Apert Syndrome Associated With Upper Airway Obstruction and Gastroesophageal Reflux Inducing Polyhydramnios in the Third Trimester

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Here, we present the case of a female infant, the first child of a 32-year-old woman and a 45-year-old man, who were healthy and non-consanguineous. The family history was unremarkable. The infant was delivered at 37 weeks' gestation with a birth weight of 2,834 g. She had midface hypoplasia, cleft palate, low-set ears, and bilateral syndactyly of the hands and feet (Figures 1–3). She had a 46,XX karyotype. DNA testing for Apert syndrome revealed a heterozygous c.755 C > G, TCG > TGG transversion leading to a Ser252Trp (S252W) mutation in the fibroblast growth factor receptor 2 (*FGFR2*; OMIM 176943) gene. The pregnancy was uneventful until the third trimester when polyhydramnios was noted (Figure 4). The fetal brain, skull shape and internal organs were normal. The amniotic fluid index was measured as 37.4 cm, 32.3 cm and 30.4 cm at 33, 35 and 36 weeks of gestation, respectively. After birth, the infant manifested respiratory distress owing to a decreased nasopharyngeal airway. Echocardiography showed an atrial septal defect. Three-dimensional computed tomography (CT) reconstruction of the skull showed brachycephaly, shallow bilateral orbital fossa due to premature synostosis of the bilateral coronal sutures, and midface hypoplasia (Figure 5). CT showed normal brain parenchyma, a normal ventricular system, maxillary hypoplasia, symmetric narrowing of both nasal cavities, choanal stenosis, and a narrow and high-arched palate (Figures 6 and 7). The infant underwent tracheostomy at 2 months of age for the treatment of cyanotic episodes, obstructive stridor, and sleep apnea. Bronchoscopy performed prior to surgery revealed upper airway obstruction with nasal stenosis, tongue drop, and laryngomalacia. The subglottis, glottis, trachea and bronchus were normal. She underwent gastrostomy, pyloroplasty and fundoplication at 12 months of age for the treatment of gastroesophageal reflux, frequent vomiting, and poor feeding. She underwent first-stage hand surgery at 2 years of age and second-stage hand surgery at 3 years of age for the treatment of bilateral syndactyly.

Apert syndrome (OMIM 101200) is characterized by acrocephaly, craniosynostosis, a flat occiput, midface hypoplasia, and "mitten-like" syndactyly of the hands and feet [1]. The prevalence at birth of Apert syndrome is estimated to be 1 in 160,000 to 1 in 164,500 [2,3]. Two mutations of the *FGFR2* gene, Ser252Trp (S252W) and Pro253Arg (P253R), account for over 98% of cases with Apert syndrome [4,5]. Most cases of Apert syndrome arise *de novo* but autosomal dominant inheritance and germline mosaicism have been described [6]. Advanced paternal age can be a risk factor [2,7,8]. Although cases of prenatally diagnosed Apert syndrome have been reported [9], prenatal diagnosis of Apert syndrome remains difficult. Many cases of Apert

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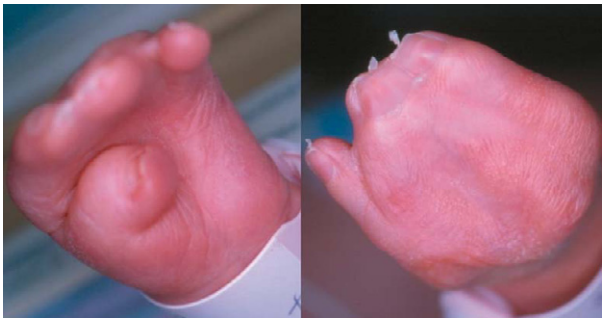

Figure 1. "Mitten-like" syndactyly of the hands.

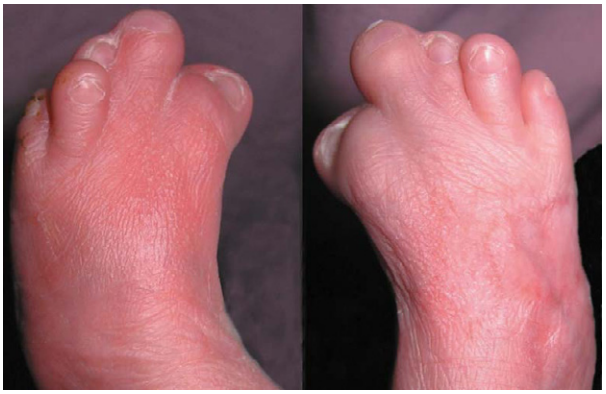

Figure 2. "Mitten-like" syndactyly of the feet.

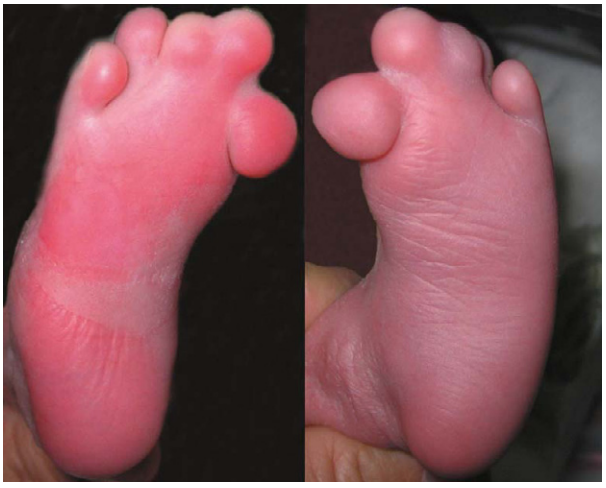

Figure 3. "Mitten-like" syndactyly of the feet.

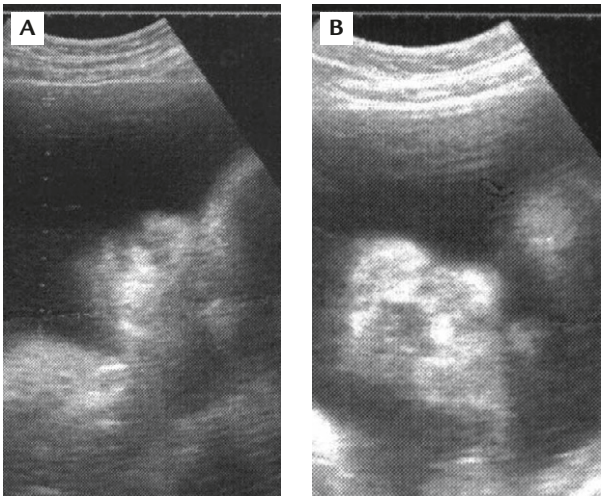

Figure 4. (A) Lateral and (B) anterior views on prenatal ultrasound showing a depressed nasal bridge and midface hypoplasia.

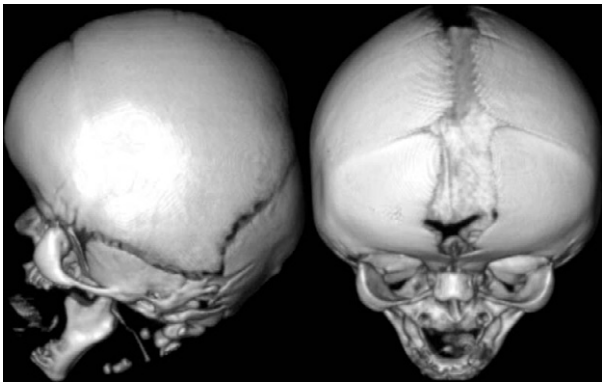

Figure 5. Three-dimensional computed tomography reconstruction of the skull.

syndrome were undiagnosed until delivery, or diagnosed in late gestation when polyhydramnios and craniofacial deformities became evident.

The present case had the S252W mutation. von Gernet et al [10] observed more severe midface and dental findings in S252W patients than in P253R patients, and conversely, more severe syndactyly of hands in P253R patients than in S252W patients. Airway obstruction has been observed in 40% of patients with severe craniosynostostic syndromes [11,12]. In patients with Apert syndrome and midface hypoplasia, the maxilla is narrow and retruded, resulting in a narrow and high-arched palate, small postnasal space and clivus, narrowing of the bony nasal cavities, and choanal stenosis [13]. Airway obstruction may be secondary to midface hypoplasia and may result in sleep apnea and cor pulmonale that require tracheostomy [11,14–18].

Polyhydramnios may develop in the third trimester in pregnancies with fetal Apert syndrome [19]. Nyberg et al [20] suggested that polyhydramnios associated with Apert syndrome is developed from decreased fetal swallowing related to central nervous system abnormalities. However, the present case did not have central nervous system abnormalities. The present case had upper airway obstruction which can cause decreased fetal swallowing. The present case provides evidence that a reduced nasopharyngeal airway can be a principal causative factor of polyhydramnios in pregnancies with fetal Apert syndrome. Fetal Apert syndrome associated with polyhydramnios in the third trimester should be indicative of upper airway obstruction. In such cases, prompt early diagnosis and intervention after birth are necessary to reduce perinatal morbidity.

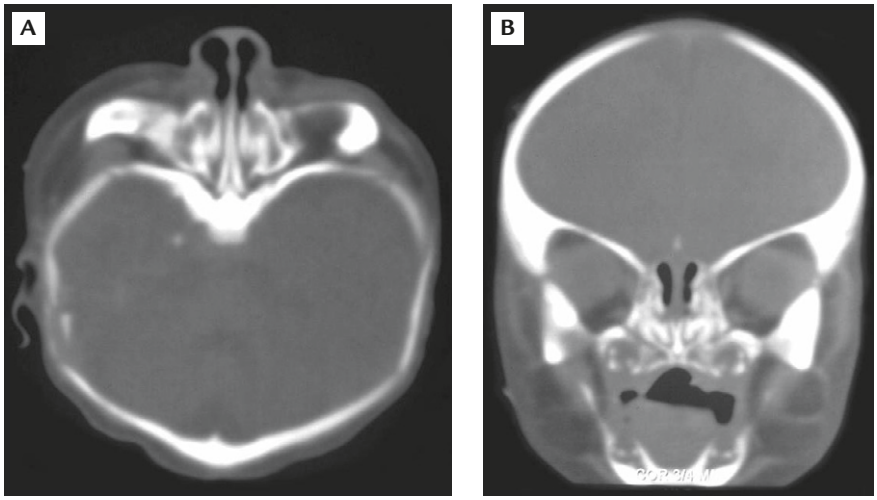

Figure 6. (A) Axial and (B) coronal computed tomography scans of the nose and the paranasal sinuses showing symmetric narrowing of both nasal cavities.

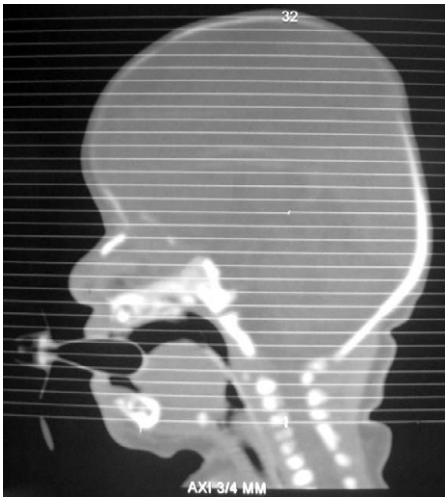

Figure 7. Sagittal computed tomography scan of the skull showing brachycephaly, midface hypoplasia, a narrow and retruded maxilla, a high-arched palate, and a decreased nasopharyngeal airway.

Acknowledgments

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