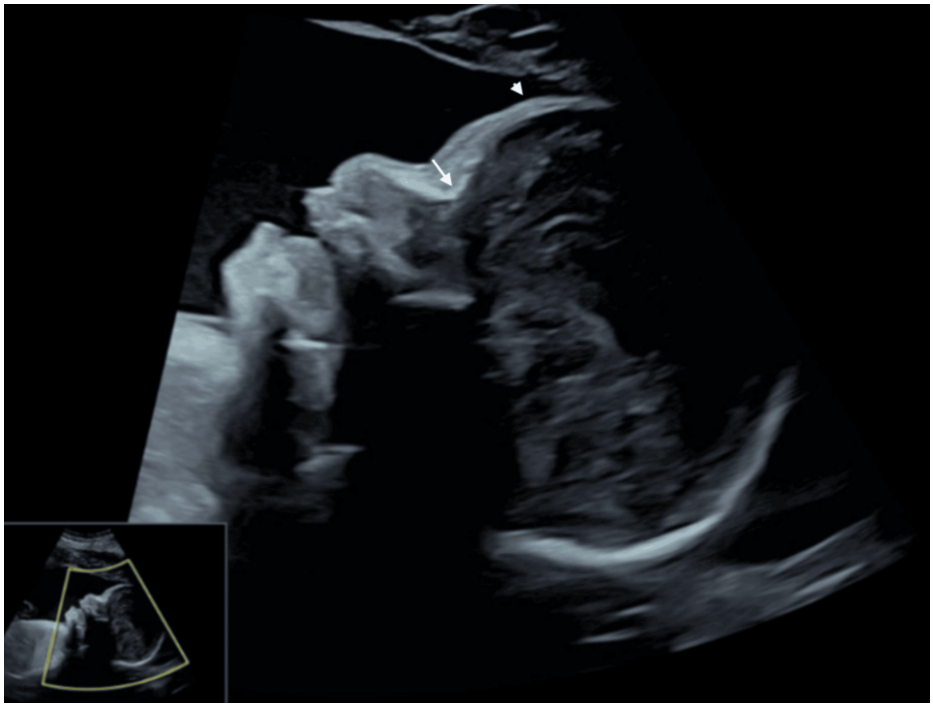


FIGURE 3: Second-trimester ultrasound at 21 weeks of gestation. Midsagittal view showing a prominent frontal bone (arrowhead) and a depressed nasal bridge (arrow).

Subsequently, during the third-trimester assessment at 28 weeks of gestation, abnormalities in cranial morphology were again observed, with persistent frontal prominence. Bilateral hand syndactyly was also

identified, involving the second, third, and fourth digits, with apparent fusion of the phalanges (Figure 4).

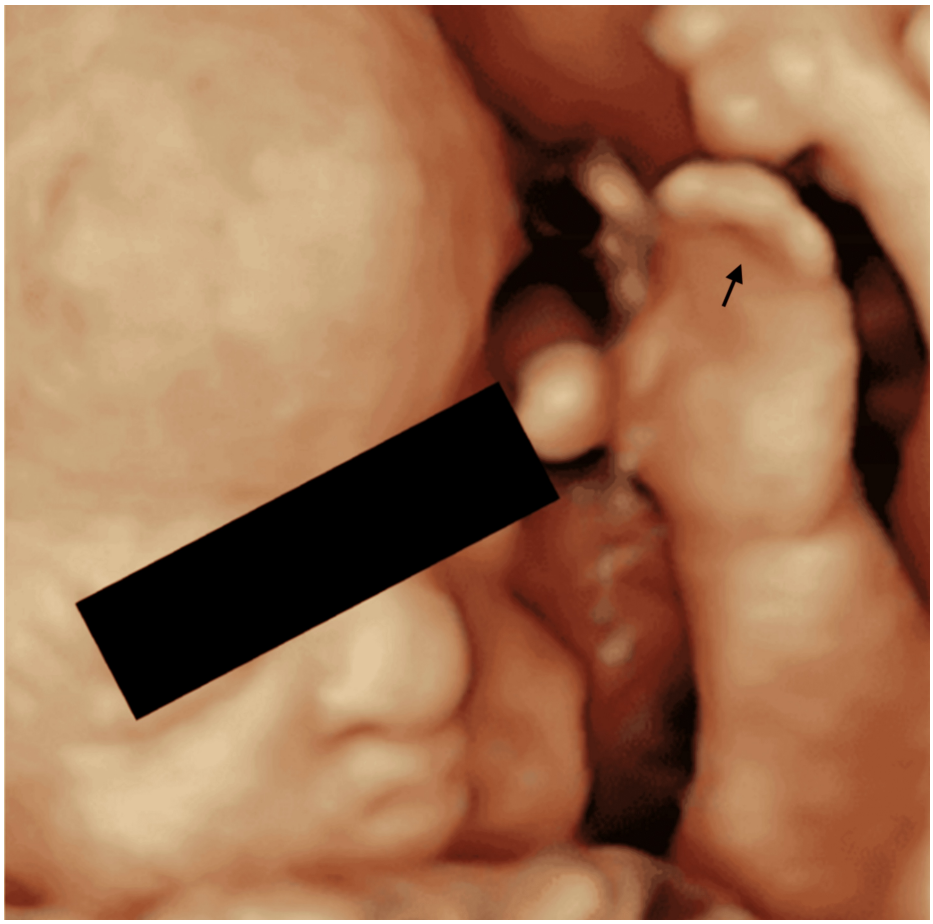


FIGURE 4: Three-dimensional ultrasound at 28 weeks of gestation showing abnormal cranial morphology with frontal prominence and bilateral syndactyly of the hands, with apparent fusion of the second, third, and fourth digits (arrows).

The combination of craniosynostosis and complex bilateral syndactyly raised suspicion of Apert syndrome. Based on these findings, amniocentesis was performed at 28 weeks of gestation for genetic analysis using whole exome sequencing. The sample was shipped from Mexico City to a reference laboratory in Germany. Whole exome sequencing identified a heterozygous pathogenic variant in *FGFR2*, NM_000141.5:c.755C>G (p.Ser252Trp) (chr10:123279677 G>C, hg19), consistent with a diagnosis of Apert syndrome. The result was communicated to the treating physicians at 31 weeks of gestation.

At 32.5 weeks of gestation, the patient subsequently presented for evaluation due to decreased fetal movements. Ultrasound examination revealed the absence of fetal cardiac activity, and the patient was admitted for delivery. A female fetus weighing 1,990 g was delivered. The examination of the umbilical cord revealed a true knot.

Physical examination after delivery confirmed phenotypic findings consistent with Apert syndrome, including characteristic facial features such as midface hypoplasia, hypertelorism, low-set ears, and a depressed nasal bridge. Complex bilateral syndactyly involving the second, third, and fourth digits of both hands was also observed, as well as syndactyly of the feet (Figures 5, 6).



FIGURE 5: Clinical photograph of the stillborn fetus after delivery showing syndactyly of the hands and feet and a true knot in the umbilical cord (arrow). The eyes and genitalia are covered to preserve patient privacy.

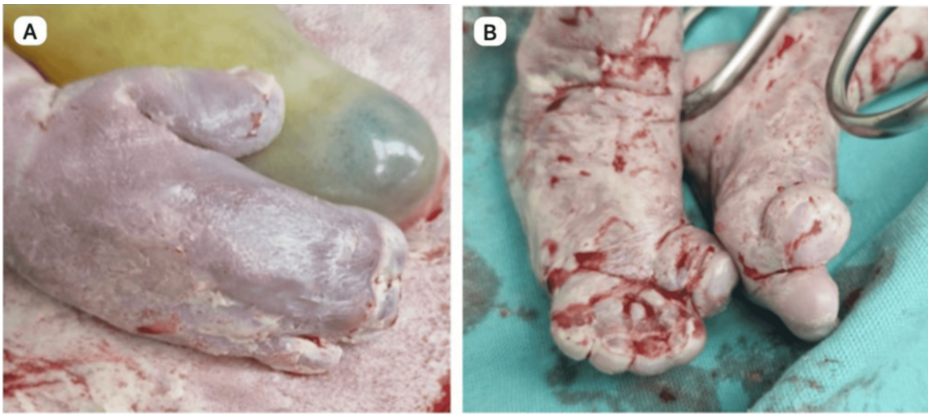


FIGURE 6: (A) Syndactyly of the fingers, showing the fusion of the digits. (B) Syndactyly of the toes, showing the fusion of the digits.

Discussion

Apert syndrome is a rare genetic disorder marked by craniosynostosis, craniofacial abnormalities, and complex syndactyly of the hands and feet, and it is closely tied to pathogenic variants in the *FGFR2* gene. While many of its features can be identified during prenatal evaluation, reaching a diagnosis is not always straightforward. Phenotypic expression varies considerably from case to case, and some findings may not yet be sufficiently developed to be visible in early gestation [1,3,4,6].

A notable finding in this case is the discrepancy between the NIPT result and the structural abnormalities that were identified later in pregnancy. NIPT using cell-free fetal DNA was low risk for the major aneuploidies, which is consistent with the fact that this test is designed mainly to catch common numerical chromosomal abnormalities. However, a low-risk result does not rule out monogenic disorders, structural chromosomal abnormalities, or rare genetic syndromes. Standard NIPT is unable to detect the underlying *FGFR2* variant. This is a useful reminder that prenatal screening should always be read alongside ultrasound findings, not on its own.

The detailed structural ultrasound was key to the diagnosis. In the second trimester, an abnormality in cranial morphology was identified. The coronal suture could not be visualized, and there was frontal bossing, which raised suspicion for craniosynostosis. Later, at 28 weeks, bilateral syndactyly involving the second, third, and fourth fingers was identified, with what looked like the fusion of the phalanges. This pairing of craniosynostosis with complex syndactyly is not incidental; it is exactly the kind of association that should point toward a syndromic form of craniosynostosis and Apert syndrome specifically [1,3]. The limb findings were what allowed the craniofacial abnormalities to be linked to a specific genetic syndrome. Craniosynostosis on its own can be isolated or part of several different syndromes, but when it shows up alongside complex bilateral syndactyly, the suspicion narrows considerably, since that combination is a hallmark of Apert syndrome. Serial ultrasound follow-up, tracking how these findings progressed, is what ultimately justified molecular genetic testing [1,3].

Molecularly, Apert syndrome is mainly linked to pathogenic variants in *FGFR2*, which encodes a fibroblast growth factor receptor with a central role in embryonic development and bone formation. The p.Ser252Trp and p.Pro253Arg variants are the best known and the ones classically tied to this syndrome; both lead to the abnormal activation of *FGFR2* signaling, which in turn disrupts the normal development of the cranial sutures and limbs [6-8].

In this particular case, the clinical and ultrasound findings were confirmed through whole exome sequencing, which identified the pathogenic *FGFR2* variant. That underscores how valuable molecular testing is once a genetic syndrome is suspected prenatally, especially when ultrasound findings do not fit a common aneuploidy. Molecular confirmation, such as whole exome sequencing, does not just establish the etiologic diagnosis; it also allows for more precise genetic counseling, including insight into prognosis and recurrence risk [2,3].

There was a correlation between the prenatal findings, the whole exome sequencing, and the phenotype observed after delivery. The craniosynostosis and bilateral syndactyly picked up before birth matched what was observed at examination after delivery: midface hypoplasia, hypertelorism, low-set ears, a depressed nasal bridge, and complex syndactyly of the hands and feet. This genotype-phenotype correlation confirms the accuracy of the prenatal diagnosis and reinforces the value of a detailed ultrasound examination as the first tool for suspecting craniosynostotic syndromes [1,3,4].

Parental age was also advanced: 44 years for the mother and 48 years for the father. Apert syndrome follows an autosomal dominant inheritance pattern, and most cases arise from de novo variants. There is also a documented link between de novo *FGFR2* variants and advanced paternal age, sometimes called the paternal age effect, a pattern that has been seen in other autosomal dominant disorders caused by de novo variants as well. This is a clinically relevant finding; however, on its own, it cannot establish the diagnosis [3,10].

Finally, the pregnancy outcome requires careful consideration. At 32.5 weeks of gestation, the absence of fetal cardiac activity was documented, and the subsequent evaluation revealed a true knot in the umbilical cord. This finding can compromise fetoplacental circulation and lead to fetal death; however, without further evidence of hypoxic compromise, it is not possible to say with certainty that this was the cause. Likewise, it cannot simply be assumed that Apert syndrome and its structural abnormalities were directly responsible for the outcome. Placental histopathology and autopsy were not performed, so the contribution of the true umbilical cord knot, or of other factors, to fetal demise cannot be determined.

Conclusions

This case highlights the need to integrate prenatal screening, detailed structural ultrasound evaluation, and molecular genetic testing, such as whole exome sequencing. A low-risk result on standard NIPT for common aneuploidies should not be interpreted as a general exclusion of genetic disorders. When fetal structural abnormalities are identified, particularly characteristic combinations such as craniosynostosis and complex syndactyly, a monogenic disorder should be considered, and targeted *FGFR2* testing or exome sequencing should be pursued. In our case, whole exome sequencing established a prenatal diagnosis of Apert syndrome, which was subsequently corroborated by the phenotypic findings at delivery, underscoring the importance of a multidisciplinary approach to the diagnosis and counseling of patients with fetal craniosynostosis syndromes.

As a single case report, these observations should be interpreted within the scope of the available clinical data. The diagnosis was supported by detailed prenatal imaging, whole exome sequencing, and external examination after delivery, which together provide a coherent phenotype-genotype correlation. Further reports and series will help to refine the prenatal presentation and perinatal course of Apert syndrome.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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