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CASE REPORT

Apert syndrome without craniosynostosis

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Abstract

Background Apert syndrome is a rare form of syndromic craniosynostosis, also known as acrocephalosyndactyly, which is a disorder characterized by a unique set of craniofacial, hand, and foot abnormalities. Diagnosis is made through a genetic analysis, where the mutation of FGFR2, Ser252Trp, and Pro253Arg confirms the diagnosis.

Case presentation Although craniosynostosis is the most common characteristic in clinical presentation, we present an atypical case of a one-and-a-half-year-old girl with Apert syndrome confirmed by genetic testing but without craniosynostosis.

Keywords Apert syndrome · Craniosynostosis · Fibroblast growth factor receptors (FGFR)2 · Atypical case

Introduction

Apert syndrome, also known as acrocephalosyndactyly, was first described by the French pediatrician Eugene Apert in 1906 as a condition in which patients have a unique set of craniofacial, hand, and foot abnormalities [1]. The main findings are severe bicoronal craniosynostosis, proptosis, midfacial hypoplasia, and cutaneous and bony syndactyly of the hands and feet [2]. It is a rare disease. Although it is sporadic in the majority of cases, it has an incidence of one in 50,000 births [3] and is markedly associated with paternal age [4]. It shows the mutation of fibroblast growth factor receptors (FGFR)2 (Ser252Trp and Pro253Arg) in almost all cases [2, 5, 6]. Although the diagnosis is only confirmed through genetic analysis, the disease is easily suspected due to its highly distinct clinical characteristics, especially compared to another syndromic craniosynostosis. Nevertheless, we present an unusual case of Apert syndrome in a one-and-a-half-year-old girl confirmed by genetic testing without craniosynostosis.

Case report

A one-and-a-half-year-old girl delivered by C-section received prenatal diagnoses of mitral and aortic hypoplasia, aortic arch hypoplasia, and coarctation corrected by surgery on the 17th day of life. Despite the consanguineous marriage of the parents (second-degree cousins), there are no other genetic risks in the family. The child showed neuropsychological development delays, and she still cannot talk or walk. During the physical examination, we found a high, broad forehead; proptosis and hypertelorism; a flat face with retrusion of the maxillae and upper palate; and type I syndactyly of the hands and feet (Fig. 1). Her head circumference was 48.5 cm, the cephalic index (CI) was 0.84 (brachycephalic pattern), and there was a large, broad anterior fontanel. The otologic study with BERA was suggestive of bilateral conductive alterations. Although the cephalic index and all the other characteristics point to the brachycephaly diagnosis, the CT scan did not show the premature suture fusion, just confirmed an open and large anterior fontanel usually seen in a brachycephalic pattern (Fig. 2). The genetic testing came out with a normal female karyotype (46XX), but a molecular study through Sanger sequence was signaled a heterozygotic and pathogenic variation of gene FGFR2, Ser252Trp, compatible with Apert syndrome.

Discussion

Apert syndrome is characterized by abnormalities in the cranial vault, midfacial malformations, and syndactyly of hands

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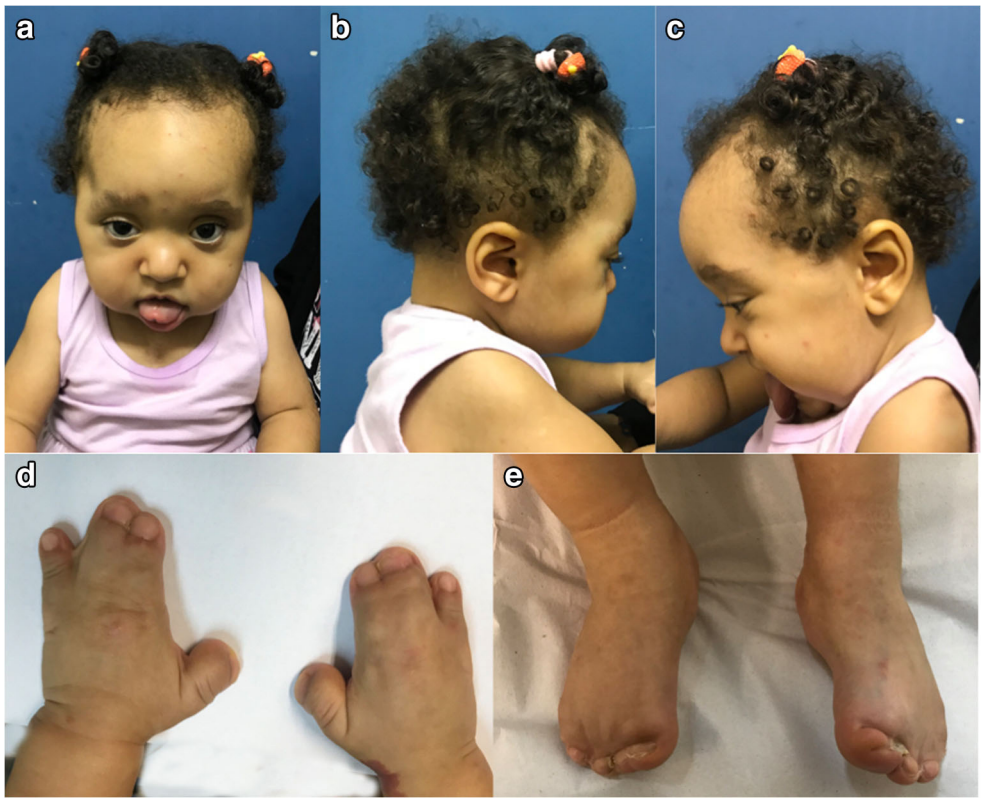

Fig. 1 **a** High and broad forehead, proptosis, and hypertelorism. **b**, **c** Flat face with retrusion of maxillae. **d**, **e** Type I syndactyly of hands and feet

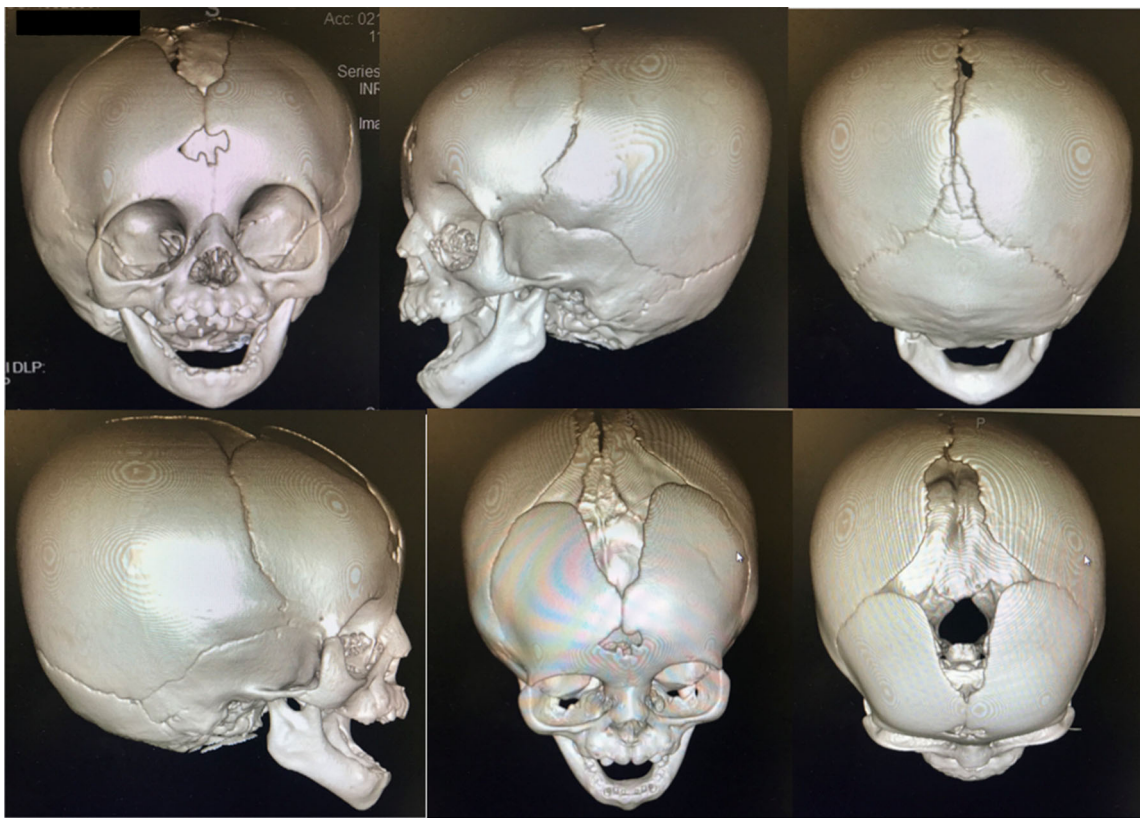

Fig. 2 3D reconstruction of head CT, shows a brachycephalic shape of the cranial vault, without craniosynostosis, with retrusion of maxillae, and a large anterior fontanel

and feet [7]. Severe bicoronal craniosynostosis is the major finding, although it is not unusual to encounter unilateral coronal craniosynostosis or even multiple suture closures [2, 5]. The main findings in midface are exorbitism, hypertelorism, a dystopia of outer canthus and a hooked nose. Many central nervous system developmental disorders can be noted, as corpus callosum and limbic structures agenesis, megalencephaly, gyral and pyramidal tract abnormalities, white matter hypoplasia, heterotopy of gray matter and others, that could explain why some patients are mentally disabled [8]. Otologic disorders and even deafness are not unusual [2, 5]. The pathogenesis of the craniofacial disorder is an alteration of synchondroses of the cranial base, in particular, the sphenoethmoidal and spheno-occipital synchondroses, that involve the coronal and lambdoid suture systems, giving rise to the external amplification of malformation [7].

Although the clinical findings are unique for Apert syndrome, the diagnosis is only confirmed through genetics, and two mutations have been reported in exon IIIa of the FGFR2 gene: Ser252Trp or Pro253Arg [2]. These mutations are restricted to two codons, and this small number of mutated codons had a high contrast with the multiple mutation sites of FGFR2 seen in other syndromes such as Crouzon, Pfeiffer, and Jackson-Weis, because the mutations observed in Apert syndrome are confined to a specific region of FGFR2 exon IIIa in 99% of the cases [6, 9–11] and are expressed on cranial sutures [12].

The case reported in this study showed all the syndromic descriptions; nevertheless, despite the cranial characteristics, the CT scan did not confirm the craniosynostosis. Only a few cases like this had been published before [2, 5, 13], and two of the studies did not mention the children ages or a follow-up, only that they were born without craniosynostosis. Nevertheless, Coomaralingam et al. reported the case of a female girl with confirmed Apert syndrome by genetic testing, who did not show any suture fusion until her 14th month of age. It is generally reported that progressive or delayed suture fusion could occur [14], especially in syndromic craniosynostosis, but what is unusual is that in Apert syndrome, premature coronal fusion is part of the syndromic diagnosis. These cases raise two questions: (1) May there be a different pattern for suture fusion regarding child aging? and (2) For how long should we follow those children to program surgical interventions. It is important to notice that even if the patient has had a coronal fusion, we should determine the proper moment to conduct surgical treatment since other sutures could be fused during this time.

Conclusion

Although extremely rare, an Apert syndrome diagnosis without craniosynostosis is possible. Long-term follow-up is crucial in these cases concerning the risk of further fusions, which may require surgical treatment. However, the extremely low incidence of these cases limits the conclusion that there exist a pattern and a median time during which other sutures may fuse. Hence, further case reports and analyses are still required.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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