A third report of Apert syndrome in association with diaphragmatic hernia

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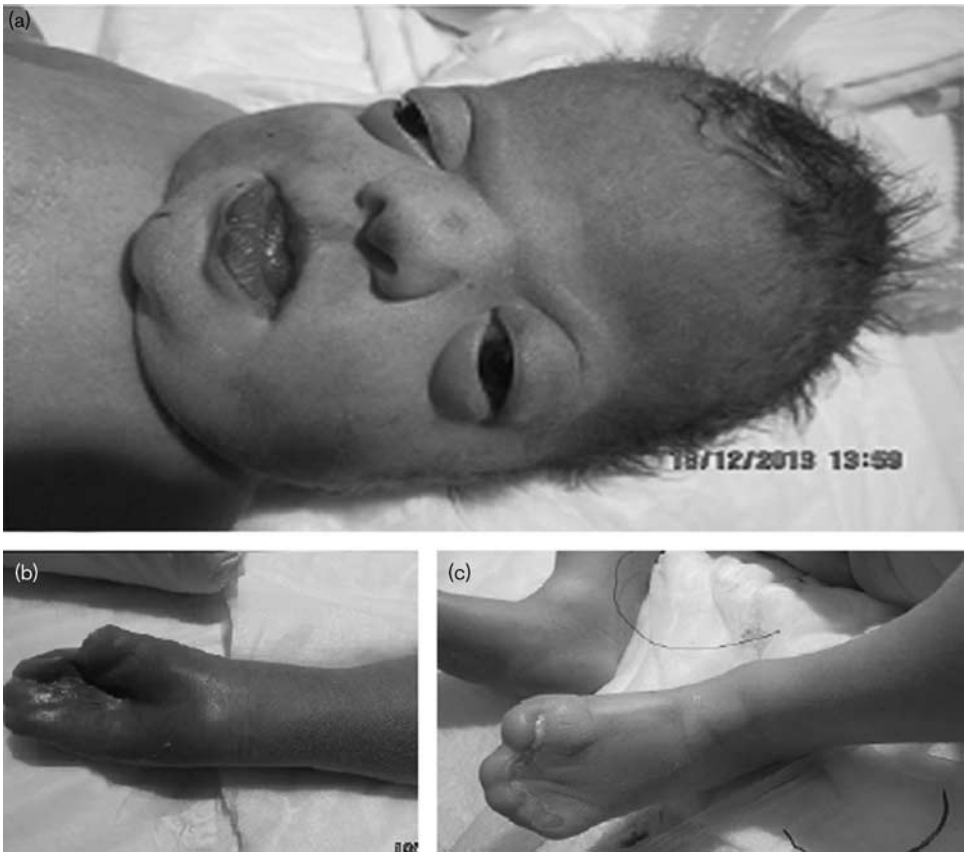
List of key features

Cleft palate
Midfacial defects in the form of brachycephaly
Hypertelorism
Depressed nasal bridge with a large nose
Frontal bossing
Protruded eyes
Maxillary hypoplasia

Introduction

Apert syndrome is a rare acrocephalosyndactyly syndrome characterized by craniosynostosis, midface hypoplasia and syndactyly of the hands and feet (Bhatia *et al.*, 2013). It is caused by autosomal dominant mutations of *FGFR2* on chromosome 10q (10q25-26) (Slaney *et al.*, 1995). Apert syndrome was first reported by Wheaton in 1894 and the French paediatrician Eugene Apert published a series of nine cases in 1906. Most cases of Apert

Fig. 1



(a) Midfacial hypoplasia, protuberant frontal region, ocular proptosis, downward-slanting palpebral fissures, depressed nasal bridge with a large nose and maxillary hypoplasia; (b) hand syndactyly; and (c) foot syndactyly.

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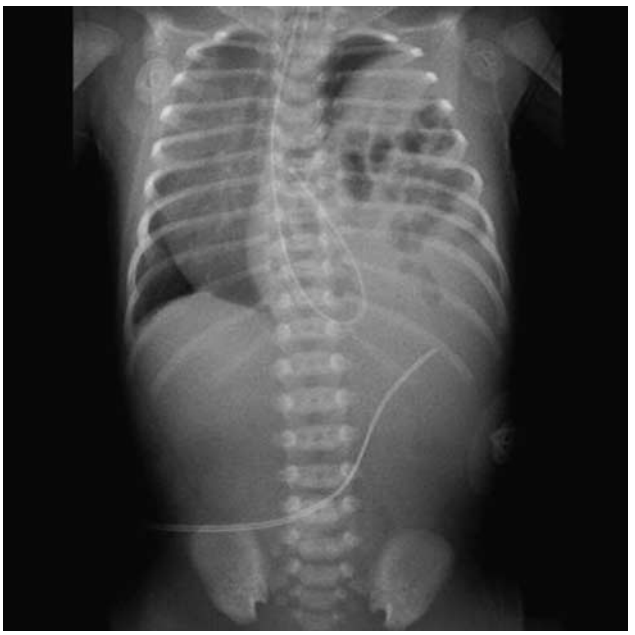
syndrome are sporadic, with equal numbers of affected males and females, and increased paternal age, with an estimated frequency of 1 : 160 000 newborns, and accounting for about 4.5% of all cases of craniosynostosis (Athanaasiadis *et al.*, 2008). Apert syndrome carries a high mortality rate (about 10%) especially during early infancy (Blank, 1960). Surviving infants need care from a multidisciplinary team (Madhura and Naresh, 2010).

Case report

A male infant was born to a 23-year-old primigravida Syrian woman, who had received no antenatal care, at full term by normal vaginal delivery. The infant's birth weight was 2.3 kg and he had Apgar scores of 0 and 5 at 1 and 5 min, respectively. He showed no respiratory effort and was cyanosed and limp. He was immediately found to be dysmorphic, with abnormal craniofacial features and syndactyly of the hands and feet (Fig. 1). He was intubated and ventilated with high settings and transferred to the neonatal ICU. His first arterial blood gas after arriving in the neonatal ICU was as follows: pH: 7.22, PCO_2: 42, PO_2: 78 and HCO_3: 19.6. He was administered 100% oxygen. Chest radiography showed a left congenital diaphragmatic hernia (CDH), with the bowel occupying almost the entire left chest, pushing the heart and mediastinum to the right side (Fig. 2). Subsequent blood gases showed progressive metabolic acidosis and hypoxia and the baby rapidly deteriorated, with progressive and persistent desaturation associated with bradycardia, and finally arrested at the age of 6 h, with no response to 30 min of cardiopulmonary resuscitation. Detailed examination of the baby after death showed the presence of coronal craniosynostosis with bridging leading to turribrachycephaly. He also had frontal bossing, protruding eyes, midfacial hypoplasia, a depressed nasal bridge, a large nose, cleft palate and maxillary hypoplasia. There was severe syndactyly of all four extremities, with complete webbing of adjacent digits. The thumbs of both hands were short, with radial deviation (Fig. 1). The clinical features were consistent with the diagnosis of Apert syndrome, which was confirmed by the presence of the P253R point mutation in *FGFR2*.

Fig. 2



Chest radiograph showing congenital left diaphragmatic hernia.

This case report was approved by the institutional review board. Written informed consent was obtained from the father for the publication of this case report and any accompanying images.

Discussion

Apert syndrome is one of the most commonly described craniosynostosis syndromes. It can be distinguished clinically from Crouzon syndrome by the presence of syndactyly of the hands and feet; cleft or pseudocleft palate is a frequent finding in Apert syndrome, whereas these traits are rare in Crouzon syndrome (Carinci *et al.*, 2005). The presence of CDH in our patient dominated the clinical presentation and was the major concern and challenge in the management of the baby, resulting in his death. To our knowledge, only two cases of Apert syndrome with CDH have been reported previously; the first case (Witters *et al.*, 2000) was a male foetus with left diaphragmatic hernia detected by antenatal ultrasound at 22 weeks of gestation who also had craniofacial dysmorphic features and syndactyly of both the hands and the feet. He was delivered at 33 weeks of gestation and died immediately after birth of respiratory failure. The diagnosis of Apert syndrome was confirmed by the presence of mutation in the *FGFR2* gene. The second case (Bulfamante *et al.*, 2011) was a female foetus with left CDH discovered by antenatal ultrasound at 20 + 6 weeks of gestation, with dysmorphic features suggestive of genetic craniosynostosis. Pregnancy was terminated at 21 + 3 weeks of gestation at the parents' request. The diagnosis of Apert syndrome was confirmed by a molecular analysis of *FGFR2*, which showed a heterozygous S252W mutation. Witters *et al.* (2001) suggests that the association of diaphragmatic hernia with other features of a genetic syndrome leads to poor survival rates, as low as 31%.

Conclusion

Apert syndrome is a rare condition that is encountered in the newborn period, but usually has a good survival rate and can be managed with a multidisciplinary approach that can lead to acceptable long-term outcomes. However, the presence of potentially lethal conditions such as CDH may complicate the outcome and lead to death in the newborn period. This description of a third

case with the combination of Apert syndrome and CDH suggests that CDH should now be considered a rare feature of this syndrome.

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Conflicts of interest

There are no conflicts of interest.

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