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Rare Case Report of Ambiguous Genitalia With Apert Syndrome

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Abstract

Apert syndrome is a rare developmental malformation [1]. It's also known as, Acrocephalosyndactyly, characterized by premature fusion of the cranial suture (Craniosynostosis), malformation in the skull, the face, the hands and the feet [2], [3]. We here report an unusual presentation of Apert syndrome in a one day old baby presented with Acrocephalofacial malformation associated with ambiguous genitalia.

Keywords: Apert syndrome; Acrocephalosyndactyly; Ambiguous genitalia.

1. Introduction

Apert syndrome was first reported by Wheaton in 1894 and French pediatrician Eugene Apert published a series of nine cases in 1906 [1]; [4]. It's one of the rare causes of craniofacial syndrome or deformity, characterized by malformation such as Craniosynostosis, a cone-shaped calvarium (Acrocephaly), hypertelorism, midface hypoplasia, pseudo cleft-palate, a parrot beak-shaped nose, pharyngeal attenuation, and syndactyly of the hands and feet [1]. The inheritance of Apert's syndrome is autosomal dominant with the locus of a mutation of FGFR2 (fibroblast growth factor receptors) on chromosome 10q (10q25–26). Rynearson [1] But sporadic cases have been reported and probably represent new mutations [5]. Central nervous system abnormalities (megalocephaly, pyramidal tract abnormalities), skeletal abnormalities (limited mobility of glenohumeral joint, elbow joint, etc.), cardiovascular, genitourinary and gastrointestinal, mental retardation, visual and hearing, speech defects have also been recorded [6]. Therefore, one of the rare presentations is Apert syndrome with pseudohermaphrodism described in this case report.

2. Case Report

Our case report is product of thirty weeks newborn, delivered in our service, by cesarean section due to placenta accreta. The baby was product of the second pregnancy to a 23 years old mother and 34 years old father who were non consanguineous. The pregnancy wasn't well followed. Mother stated a history of afebrile urinary tract infection during the second trimester, treated by oral unknown antibiotic. In addition, she has hypothyroidism maintained on Levothyroxine. The baby was transferred immediately after birth to the neonatal intensive care unit because of prematurity and respiratory distress syndrome. Birth weight was 1600g, length 46 cm and head circumference 33cm. On physical examination, we noticed dysmorphic features with palpable large open sagittal sutures, large open anterior fontanel 3x3 cm and posterior fontanel 1x1cm. Furthermore, there is acrobrachycephaly; the forehead was flattened and wide. In addition, the nasal bridge was depressed, also had bilateral eyelids ptosis (figure 1). Baby also has bilateral hands and feet syndactyly (figure 2). Surprisingly the external genitalia were ambiguous (figure 3). First hemogram and biochemistry profile results were normal. A complete sepsis workup done and was negative for any abnormality. As course in Hospital, we did further investigation to narrow our differential diagnosis. Ct-Scan of brain revealed abnormal skull shape with prominent frontal with dilated lateral ventricles. A suspicion of Apert syndrome was top of the list in our differential but what about associated ambiguous genitalia in addition? To confirm our suspicion a genetic test was ordered to reveal a FGFR2 gene mutation with Pser252 Trp (C.755C > G). A Doppler echocardiography showed a patent ductus arteriosis (PDA) with left to right shut and patent foramen oval of 2,8 mm in diameter. Furthermore, to confirm the associated sex abnormality of the patient an abdominal ultrasound requested to reveal presence of uterus (15x3 mm), but there is absence of ovaries. Karyotype showed 46 XX. Finally, the patient was diagnosed as having Apert syndrome with sexual disorder that showed a female

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karyotype (46 XX) and absence of the ovaries. The baby was discharged from the hospital against medical advice for social reason.

Figure-1. Typical face appearance of the patient

Figure-2. Complete syndactylia

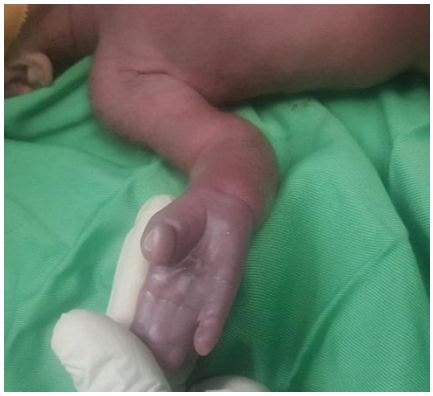
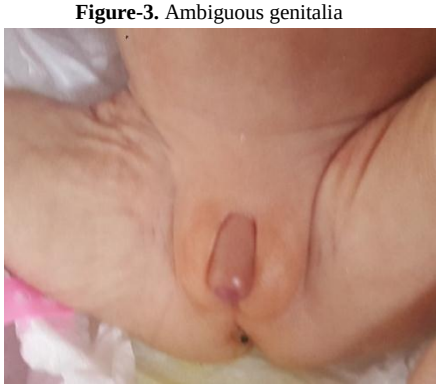


Figure-3. Ambiguous genitalia



3. Discussion

Apert syndrome (Acrocephalosyndactylia) is a developmental malformation, described by Dr. Eugene Charles Apert, a French Physician in 1906 [2]. The incidence is 1:160 000; However due to high infant mortality, the incidence in the general population is lower [7]. It has been described as a branchial arch syndrome, affecting the first branchial (orpharyngeal) arch, the precursor of the maxilla and mandible [8] ; [9]. Linguistically "acro" is a Greek word for "Peak" referring to a "Peaked" head that is common in the syndrome. "Cephalo", also a Greek, is a combining form meaning "head". "Syndactyly" refers to webbing of fingers and toes [8]. The disease characterized by craniosynostosis, a cone-shaped calvarium (acrocephaly), hypertelorism, midface hypoplasia, pseudo cleft-palate, a parrot beak-shaped nose, pharyngeal attenuation, and syndactyly of the hands and feet [1]. The prodromal characteristics typical turribrachycephalic head shape is early craniosynostosis of coronal sutures and agenesis of sagittal and metopic sutures which results as a wide defect extending from glabella to posterior fontanels [6]. Premature fusion of sutures with continued brain growth can lead to increased intracranial pressure which can be seen as increased convolutional markings on skull radiographs [6]. The complex multiple sutured synostosis frequently extends to premature fusion of the sutures at the base of the skull, causing midfacial hypoplasia, shallow orbits, a foreshortened nasal dorsum, maxillary hypoplasia and occasional upper airway obstruction [6]. Syndactylia or webbing of fingers causes immobility of fingers due to ossification of interphalangeal joints due to segmentation of embryonic phalanges. Involvement of the first or fifth digits in this bony mass is variable. There can be a similar deformity involving the foot (mitten hand and sock foot) [10]. According to the literature, Apert's and Crouzon's syndrome seem to be the same syndrome, with the exception of syndactyly of hands and feet in Apert's syndrome. Cleft or pseudo cleft palate is a frequent finding in Apert's syndrome, whereas these traits are extremely rare in Crouzon's syndrome [11]. Central nervous system abnormalities (megalocephaly, pyramidal tract abnormalities), skeletal abnormalities (limited mobility of glenohumeral joint, elbow joint, etc.), cardiovascular, genitourinary and

gastrointestinal, mental retardation, visual and hearing, speech defects have also been recorded [6]. The literature also reports skin manifestations in Apert syndrome, such as acne, hyperhidrosis, hypopigmentation and hyperkeratosis of plantar surfaces [6]. One of the genital presentations is the disorders of sexual development reported in this case. Ambiguous genitalia are rarely associated with craniosyostosis syndrome. It has been reported in Antley-Bixler syndrome which is a severe form of congenital adrenal hyperplasia characterized by ambiguous genitalia in both sexes and craniosynostosis with other skeletal, renal anomalies and mental retardation [12]. In other hand, the craniofacial syndrome and ambiguous genital was noted in skeletal abnormalities, cutis laxa, craniostenosis, psychomotor retardation, and facial abnormalities (SCARF syndrome). [13] The presentation of ambiguous genitalia and Apert syndrome was extremely rare. The mode of transmission for Apert syndrome is well known as inheritance of autosomal dominant with the locus of a mutation of FGFR2 on chromosome 10q (10q25–26) as a small fraction [1]. While sporadic cases are majority and frequent. Sporadic transmission indicates that a family may have a child with Apert when no other member of the family is affected. The recurrence risk of having another child with Apert syndrome for two unaffected parents is negligible. However, there is a higher mutation rate in males because the germ-cell divisions in males are greater than those in females. Hence, the mutation rate increases with increased paternal age [14] ; [5]. Apert syndrome diagnosis is often suspected by the physician as clinical Apert syndrome or another craniosynostosis syndrome at birth because of a newborn's appearance. Genetic testing can usually identify Apert syndrome or another cause of abnormal skull formation [15]. Treatment of Apert syndrome begins at birth and a multidisciplinary approach is required arrive at a collaborative corrective plan for the deficiencies [1]. Craniectomy is often performed during 6 months of age to treat the craniosynostosis. Corrective surgery for syndactyly is done in first year of life and completed by 3 to 4 years of age. Cosmetic correction for midface deficiency and pseudo cleft is at 4 to 6 years age [16]. Orthodontic and orthognathic surgery is performed after eruption of permanent dentition and completion of growth. Nonsurgical manipulation of Apert syndrome may be a possibility in the future [16]. Genetic counseling is an important factor as recurrence risk for an affected individual to have an affected offspring is 50% [17].

4. Conclusion

This case presented the clinical manifestation of Apert syndrome associated with rare presentation of ambiguous genitalia. The diagnosis and the genetic counseling play an important role to decrease the recurrence of the disorders in affected families.

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