

Apert Syndrome: Case Presentation

Atiye Fedakâr^{1*} and Zakir Sakc²¹Department of Pediatrics, Afiyet Hospital, Turkey²Department of Radiology, Sağlık Bilimleri Üniversitesi, Ümraniye Eğitim Araştırma Hastanesi, Turkey

Article Information

Received date: Oct 28, 2016

Accepted date: Dec 19, 2016

Published date: Dec 21, 2016

*Corresponding author

Atiye Fedakâr, Department of Pediatrics,
Armağan evler mah, Akdeniz cd, Sandra
evleri c blok d-4. 34762 Ümraniye,
Istanbul, Turkey, Tel: +905327439762,
Email: atyfedakar@hotmail.com

Distributed under Creative Commons
CC-BY 4.0

Keywords Apert Syndrome; Newborn
infant; Craniosynostosis

Abstract

Apert syndrome belongs to acrocephalosyndactyly group of disorders, and it is a autosomal dominantly inherited rare disorder characterized by craniosynostosis, midline facial hypoplasia, severe symmetrical cutaneous syndactyly of the hands and the feet, as well as central nervous system, heart and kidney abnormalities. It is caused by a mutation of the fibroblast growth factor gene located in the 10th chromosome (10q25-26). Clinical presentation of the disease was first described in 1906 by Apert, and it is an easily recognizable disorder with particularly typical physical examination findings. In the light of the current literature, this article reviews and presents a case of Apert syndrome diagnosed based on physical examination findings and chromosomal analysis.

Introduction

Apert syndrome belongs to acrocephalosyndactyly group of disorders, and it is a rare congenital disorder characterized by craniosynostosis, brachycephalia, and midline facial hypoplasia, symmetrical syndactyly of the hands and the feet, as well as heart and kidney abnormalities [1,2]. Apert syndrome was first mentioned by Baumgartner in 1842 and by Wheaton in 1894, while the disorder is named after a French pediatrician Eugene Apert who, in 1906, described 9 patients experiencing similar symptoms [3-6]. Cohen estimated that Apert syndrome is responsible from almost 4% of all craniosynostosis cases and its prevalence is 13.7/10, 00,000 [7]. In the light of the current literature, this article reviews and presents a case of Apert syndrome diagnosed based on physical examination findings and chromosomal analysis.

Case

The case involves a baby girl, delivered by C/S due to breech presentation and was the first pregnancy of a 21-years old mother and 32-years old father who were non-kin. She was internalized in the neonatal intensive care unit with the diagnosis of Neonatal Transient Tachypnea (TTN) due to respiratory distress. The mother was not monitored during pregnancy. She was given antibiotics due to a urinary tract infection during pregnancy. The family had no history of a similar disorder and the father was 32 years old.

The patient's body weight was 3410 grams, height was 50 cm and her head circumference was 37.5 cm. In physical examination, large sagittal sutures were palpated; sized 3×3 cm in the anterior and 1×1 cm in the posterior fontanel. She had acrobachycephaly, her forehead was flattened and wide, she had bilateral proptosis, and her nasal bridge was compressed. Bilateral fingers and toes presented cutaneous syndactyly. (Figures 1 to Figure 4) Hemogram and biochemical test results were within normal limits and her CRP level was 0.6mg/dl (<0.5). Echocardiography indicated an Atrial Septal Defect (ASD) + patent ductus arteriosus (small). Abdominal ultrasonography was normal. In cranial USI, anterior fontanel was noted extremely on the front and cranial posterior fossa was not clear, lateral ventricle frontal horns were dilated. FGFR2 gene mutation screening of the patient indicated a Pro253 Arg dislocation. The patient was diagnosed with Apert syndrome



Figure 1: Typical face appearance of the patient.



Figure 2: Bilateral cutaneous complete syndactyly on the patient's hands.



Figure 3: Complete syndactyly appearance on the patient's feet.



Figure 4: Lateral view of the patient.

based on physical examination findings and genetic investigations. Investigations performed on the 3rd day of hospitalization showed CRP (+), antibiotics were administered in addition to TTN therapy and cultures were obtained for early sepsis. The patient was discharged from hospital on the 7th day of hospitalization.

Currently, the patient is 7 months old and being monitored in collaboration with the neurosurgery, pediatric cardiology, plastic and reconstructive surgery, orthopedics, neurology and psychiatry clinics.

Discussion

Apert syndrome belongs to acrocephalosyndactyly group of disorders, and it is a genetic disorder characterized by craniosynostosis, midline facial hypoplasia, severe symmetrical cutaneous syndactyly of the hands and the feet, as well as central nervous system, heart and

kidney abnormalities. Craniofacial findings of the Apert syndrome include closed coronal suture during birth and the presence of a large fontanel glabella. The forehead is upfront, more prominent and elevated, while the super ciliary arch is depressed [6]. Due to anterior dislocation of the sphenoid bone, temporal regions appear protruding while the occiput is flattened. This arrangement negatively effects the development of maxillary bone, thus prevents development of the nasopharyngeal cavity. As a consequence, the patient might present with severely impaired respiratory functions, obstructive sleep apnea, cor pulmonale and sudden death. Typical ophthalmologic findings of the Apert syndrome include hypertelorism, papilla oedema and proptosis [8,9]. The case presented here had decreased head front-back diameter, flattened forehead, protruding temporal regions, and bilateral proptosis (Figures 1,4). In Apert syndrome, syndactyly is characterized by progressive fusion of the bones of the hands and feet during skeletal development. Symmetrical syndactyly most frequently occurs between the second, third and fourth fingers, while the first and the fifth fingers are generally free [8,9]. The case presented here had total syndactyly involving all fingers (Figures 2,3).

In addition to musculoskeletal abnormalities, abnormalities of the cardiovascular system (23.5%), cleft palate (23.5%), genital urinary system (5.9%) and central nervous system (5.9%) can also be encountered. Among these cases, the most common cardiovascular abnormalities are Ventricular Septal Defects (VSD) and dextra positioning of the aorta, which may lead to early death [10,11]. In their study including 136 patients with Apert syndrome, Cohen and Kreiborg'un reported that 10% of the patients had cardiovascular system abnormalities consisting of Fallot's tetralogy and VSD, 9.6% had genitourinary system abnormalities such as hydronephrosis and cryptorchidism, while 1.5% had gastrointestinal system abnormalities including tracheoesophageal fistula [12]. Echocardiography investigations of the patient described here indicated an Atrial Septal Defect (ASD) + patent ductus arteriosus (small). The patient's abdominal ultrasonography was normal and no genitourinary or gastrointestinal system pathology was identified.

While the majority of the cases are sporadic, some cases are associated with autosomal dominant inheritance. Sporadic cases are believed to be due to old father age. The rate of occurrence is equal between men and women [5,13]. Apert syndrome is a result of Ser252 Trp or Pro253Arg mutations in the Fibroblast Growth Factor Receptor (FGFR)-2 gene located on the 10th chromosome (10q2526) [14]. Literature indicates that the frequency of cleft palate increases particularly in the presence of Ser252 Trp mutation, while the frequency of severe syndactyly correlates with Pro253Arg mutation [15]. In a study performed by Tolarova et al. over a period of 10-years, mean father age of 53 cases with Apert syndrome was found as 34.1 ± 6.2 years [16]. FGFR2 gene mutation screening of our patient indicated a Pro253 Arg dislocation and in line with the literature, the patient had severe syndactyly and father's age was old.

Mental retardation is frequent among cases with Apert's syndrome. Previous studies indicated that 52% of the patients have an IQ lower than 70 [17]. In addition, clinically significant speaking difficulties, attention deficits and developmental problems have also been reported [18]. Since our patient was only 7 months old, her mental status could not be comprehensively evaluated.

Differential diagnoses should include evaluation of other genetic disorders associated with craniosynostosis. The most

common genetic disorders accompanying craniosynostosis include Crouzon, Apert (Acrocephalosyndactyly Type I), Carpenter, Apert-Crouzon syndrome (Acrocephalosyndactyly Type II), Jackson-Weis syndrome and Pfeifer syndrome. Apert syndrome can be differentiated by genetic analysis and typical face appearance [15,17]. Prenatal diagnosis can be made by establishing craniosynostosis and syndactyly in ultrasonography. Craniosynostosis and syndactyly may not be concomitantly visualized in a fetus. The earliest gestational week to notice these findings varies between weeks 16 to 32 [19]. In patients with a family history of the disorder, demonstration of craniosynostosis or syndactyly during prenatal USI is sufficient for diagnosis. In sporadic cases, on the other hand, molecular genetics investigations support the diagnosis [20].

Treatment of patients with Apert syndrome requires a multidisciplinary approach, involving follow-up therapies provided by plastic and reconstructive surgery, neurosurgery, neurology and psychiatry specialists. Cardio-respiratory problems and interventions against brain compression should be prioritized during neonatal period. Multiple surgeries are required. Front-orbital correction and surgical intervention to reconstruct cranial anatomy are recommended to be performed at the age of 3 months, the earliest [21]. Reconstruction surgery for synostosis is recommended after 6 years of age [22]. Majority of patients with Apert syndrome have mental retardation and only a small minority have normal intelligence. Mental status of these patients is influenced by surgical therapies, accompanying brain abnormalities, family and environmental factors. Therefore, the patients' psychological condition should also be regularly evaluated and psychological consultation should be provided [23]. Our patient is currently being followed-up in collaboration with plastic and reconstructive surgery, neurosurgery, neurology and psychiatry departments.

Conclusion

In conclusion, Apert syndrome is a rare disorder that cannot be cured completely, and it represents both an economical and a moral burden to the patients, to the patients' families, and to national economy. Therefore, prenatal early diagnosis and recommending termination of pregnancy to the parents can be a fundamental approach. Since the majority of the cases are associated with de novo mutations, craniosynostosis and syndactyly should be evaluated during prenatal ultra sonographic examinations of all pregnant women even in the absence of a family history of the disorder, and further molecular genetic testing should be performed in suspected cases.

References

- Amar T, Krishna V, Sona K. Apert syndrome: A rare presentation. *J Indian Acad Clin Med.* 2007; 8: 245-246.
- Martelli H Jr, Paranaíba LM, de Miranda RT, Orsi J Jr, Coletta RD. Apert syndrome: Report of a case with emphasis on craniofacial and genetic features. *Pediatr Dent.* 2008; 30: 464-468.
- Athanasiadis AP, Zafarakas M, Polychronou P, Florentin-Arar L, Papasozomenou P, Norbury G, et al. Apert syndrome: The current role of prenatal ultrasound and genetic analysis in diagnosis and counselling. *Fetal Diagn Ther.* 2008; 24: 495-498.
- Madhura D, Naresh S. Apert's syndrome: A rare case report. *J Indian Acad Oral Med Radiol.* 2010; 22: 232-235.
- Bhatia PV, Purv S Patel, Yesha V Jani, and Naresh C Soni. Apert's syndrome: Report of a rare case. *J. Oral Maxillofac Pathol.* 2013; 17: 294-297.
- Apert ME. De l'acrocephalosyndactylie. *Bull Mem Soc Med Hop.* 1906; 23: 1310-1330.
- Cohen MM Jr, Kreiborg S. New indirect method for estimating the birth prevalence of the Apert's syndrome. *Int J Oral Maxillofac Surg.* 1992; 21: 107-109.
- Katzen JT, McCarthy JG. Syndromes involving craniosynostosis and midface hypoplasia. *Otolaryngol Clin North Am.* 2000; 33: 1257-1284.
- Açıkgöz Y, Belet N, Yalın T, İncesu L, Küçüködük Ş. Apert Sendromu: Olgu Sunumu ve Literatürün Gözden Geçirilmesi. *O.M.Ü. Tıp Dergisi.* 2006; 23: 59-64.
- Arroyo Carrera I, Martínez-Frías ML, Marco Pérez JJ, Paisán Grisolia L, Cárdenas Rodríguez A, Nieto Conde C, et al. Apert syndrome: clinico-epidemiological analysis of a series of consecutive cases in Spain. *An Esp Pediatr.* 1999; 51: 667-672.
- Cohen MM Jr, Kreiborg S. Visceral anomalies in the Apert syndrome. *Am J Med Genet.* 1993; 45: 758-760.
- Cohen MM Jr, Kreiborg S. Agenesis of the corpus callosum. Its associated anomalies and syndromes with special reference to the Apert syndrome. *Neurosurg Clin N Am.* 1991; 2: 565-568.
- Breugem CC, Fitzpatrick DF, Verchere C. Monozygotic twins with Apert syndrome. *Cleft Palate Craniofac J.* 2008; 45: 101-104.
- Mantilla-Capacho JM, Arnaud L, Diaz-Rodriguez M, Barros-Núñez P. Apert sendromu with preaxial polydactyly showing the typical mutation Ser252Trp in the FGFR2 gene. *Genet Counsel.* 2005; 16: 403-406.
- Wilkie AO, Slaney SF, Oldridge M, Poole MD, Ashworth GJ, Hockley AD, et al. Apert syndrome results from localized mutation of FGFR2 and is allelic with Crouzon syndrome. *Nat Genet.* 1995; 9: 165-172.
- Tolarova MM, Harris JA, Ordway DE, Vargervik K. Birth prevalence, mutation rate, parents' age and ethnicity in Apert syndrome. *Am J Med Genet.* 1997; 72: 394-398.
- Jones KL. Smith's recognizable patterns of human malformation. Philadelphia: Elsevier Saunders. 2006; P.474-475.
- Shipster C, Hearst D, Dockrell JE, Kilby E, Hayward R. Speech and language skills and cognitive functioning in children with Apert syndrome: a pilot study. *Int J Lang Commun Disord.* 2002; 37: 325-343.
- Narayan H, Scott IV. Prenatal diagnosis of Apert syndrome. *Prenat Diagn.* 1991; 10: 187-192.
- Fereira JC, Carter SM, Bernstein PS, Jabs EW, Glickstein JS, Marion RW, et al. Second-trimester molecular prenatal diagnosis of sporadic Apert syndrome following suspicious ultrasound findings. *Ultrasound Obstet Gynecol.* 1999; 14: 426-430.
- Yacubian-fernandes A, Palhares A, Giglio A, Gabarra RC, Zanini S, Portela L, et al. Apert syndrome: analysis of associated brain malformations and conformational exchanges Determined by surgical treatment. *J Neuroradiol.* 2004; 31: 116-122.
- Dao KD, Shin AY, Kelley S, Wood VE. Synostosis of the ring-small finger metacarpal in Apert acrosyndactyly hands: incidence and treatment. *J Pediatr Orthop.* 2001; 21: 502-507.
- Sarimski K. Social adjustment of children with a severe craniofacial anomaly (Apert syndrome). *Child Care Health Dev.* 2001; 27: 583-590.