Case Report

Apert's Syndrome: A Rare Case Report

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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. Although it is inherited as an autosomal dominant trait, many cases are sporadic and present as de novo mutations arising from unaffected parents. The rarity of the syndrome and similarity of features with other craniosynostosis syndromes makes it a diagnostic dilemma. Genetic counselling and early intervention form an essential part of treatment. Because of the paucity of reported cases in Indian literature and typical features in oral cavity, a dentist should be competent to diagnose and form a part of the multidisciplinary management team. Here, we report a case of 18-year-old girl with characteristic clinical and radiographic features of Apert's Syndrome (AS).

Key words: *Apert's Syndrome, Craniosynostosis, Syndactyly.*

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 it as a triad of craniosynostosis, syndactyly and maxillary hypoplasia. [1] According to Cohen (1992), the prevalence of the syndrome is estimated to be approximately one in 65,000 newborns and accounts for about 4.5% of all cases of craniosynostosis [2]. More than 98% of cases with AS are caused by specific missense substitution mutations, involving adjacent amino acids (i.e., Ser252Trp, Ser252Phe, Pro253Arg) in the linker between the second and third extracellular immunoglobulin domains of fibroblast growth factor receptor 2(FGFR2), which maps to chromosome bands 10q25q26 [3]. The purpose of this case report is to focus on the assessment of clinical and conventional radiographic imaging of a patient with Apert syndrome and correlate it to the bone abnormalities of cranium, face, skull and syndactyly of hands and feet.

CASE DESCRIPTION

An 18-year-old girl reported to the department of oral medicine and radiology with the chief complaint of difficulty in chewing since past 2 months. Since the girl's facial appearance was not normal, medical and family history was taken in detail. Patient's parents gave history of impairment in hearing and complete blindness since birth. She was kept on regular follow up by a neurophysician because of her atypical facial appearances. She was referred to a neurosurgeon that carried out a skull surgery at 6 months of age. She was on medications for 2

months after surgery and then discontinued the medications on doctor's advice. No other relevant past medical/surgical history was present. Her mother had a normal delivery without any history of trauma, infection and drug used during the term. Mother's age at the time of birth was 37 years and father's age was 40 years. There were no anomalies reported in any siblings or near relatives.

On extraoral examination, obvious dysmorphic cranial and facial features like the enlarged cranial vault with maxillary hypoplasia and relative mandibular prognathism were found. Forehead was high and wide. Depressed nasal bridge, deviated nasal septum and wide beaked nose were present. Nose was short and wide with a bulbous tip giving a "parrot beaked" appearance. Other facial features included concave profile, short-incompetent upper lip and nonconsonant smile (Figure 1)**.** Ocular manifestations such as shallow orbits, hypertelorism, bilateral proptosis, exophthalmos, strabismus, and divergent squint were present. Upper eyelid having anti-mongoloid features was giving a frog-face appearance to the patient (Figure 2). Extremities and Digits showed syndactyly involving hands and feet giving Mitten-hands and Sock feet appearance. Nail beds were contiguous (synonychia) (Figure 3).

On intra oral examination, V-shape maxillary arch with high arched palate and pseudo-cleft in midline were present. Mucosal folding was observed on palatal mucosa extending from anterior part of hard palate to the anterior part of soft palate. Rugae were not appreciable. Malposed and ectopic eruption of teeth were present in upper arch. Shovel-shaped incisors were present in upper arch (Figure 4). In lower arch teeth missing in relation to 32 and 42. Posterior cross bite was observed along with anterior open bite. Skeletal Class III mal-occlusion was present (Figure 5). Patient was then subjected to radiological examination.

Orthopantomogram (OPG) depicts occlusion of only molars with an anterior open bite and dental crowding. Other bilateral findings included, thin and narrow condyles, maxillary sinus hypoplasia and elongated styloid processes (Figure 6). Lateral cephalogram showed depressed nasal bridge, retruded maxilla, relative mandibular prognathism, anterior open-bite and incompetent lips. Tie wires suggesting previous surgery were also observed (Figure 7). PA Skull radiograph showed cant of mandible on left side along with tie wires (Figure 8). Hand and wrist radiograph showed osseous syndactyly involving third and fourth fingers, cutaneous syndactyly involving second and third fingers, multiple synostosis involving distal phalanges and delta-shaped deformity of proximal phalanx of thumb (Figure 9).

Other systemic examination was found to be normal. Routine haematological and biochemical tests were within normal limits. Based on clinico-radiological evaluation a diagnosis of Apert's Syndrome was made.

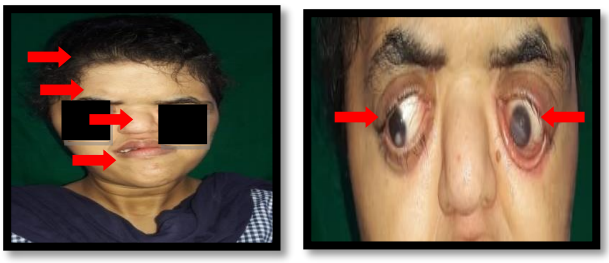

Figure 1: Extra oral photograph depicting cranial and facial manifestations.

Figure 2: Ocular manifestations like shallow orbits, hypertelorism, bilateral proptosis, exophthalmos, strabismus, divergent squint, and antimongoloid upper eye lid.

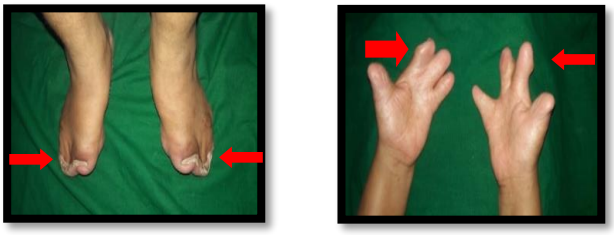

Figure 3: Syndactyly of hands and feet digits giving Mitten hands and sock feet appearance.

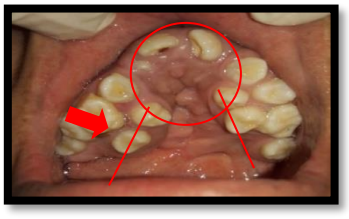

Figure 4: Intra oral photograph depicting V-shape maxillary arch, malposed and ectopic eruption of teeth. Mucosal folding is observed on hard palatal mucosa extending till anterior part of soft palate.

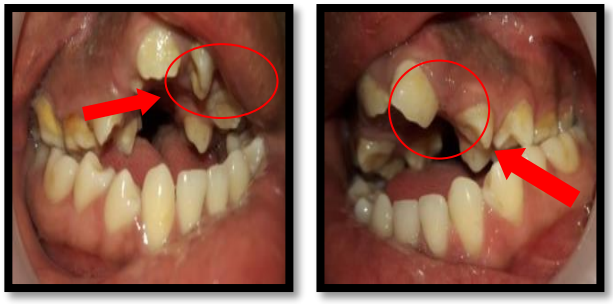

Figure 5: Posterior cross bite along with anterior open bite. Missing 32 and 42. Skeletal Class III mal occlusion is present.

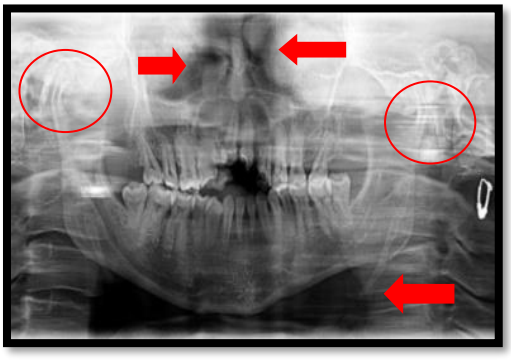

Figure 6: OPG showing occlusion of only molars with anterior open bite and dental crowding. Other findings like, thin and narrow bilateral condyles, bilateral maxillary sinus hypoplasia and bilateral elongated styloid processes were also present.

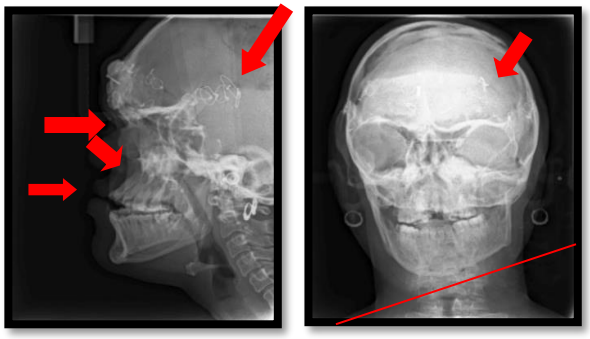

Figure 7: Lateral cephalogram showing depressed nasal bridge, retruded maxilla, relative mandibular prognathism, anterior open-bite, incompetent lips and tie wires suggesting previous surgery.

Figure 8: PA Skull radiograph showing cant of mandible on left side along with tie wires.

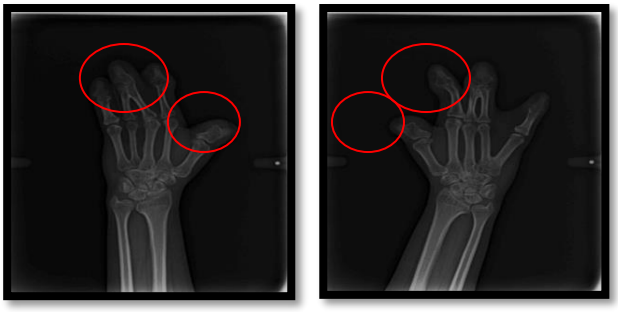

Figure 9: Hand and wrist radiograph showed osseous syndactyly involving third and fourth fingers, cutaneous syndactyly involving second and third fingers, multiple synostosis involving distal phalanges and delta- shaped deformity of proximal phalanx of thumb.

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) [4]. Apert's syndrome was described by Wheaton in 1894. In 1906, Apert published a summary on nine cases [5].

Molecular basis of Apert syndrome is very specific. AS is an autosomal dominant disorder caused due to mutation of fibroblast growth factor receptor-2 (FGFR-2) mapping to chromosomal bands 10q (10q25-26). Suture progenitor cells with mutated fibroblast growth factor receptors (FGFR2) cannot transduce signals from extracellular fibroblast growth factors (FGFs) and therefore do not produce the necessary fibrous material essential for a normal calvarial suture. Two different types of mutation have been demonstrated in the binding site between immunoglobulin like loop- 2, and immunoglobulin like loop -3 on fibroblast growth factor receptor -2 (FGFR2). Besides the intracellular signals oriented by FGFR, this growth factor receptor also plays an important role in the embryogenesis, and in its deficiency, premature gastrulation, implantation anomalies, impairment of epithelial-mesencyhmal interaction, and defects in membranous, and endochondral bone formation are seen [6].

The following etiological hypotheses have been proposed: Virus embryopathy following maternal

infection; antenatal drug consumption by mothers; an inflammatory process at the base of the skull; maldevelopment of the skull; and high paternal age [3].

The clinical and oral features of Apert's syndrome are well established and in agreement with the case described in the present report. 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 mid face is hypoplastic [7]. Ocular proptosis, down slanting of lateral canthus and palpebral fissures (antimongoloid slant), hypertelorism are present due to shortening of the bony orbit. There is depressed nasal bridge with deviated nasal septum. The maxilla is hypoplastic and retro positioned. The lips are bow shaped and often unable to form a lip seal [8].

Syndactyly (Greek *Syn* = together; *Dactylos* = digit) is a digital malformation in which adjacent fingers and/or toes are webbed because they fail to separate during limb development [9]. In Apert syndrome, syndactyly involves the hands and feet with partial to complete fusion of the digits, often involving second, third and fourth digits, and is often termed as mitten hands and sock feet [10].

Regarding the intraoral characteristics, a pseudo cleft due to the accumulation of the proliferated lateral palatal tissue mass was recorded in our patient. In Apert syndrome cases, the swellings are usually present in infancy and increase in mass as the child grows older. The cumulative tissues can proliferate to such an extent as to lead sometimes to a mistaken diagnosis of cleft palate. The prevalence of a real cleft palate was reported between 25 to 75% of Apert subjects [11].

As a common condition for Apert syndrome patients, in this clinical case, orthodontic anomalies and malocclusion were recorded, directly related to the maxillary hypoplasia. Malposed teeth generated a parallel row with normally erupted teeth. In patients with Apert syndrome, severe skeletal Class III open bite malocclusion can be observed due to the maxillary deficiency and the inclination of the upper jaw. The maxillary dental arch is V-shaped and there can be some compensatory growth of the alveolar base. Most probably, the alveolus thickens to accommodate the teeth that are impacted and crowded to an extreme degree in a small maxilla. The maxilla slants down posteriorly. As a result, open bite is common [12].

Intelligence varies from normal to subnormal in apert syndrome. Our patient had normal intelligence. Papilledema and optic atrophy with loss of vision may be present in cases of subtle increase in transcranial pressure [10]. Commonly associated systemic features include cardiac anomalies like atrial septal defect, patent ductus arteriosus, ventricular septal defect, and pulmonary stenosis. Gastro-intestinal, genitourinary, and respiratory symptoms like upper respiratory tract infections and sleep apnea may be present in a small percentage of cases [10]. Acne is usually severe, extensive, and resistant to treatment. Skin, eyes, and hair may show pigmentary dilution [13]. However, the case reported here did not present any related complaint of these anomalies during clinical examination.

Prominent cranial markings of the inner surface of cranial vault may be seen as multiple radiolucencies appearing as depressions resulting in hammered silver/beaten metal/copper beaten appearance on skull radiograph. A copper beaten skull indicates internal remodelling of the calvaria due to an increase in intracranial pressure, as a result of premature cranial suture fusions. [14] In present case, characteristic copper beaten skull was not observed and it can be linked to early surgical history given by the patient along with the presence of tie wires on lateral cephalogram and PA skull radiograph.

Ultrasonic 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 counselling [15].

Differential diagnosis of Apert syndrome includes Crouzon syndrome, Carpenter syndrome, and Pfeiffer syndrome. When compared to the Apert syndrome, in the Crouzon syndrome, extremities are unaffected, and craniofacial deformities with a milder course are noted; in the Pfeiffer syndrome, enlarged thumb and toes are typical; whereas in the Carpenter syndrome, the cloverleaf skull is a typical manifestation along with facial paralysis [16].

Due to the complexity of Apert syndrome, the treatment of these patients is multidisciplinary, with

approaches from various medical areas such as respiratory, cerebral, maxillo-facial, dental, ophthalmological and orthopedic. Developmental delay, abnormalities in central nervous system and extremities, as well as midface hypoplasia establish the need for multiple reconstructive surgeries and coordination with orthopedic and dental specialists [17].

Treatment of Apert syndrome should begin at birth with proper diagnosis. For the correction of craniosynostosis, craniectomy is performed during 6 months of age. Cosmetic correction for syndactyly of digits is done in first year of life and completed by 3 to 4 years of age whereas for midface deficiency and pseudo cleft between 4 to 6 years of age. Orthognathic surgery is performed after permanent teeth eruption and completion of growth. By using selective inhibitors of the FGFR-kinase domain, nonsurgical management of Apert syndrome may become a possibility in the future. Genetic counselling is an important factor as recurrence risk for an affected individual to have an affected offspring is 50% [18].

CONCLUSION

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. Thus, a team approach is essential to determine the best collaborative plan for the deficiencies of the child.

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