An Insight Into The Spectrum Of Apert Syndrome – A Case Study

R Narang, S Sandhu, S Padda, J Sandhu, A Manchanda

Citation


Abstract

Apert’s syndrome (Acrocephalo-syndactyly) is a rare congenital, autosomal dominant condition characterized by primary craniosynostosis, mid face malformations and symmetrical syndactyly of the hand and feet. Untreated craniosynostosis leads to inhibition of brain growth and an increase in intracranial and intraorbital pressure. Despite of tremendous advances which have been made in the prevention and treatment of developmental anomalies, they still remain a significant cause of morbidity worldwide. As such, it is incumbent on clinicians to learn as much as possible about this condition so as to improve their ability to handle and prevent them. We present a case of Apert’s syndrome seen in a 10 year old boy. Because of the multiple alterations in patients with Apert syndrome, a multidisciplinary approach, including dentists and neurosurgeons, plastic surgeons, ophthalmologists and geneticists, is essential for a successful planning and treatment. The differences between Apert and Crouzon’s syndrome are also highlighted.

INTRODUCTION

Apert syndrome (Acrocephalo-syndactyly) is a rare condition characterized by craniosynostosis. Though this syndrome was mentioned as early as 1842 by Baumgartner, the eponymic credit was given to a french paediatrician Eugene Apert for his presentation of the syndrome in 1906. He described a triad of craniosynostosis, syndactyly and maxillary hypoplasia.\(^1\)

Acrocephalosyndactyly is a variant of craniosynostosis which is characterized by acrocephaly and syndactyly of hands and feet often combined with anomalies of other organs. Some investigators state that 4.5 percent of all craniosynostosis represent Apert syndrome.\(^2\) Though this syndrome has typical clinical features, the relative rarity (1:100,000 to 1:160,000 births) of the condition still poses a diagnostic dilemma.\(^3\) Apert’s syndrome is known to be inherited in an autosomal dominant fashion, but most cases are sporadic.\(^1\) It is caused by nucleotide alterations resulting in amino-acid substitutions, leading to a mutation in the FGFR2 (Fibroblast growth factor receptor) gene located on chromosome number 10. Fibroblast growth factor receptors have a high affinity for fibroblast growth factors that, when bound to their specific receptors, play a role in signaling pathways with multiple biologic effects including cranial development and growth.\(^4,5\)

The following etiological hypotheses have been proposed for Apert syndrome: antenatal drug consumption by mothers; virus embryopathy following maternal infection; high parental age; inflammatory process at the base of the skull and maldevelopment of skull.\(^3\) The clinical features are distinctive. The coronal suture fuses prematurely (at less than 3 months), leading to an acrocephalic (cone-shaped) head with shortened antero-posterior diameter, and a high prominent forehead. The midface is hypoplastic. Occular anomalies include hypertelorism, proptosis, and down slanting palpebral fissures. The nose is short and wide with depression of the nasal bridge.\(^6,7,8\) Previous studies report affected individuals with anomalies of the viscera, elbows and shoulders, skeleton and central nervous system, which often results in impaired mental function.\(^8,9\) The oral cavity of Apert patients is also characteristic.

Purpose of this case report is to focus on the assessment of clinical and conventional radiographic imaging of a patient with Apert syndrome correlating the bone abnormalities of cranium, face, skull and syndactyly of hands and feet.

CASE STUDY

A 10 year old male child visited the Department of Oral Medicine and Pathology, complaining of irregularly arranged upper and lower front teeth and difficulty in closing his lips. The patient presented with unusual craniofacial and
dental features, which prompted a further detailed examination. Physical examination revealed syndactyly (fusion of the digits of hand and feet).

Familial medical history revealed increased parental age (>40 years) without parental consanguinity. History was negative for any kind of infection, use of drugs or trauma during pregnancy. The patient’s medical history revealed surgery for correction of cleft palate and syndactyly. However craniectomy was not performed. The child was of normal intelligence with an intelligence quotient in the normal range of 85. The developmental milestones were normal. Clinical examination revealed the following features: Skull and face exhibited peaked and vertically elongated head (Turribrachycephaly), flat occiput, protuberant frontal region, maxillary hypoplasia with retracted midface and flattened face (Figure 1 & 2). The eyes had downward slanting palpebral fissures, hypertelorism, shallow orbits, proptosis and exophthalmos (Figure 1, inset). The nose was short, wide with a bulbous tip and had a markedly depressed nasal bridge. The patient had an open mouth appearance (Trapozoid appearance when relaxed).

Figure 1
Figure 1

Figure 2
Figure 2

Figure 1 & 2: Frontal and lateral view showing typical features of Apert Syndrome. Figure 1, inset shows the ocular features

Extremities and Digits showed syndactyly involving hands and feet. Second, third and fourth digits were completely fused to first and fifth digits (Mitten-hands and Sock-feet). Nail beds were contiguous (synonychia). (Figure 3 and 4).
Intra-oral examination revealed an anterior open bite, crowding of anterior teeth (Figure 5), rotated central incisors with over retained root stumps of deciduous teeth. It was observed that the maxillary arch was high arched, narrow V-shaped with cleft in hard palate (Figure 6). The patient had class III molar relationship with posterior cross bite (Figure 7).
Lateral view of the skull on radiographic appearance showed a relatively abnormal shaped skull (Brachycephaly) and an increased digital marking (beaten metal appearance) especially in the anterior portion (Figure 8). Orthopantomogram revealed occlusion of only molars with an anterior open bite because of hypoplastic maxilla, dental crowding and multiple retained deciduous teeth (Figure 9).

The findings of the cephalometric lateral skull radiograph are enumerated as follows:-

- Cranial base length shorter than normal
- Height of cervical column shorter than normal
- Nasal bridge – depressed
- Nasal length and depth – smaller than normal
Based on clinico-radiological evaluation a diagnosis of Apert Syndrome was made. The Ser 252 Trp mutation of the FGFR2 gene was found, confirming the diagnosis.

**DISCUSSION**

Craniosynostosis refers to a premature fusion of the calvarial sutures. Historically, the clinical description of craniosynostosis date back to Hippocrates and Galen, but first historical reference to craniosynostosis was made by Mestrius Plutarchus (46–127 AD). The identification of two pre-Columbian skulls with sagittal synostosis (dated at 6000 and 250 BC) confirms that craniosynostosis is an ancient disorders of humans.

Most of the molecularly characterized cases of Apert syndrome result form two specific mutations of a gene located on chromosome 10q26, encoding (FGFR2. The two mutations involve C-to-G transversions at adjacent codons in exon IIIa of the gene. The first mutation is C934G transversion, leading to a change of codon TCG to TGG, producing a serine-to-tryptophan substitution at amino acid 252 (S252W or Ser252Trp). The second mutation is a C937G transversion, changing codon CCT to CGT, resulting in proline-to-arginine substitution at amino acid 253 (P253R or Pro253Arg). The former (S252W) is the most common mutation, occurring in 67% of patients and has been proposed to be associated with more severe craniofacial anomalies, whereas the later (P253R) may be associated with more severe syndactyly. These mutations affect the region linking the immunoglobulin-like domains II and III of FGFR2 and result to increased affinity and altered specificity of ligand binding. This in turn leads to deregulation of cell migration, proliferation and differentiation and ultimately to premature osteogenesis and skeletal abnormalities that characterized the syndrome.

Apert syndrome refers to primary craniosynostosis characterized by premature fusion of the coronal suture and agenesis of sagittal and metopic sutures, resulting in a wide calvarial midline defect that starts at the glabella and ends at the posterior fontanelle. Premature fusion of the cranial sutures (craniosynostosis), especially before brain growth is complete results in changes in the brain and adjoining structures such as raised intracranial pressure, reduced orbital volume, exophthalmos, optic atrophy, severe maxillary hypoplasia and occlusal derangement. In the present case, the patient did not undergo surgery to separate cranial bones and facilitate brain development.

The syndrome is characterized by progressive calcification and fusion of bones of hands, feet and cervical spine. Consistent post-natal growth failure, might lead to rhizomelic shortening of the lower limbs at adolescence. Many of those affected also have agenesis of the corpus collosum, progressive hydrocephalus, and hippocampal abnormalities.

As observed in our case, most readily observed dental findings are anterior open bite, crowding of anterior teeth, high arched, narrow V-shaped palate, cleft palate. The skeletal class III occlusal relationship observed in our case is probably due to sagittal maxillary hypoplasia and not as a result of a prognathic mandible as observed by Avantaggiato et al.

Ultrasound prenatal diagnosis is of vital importance especially when the parental age is high and there is history of maternal infection with antenatal drug consumption. Apert syndrome can be accurately suspected in the second-trimester by careful ultrasound examination of the fetus including the extremities and skull shape. 3D ultrasound can be a useful adjunct to 2D examination for parental counseling.

In the same category of major craniosynostosis syndromes associated with a mutation of the fibroblast growth factor receptor family as Apert syndrome, belong others well defined clinical entities: Crouzon syndrome, Jackson–Weiss syndrome and Pfeiffer syndrome. Apert syndrome needs to be distinguished from Crouzon syndrome as both these syndromes share common clinical and radiographic features. However, some quantitative craniofacial traits show marked differences between the two syndromes.

Cleft palate and bifid uvula are frequent findings in Apert’s syndrome whereas these traits are extremely rare in Crouzon’s syndrome.

The frequency and distribution of cervical spine conditions differ significantly in the two syndromes:
Apert patients have cervical fusion twice as frequently as Crouzon patients.

The C2-C3 interspace is involved in over half the Crouzon patients; C2-C3 interspace involvement is not seen in the Apert patients.

Fusion of the C5-C6 is seen in two thirds of the Apert patients but in only half the Crouzon patients.

The Crouzon syndrome fusions tend to be one interspace and simple, whereas the Apert’s have more complex and extended fusions.

The infant Apert skull is characterized by premature fusion of the coronal sutures only and by a wide calvarial midline defect extending from the glabella to the posterior fontanelle. In contrast the infant Crouzon skull shows much more extensive synostosis of calvarial sutures and no midline defects.

The two mutations that cause Apert syndrome are located in the link region between Immunoglobulin (Ig) like loops II and III on FGFR. More than two dozen mutations known to cause Crouzon syndrome are located within Ig-like loop III of the same receptor.

Articulare point is higher in Apert patients as compared to Crouzon patients. Mandibular body length is short in both, compared to normal individuals but more shorter in Crouzon patients. Effective mandibular length is also shorter in Crouzon patients compared to their Apert counterparts. The cranial base angles are nearly normal in Apert patients but decreased in the Crouzon sample.

The differences between the two syndromes are more pronounced during infancy but become less exaggerated with age.

The necessity for a dentist to be capable of recognizing and dealing with genetic disease is becoming increasingly important due to the number of recognized genetic traits and diseases that involve oral facial structures. Until there are means to correct the molecular defect, a multidisciplinary approach is required for management of functional and cosmetic defects of the condition. The management includes correction of craniosynostosis by performing craniectomy during the first year of life and correction of limb defects between one and two years of age.21 When the patient is a young adult, orthognathic surgeries and orthodontic treatment is often required to normalize appearance and to correct malocclusion.

Prognosis is dependent upon severity of brain malformation and on early surgical interventions. Advances in craniofacial surgery have enabled patients of Apert’s syndrome to attain intellectual and physical competence and thus lead a normal life.22

CONCLUSION

Innovations in craniofacial surgery have enabled children with Apert syndrome to achieve their full potential by maximizing their opportunities for intellectual growth, physical competence, and social acceptance. However, at each developmental phase they are confronted with different challenges to their emotional and social adaptation that must be overcome. Children with Apert syndrome continue to face erroneous assumptions of mental retardation and social stigmatization because of their appearance. Families and medical care providers play a critical role in fostering their adjustment and supporting them during these emotionally stressful periods. Most importantly, by understanding the unique issues of each developmental period, parents and professionals also have the capacity to maximize their opportunity for psychologic well-being. Thus, a team approach is essential to determine the best collaborative plan for the deficiencies of the child.

References


Author Information

Ramandeep S Narang, MDS
Associate Prof, Department of Oral Pathology, Sri Guru Ram Das Institute of Dental Sciences & Research

Simarpreet V Sandhu, MDS
Professor, Department of Oral Pathology, Genesis Institute of Dental Sciences and Research

Sarfaraz Padda, MDS
Associate Prof, Department of Oral Medicine, Genesis Institute of Dental Sciences and Research

Jagpreet Sandhu, MDS
Professor, Department of Orthodontics, Genesis Institute of Dental Sciences and Research

Adesh S Manchanda, MDS
Senior Lecturer, Department of Oral Pathology, Sri Guru Ram Das Institute of Dental Sciences & Research