Apert Syndrome and Repercussions in Dental Medicine

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Abstract
Apert’s syndrome is a craniosynostosis syndrome caused by mutations in the gene coding for the fibroblast growth-factor receptor 2 (FGFR2), characterized by craniosynostosis, midface hypoplasia and syndactyly of the hands and feet. It has several oral manifestations, such as ogival palate, maxillary transverse and sagittal hypoplasia, dental crowding, eruptive delay and ectopic position of the teeth.

The diagnosis of Apert’s syndrome is established in a proband with classic clinical characteristics, and genetic tests can also be performed.

Patients with this syndrome often require craniofacial team care and dental, orthodontic and orthognathic surgical management because of their esthetic and functional problems such as Class III malocclusion and midface hypoplasia.

The aim of this study is to present a literature review on oral manifestations of Apert’s syndrome and their impact on dental medicine.

Keywords: Apert syndrome; Craniosynostosis; Oral abnormalities

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Introduction
Apert’s syndrome is a rare craniosynostosis, characterized by irregular craniosynostosis, hypoplasia of the middle third of the face and syndactyly of the hands and feet. This disorder is associated with genetic mutations on chromosome 10 (q25-10q26) in the fibroblast growth factor receptor 2 (FGFR2) coding gene, following an autosomal dominant inheritance pattern [1].

Some phenotypic features of this syndrome can be observed in the oral cavity, such as the ogival palate, transverse and sagittal maxillary hypoplasia, dental crowding, delayed eruption and ectopic positioning of the teeth. In some cases, it is possible to notice a pseudo prognathism, but usually the jaw has normal size [2].

Apert’s syndrome patients need care from a multidisciplinary craniofacial team that provides them with dental and surgical treatments for the various changes in the maxillofacial complex and oral cavity.

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The present study aims to describe the most common oral manifestations observed in Apert’s syndrome patients as well as the most used treatments.

**Materials and Methods**

The work consists of a bibliographic review about Apert’s syndrome, specifically addressing its oral manifestations and the impact of these changes on dentistry.

Search was performed on the following databases: PubMed Central, Cochrane Library and Scientific Electronic Library Online (SciELO). Google Scholar was also used. The keywords used in the search were: Apert’s syndrome, craniosynostosis, oral manifestations, dental treatment.

Priority was given to papers published between 2009 and 2019, but also those published prior to this period if considered relevant for the work. This led to the selection of a total of 54 bibliographic references.

**Apert’s Syndrome**

Apert’s syndrome, also called acrocephalosyndactyly, is a rare genetic anomaly with autosomal dominant inheritance that manifests at birth. It leads to abnormal development of the cranial cage and syndactyly of the hands and feet.

This syndrome was first described in 1906 by the French paediatrician Eugene Apert, who described nine people with similar features on the face and extremities [3].

**Aetiology**

In general, syndromic craniosynostosis with a particular genetic cause are more likely to involve multiple sutures or bilateral coronal sutures. The major genes responsible for the development of genetic syndromes associated with craniosynostosis are the genes of the fibroblast growth factor receptor (FGFR) family, especially FGFR1, FGFR2 and FGFR3. It may also be associated with mutations in the Twist1 gene, which functions as an upstream regulator of the FGFRs genes [4,5] or in the EFNB1 gene encoding fibrillin 1 [6].

One third of all craniosynostosis cases involve mutations in the FGFR1, FGFR2, FGFR3 and Twist1 genes [4], however, mutations in the FGFR genes may also be present in different syndromes [5].

FGFR protein plays a central role in mesenchymal and neuroectodermal cell growth and differentiation, since it is the binding site of fibroblast growth factor (FGF). This binding triggers the onset of the signal transduction cascade [7].

Since fusion of the cranial suture is regulated by the FGFR, changes in these receptors that lead to a signal transduction defect, resulting in restraint of the growth of the skull and the middle third of the face [8].

Members of the FGFR gene family encode a tyrosine kinase receptor, which has an extracellular portion consisting of domains such as immunoglobulins (IG-I, IG-II and IG-III), a transmembrane region and intracellular tyrosine kinase domains (TK1 and TK2) [9,10]. The signalling pathway operates mainly through three distinct pathways. The RAS/MAPK pathway begins with the formation of the FRS2 complex that regulates cell proliferation and differentiation. The PI3K/AKT pathway
controls the survival and fate of the cell, being also initiated through the formation of the FRS2 complex. Activation of the PKC pathway begins with the binding of PLCγ to activated FGFR and regulates cell morphogenesis and migration [11].

The development of Apert’s syndrome resulting from mutations in the FGFR2 gene [12,13], is related to paternal inheritance and advanced age [14]. In this gene, two nitrogenous base substitutions leading to amino acid changes have been described as responsible for the development of this syndrome: The Pro253Arg mutation resulting from the 758 C>G substitution [15] and the Ser252Trp mutation that results from the replacement 755 C> G [16]. The altered FGFR2 protein appears to lead to increased signalling cascade, promoting premature fusion of the skull, hands and feet.

The Ser252Trp mutation is known to be present in two-thirds of Apert’s syndrome individuals and has been associated with more severe craniofacial anomalies and dermatological disorders [17]. In turn, the Pro253Arg mutation is associated with more severe fusion of the fingers and toes [17,18].

A study of patients with the Ser252Trp mutation showed that fibroblasts with this mutation had a greater potential for osteogenic differentiation and increased expression of genes involved in osteogenic impairment, such as the genes associated with Apert’s syndrome [19]. Cells carrying this mutation show changes in gene expression of several members of the mitogen activated protein kinase (MAPK) signalling cascade. This led the authors to assume that this pathway may be implicated in Apert’s syndrome [19].

The periosseum is a source of cells for bone remodelling, but its role in the development of craniosynostosis still needs further characterization. Yeh et al. [20] evaluated the proliferation, migration and osteogenic differentiation of periossteal mesenchymal stem cells (MSCs) and fibroblasts from Apert syndrome patients and non-syndromic individuals. Results observed that the Ser252Trp mutation had opposite effects on different cell types: in individuals with this mutation, MSCs showed less proliferation and fibroblasts were larger when compared to individuals without this mutation. Only fibroblasts from individuals with the mutation had increased migration. The presence of this mutation was found to increase osteogenic differentiation that was reversed by inhibition of N-terminal c-Jun kinases (JNK). Therefore, these researchers proposed that periossteal cells play a greater role in premature fusion of cranial sutures than previously thought, and that JNK pathway molecules can be strong candidates for the treatment of Apert’s syndrome patients [20].

In most cases, multiple suture craniosynostosis are related to changes in a single gene or chromosomal abnormalities. Metabolic diseases such as mucopolysaccharidosis, exposure to teratogens, early postnatal shunt of hydrocephalus and craniofacial irradiation are rare causes of multiple suture craniosynostosis [21].

The essential pathological condition implicit in FGFR2-associated craniosynostosis is the activation of osteoblastic bone anabolism in calvary sutures. However, the results of clinical investigations indicate that abnormal cranial base cartilage development is the first developed abnormal site in Apert syndrome. This has led some researchers to evaluate the significance of cartilage growth in the cranial base in Apert syndrome [22]. It was observed, in an animal model with a mutation in the FGFR2IIIc gene (Apert syndrome type), lack of expression of this gene in osteoblasts. An exclusive rupture of chondrocyte differentiation was also observed and the growth reproduced Apert syndrome-like acrocephaly accompanied by a short anterior cranial base with fusion of cranial base synchondrosis, maxillary hypoplasia and synostosis of the calvary sutures, without significant changes in the extremities and the trunk. Analysis of gene expression indicated acceleration of
chondrocyte maturation and cranial base hypertrophy in $FGFR2IIIc$ transgenic animals [22]. In addition, affinity and specificity of the mutant receptor for FGF2 and FGF10 have been suggested as a possible mechanism of selective activation of the FGFR2 signalling cascade at the cranial base. These researchers concluded that the acrocephaly feature of Apert syndrome is not only the result of coronal suture synostosis, but also the result of primary disturbance in cranial base growth with early endochondral ossification [22].

**Signs and symptoms**

The main signs and symptoms of Apert syndrome are related to the abnormal growth of the skull and face, which makes the patient's head look long, with high forehead, sunken eyes accompanied in most cases by altered eyelid closure. In addition, other effects of abnormal skull growth include poor intellectual development, observed in most children diagnosed with Apert syndrome, obstructive sleep apnea, and recurrent ear infections [23].

Other phenotypic features of Apert syndrome include premature fusion of cranial sutures (craniosynostosis), midface hypoplasia, and syndactyly of hands and feet [24].

Moreover, a wide variety of significant central nervous system abnormalities are also associated with Apert syndrome, probably due to the common occurrence of mental deficiency in patients diagnosed with this syndrome [25].

Hypoplasia of the middle third of the face, which leads to a concave facial profile of patients, may lead to reduced volume of nasopharyngeal and oropharyngeal spaces. This, together with possible posterior nasal stenosis, can cause chronic mouth breathing, breathing problems, obstructive sleep apnea or sudden death [26].

Visual changes may also occur in these patients due to the presence of shallow orbits with ocular proptosis. Ophthalmologic sequelae such as refractive errors, divergent strabismus, amblyopia, exposure keratopathy, and optic nerve atrophy can be observed [27].

Moreover, approximately 90% of individuals with Apert syndrome have hearing loss. Internal ear anomalies and frequent otitis associated with epipharyngeal space obstruction and cleft palate are described as some of the main causes of hearing loss in these individuals [28].

Considerable speech loss and language difficulties are expected in these children as a result of the varying degrees of mental impairment developed by these patients. Other factors that may impair the speech of these individuals are marked hearing loss and deformations in oral structures [29].

Spontaneous speech in Apert syndrome patients becomes difficult due to a combination of various factors, such as hypernasality, articular and compensatory and intraoral joint errors, nasal escape, myofunctional problems such as facial muscle hypotonicity, and mouth breathing [23].

Visible craniofacial deconfiguration in Apert syndrome has a relevant psychosocial impact and may have a negative effect on speech and language development [30].
Oral and craniofacial manifestations

The oral cavity of individuals diagnosed with Apert syndrome is characterized by a reduced jaw size (maxillary hypoplasia), dental crowding, skeletal anterior open bite, unilateral crossbite, Angle Class III malocclusion, lip with inadequate posture, cleft palate, uvula bifida in 30% of the palates, upper and ogival palate, macroglossia, retained teeth, delayed and ectopic tooth eruption, supernumerary teeth and thick gum [31,32].

Reitsma et al. [33] evaluated vertical and horizontal facial growth in children with Apert and Crouzon syndromes by cephalometry in 62 patients, of whom 37 had Crouzon syndrome and 25 apert syndrome, with ages ranging from 3.9 to 32, and a control group of 482 non-syndromic children. This study found that throughout growth, craniofacial morphology was more severely affected in the Apert syndrome group, which exhibited a more retracted jaw and contained sagittal growth. In cases with reasonably normal mandibular growth, anterior rotation and more severe maxillomandibular discrepancy were observed during adolescence. However, vertical maxillary growth was not limited by body growth. Therefore, in these patients a counterclockwise rotation of the palatal plane in relation to the anterior cranial base is expected [33].

Another study found that patients with Apert syndrome had lower depth and length of the inferior arch, as well as lower intercanine width in the maxilla than individuals without this syndrome or having Crouzon syndrome [34].

Elmi et al. [35] demonstrated that the jaws of children diagnosed with Apert syndrome have slight deviations of perfect symmetry in bilateral structures. These deviations may be caused by environmental or genetic factors [35].

Recently, a systematic review has shown that the most frequently found maxillofacial changes in Apert syndrome patients are hypertelorism and proptosis, occipital flattening, frontal skeleton projection, and flat nasal bridge [32].

Apert syndrome without cleft palate can lead to complications, such as concave profile and a Class III skeletal relationship between the cranial base and the mandible [36].

Children with Apert syndrome often have dental anomalies, such as those described above as well as enamel opacity and abnormal occlusal relationships, which require orthodontic and/or buco maxillofacial surgical treatment [30]. Upper canine agenesis is typical in these children and enamel opacity occurs in more than 40% of cases. Ectopic eruption of the first permanent upper molars is a common feature in these children [30].

The incidence of morphological and functional deformations in Apert syndrome may be variable among affected individuals. There are multiple patterns of premature fusion of the cranial vault sutures, being the most common the bilateral coronal synostosis. The cranial vault suture is related to the cranial base and facial features, being probably the anatomical site of disordered growth [37].

Considering the cranial vault suture synostosis, some authors classify Apert syndrome in three subtypes [38]. This classification is based on the complete premature closure of sutures addressing the similarities and differences between them in order to propose individualized treatment plans. The class I subtype is bilateral coronal synostosis, with involvement of the most significant nasopharyngeal area in the vertical direction. Class II is pansynostosis and class III corresponds to synostosis with perpendicular combination, which can be classified into class IIIa (unilateral coronal and metopic synostosis), class IIIb (sagittal synostosis with bilateral/unilateral lambdoid synostosis), and class IIIc (others) [38]. Classes II and III
have the most limited oropharyngeal space. Tomographic evaluations of 31 Apert syndrome patients and 51 control subjects showed that 55% were class I, 19% class II, 10% class IIIa and 6% class IIIb [38].

Apert syndrome patients have mucosal hyperplasia. In order to characterize tissue changes in the oral mucosa of these individuals, Sgarbosa [39] evaluated the proportion of tissue elements and extracellular matrix components related to the FGF/FGFR signalling pathway and the organization of collagen fibbers. Histological analysis of the excised patient tissues showed connective hyperplastic epithelium with thick collagen fibbers and notorious presence of fibroblasts. No significant difference in the proportion of fibrous connective tissue components was observed. At histochemical level, accumulation of glycosaminoglycans was found. Immunohistochemistry confirmed the presence of collagen types I and II in the tissues of patients with this syndrome. This author concluded that palatal mucosal hyperplasia of these patients’ results from tissue growth without the predominance of any of the connective tissue components [39].

A clinical and radiographic study involving nine patients with Apert syndrome, aged 6 to 15 years, not previously undergoing orthodontic or orthognathic treatment, found dental agenesis, especially of the upper canines, and enamel opacities, ectopic eruption of the first upper molars and lateral volumetric enlargements of the palatal mucosa in 88.8% of patients [40].

**Diagnosis**

Given that the causes of craniosynostosis are very heterogeneous with monogenic, chromosomal, polygenic and environmental/teratogenic factors, all playing an important role, the specific genetic diagnosis for each type of craniosynostosis can only be identified in a quarter of patients with craniosynostosis [41].

Generally, as soon as a baby is born and has a "strange" appearance, with a distorted shape of the head and face, doctors suspect that the newborn may have Apert syndrome. Confirmation of this suspicion is made by genetic tests [42].

In the development of Apert syndrome a spectrum of mutations including point mutations in exon IIIa, three insertions of the Alu sequence and one deletion in the FGFR2 gene have been identified. Although this mutation spectrum is quite restricted, affected individuals show a phenotype with drastic variability, indicating genetic heterogeneity. Moreover, other genetic syndromes such as Pfeiffer, Crouzon, Jackson-Weiss, Muenke and Saethre-Chotzen have phenotypic characteristics that overlap with those of Apert syndrome, which complicates clinical diagnosis. In this context, molecular identification plays an important criterion in these heterogeneous syndromes resulting from mutations in protein coding genes involved in the signalling cascade. For this reason, several molecular diagnostic techniques have been very useful in confirming the diagnosis of this syndrome [43].

Diagnosis of a particular craniosynostosis, such as Apert syndrome, may be performed prenatally or may require clinical examination after birth, and in some cases molecular analysis may be required. In the prenatal period, it is crucial to distinguish isolated non-syndromic cases from syndromes so that adequate family counselling is possible [44].

A study by Werner et al. [45] made prenatal diagnosis of three cases of Apert syndrome using imaging exams such as two-dimensional (2D) and three-dimensional (3D) ultrasound, magnetic resonance imaging (MRI), and 3D physical/virtual models. At diagnosis, gestational age was 32 weeks and average maternal age was 36.5 years. In two cases, pregnancy was terminated and fetal autopsies confirmed the diagnosis. The diagnosis of the third case was confirmed by genetic evaluation
during the postnatal period. On 2D and 3D ultrasound and MRI images, craniosynostosis, hypertelorism, low atrial implantation, enlarged kidney dimensions, and syndactyly of the hands and feet were observed. The 3D physical/virtual models allowed the identification of anomalies in the fetal head and extremities [45].

The dentist should be able to make an early diagnosis of Apert syndrome by the recognition of the main clinical features and provide the appropriate treatment to the patient [46].

**Social and psychological impact**

The human face is the result of the evolution and adaptation of the human being to social life and plays a relevant role in the expression of individual identity and emotional states, contributing to social interactions and personality development. The face and lips form a dynamic frame that is constantly changing during speech, smile, or as an integral form of facial expression which, from a psychosocial point of view, influences the individual [47].

Individuals with Apert syndrome, due to notorious craniofacial changes, can be viewed by society as socially disabled. Certainly, problems related to emotional affections, functional deficiencies associated with malformations of the hands, the tension caused by surgical corrections, and the possible negative social experiences caused by facial disfigurement, place individuals with Apert syndrome at risk for emotional and behavioural problems. Children with craniofacial anomalies, such as those of Apert syndrome, show dissatisfaction with social appearance that is related to higher loneliness, fewer friends, social exclusion and peer dislike [48].

Potential problems in these children include poor cognitive development, negative emotional attachment between child and parent, poor development of peer relationships, and experience of shame [49].

**Treatment**

Due to the complexity of Apert syndrome, the treatment of these patients is multidisciplinary, with approaches from various medical areas such as respiratory, cerebral, maxillomandibular, dental, ophthalmological and orthopedic. Developmental delay, central nervous system and extremities abnormalities, as well as third midface hypoplasia, establish the need for multiple reconstructive surgeries and coordination with orthodontic and dental specialists [50].

The treatment can be performed at different times, from birth to 2 years of age, during the growth period, or even in adulthood. From birth to 2 years of age, therapeutic approaches are surgical and often immediate, especially in cases of brain, respiratory and ocular bulb emergencies [51].

According to Wilkie et al. [41], as markers are now becoming available to mark suture cells at different stages of differentiation, a deeper and more detailed understanding of the complex processes implicit in normal suture homeostasis may eventually lead to prevention strategies or therapies for craniosynostosis. These authors also emphasized that, for now, surgery remains the cornerstone of treatment, although lack of consensus on time and surgical approaches remains a persistent issue in this field [41].

**Treatment of changes in the oral cavity**
During the growth period, in addition to surgical interventions, dentistry contributes to dental and orthodontic therapies to monitor tooth eruption, prevent tooth decay, guide tooth eruption and allow teeth to be aligned in the arches. In adulthood, in cases of skeletal class III malocclusion accompanied by open bite resulting from maxillary malformation, treatment is surgical by Le Fort I osteotomy and sagittal separation osteotomy of the mandible. In addition, tooth eruption should be closely monitored due to the need for teeth alignment [51].

The treatment plan that combines orthodontic interventions and orthognathic surgery can significantly improve the occlusal function and aesthetics of Apert syndrome patients [23].

In these patients, dental treatments are provided simultaneously with the execution of surgical and orthodontic treatment during all phases of the reconstructive process. In mixed dentition, the main goal of the orthodontic treatment of these patients is used to solve problems related to aberrant eruption of permanent teeth and create favourable conditions that influence occlusion when the advancement of the middle third of the face is planned. In adolescent patients with Apert syndrome, orthodontic treatment is always necessary to prepare them for orthognathic surgery, which usually involves upper arch extractions [52].

Apert syndrome patients have poor oral hygiene. Studies indicate higher accumulation of dental plaque and gingivitis in children with this syndrome [40,53].

Many of these patients have enlarged palate mucosa and, in these cases, placement of orthodontic bands and accessories may require surgical excision of hypertrophied palatine tissue [54].

According to a study by Susami et al. [55], many patients with Apert syndrome may undergo the procedure of advancing the middle third of the face, but it is desirable that before this procedure the patient be evaluated by the orthodontist, as orthodontic treatment may be necessary. Advancing the middle facial third before age six has a high risk of injuring the upper molars [55].

**Discussion**

Patients with some type of syndromic craniosynostosis, including those diagnosed with Apert syndrome, have an identifiable genetic cause for early closure of the cranial sutures. In the case of this syndrome, mutations in the FGFR2 gene located on chromosome 10 (q25-10q26) [1,4,5,12,13]. Most of these mutations occur by nitrogen base substitution that leads to a gain of function [27]. These gain of function mutations are responsible for the type of inheritance observed in Apert syndrome, an autosomal dominant transmission [10,27]. However, this syndrome can arise from de novo mutations [41].

Current evidence indicates that premature closure of the cranial, hand and foot sutures, whether multiple sutures or bilateral coronal sutures, is related to the presence of altered FGFR2 protein, which appears to lead to increased signalling cascade [7,8,10,11,17,18].

The role of FGFR in mesenchymal and neuroectodermal cell growth and differentiation is well established in the literature, regulating the fusion of cranial sutures [7,8]. Therefore, any changes in the FGFR family produce signal transduction defects and, consequently, early closure of these sutures, resulting in restraint of cranial growth and midface [8]. In the case of Apert
syndrome, the Ser252Trp mutation is related to more severe craniofacial anomalies and dermatological disorders [17], whereas the Pro253Arg mutation is associated with more severe fusion of the fingers and toes [17,18].

Fibroblasts with the Ser252Trp mutation have been shown to have altered gene expression of several members of the MAPK signalling cascade, indicating that this pathway may be implicated in Apert syndrome [19]. Another study found that the presence of this mutation increased osteogenic differentiation, and that fibroblasts from individuals with the Ser252Trp mutation may induce osteogenic differentiation in periosteal MSCs, but not in MSCs from another tissue, indicating that periosteal cells play a greater role in premature fusion of cranial sutures of Apert syndrome patients [20].

Apert syndrome can be diagnosed during the gestational period (prenatal), immediately after birth or throughout the individual's life [43,44]. Several studies have emphasized the importance and feasibility of prenatal diagnosis through genetic [42-44,46] and imaging assays [45].

Since patients with Apert syndrome have many oral changes, treatment needs are also high. Therefore, the dentist should be aware of the oral changes resulting from this syndrome in order to establish a treatment plan suitable for the patient.

Studies show agreement on the need for orthodontic assessment and treatment prior to facial surgery in order to create a favourable environment for the occlusal and aesthetic function of the patient [23,51,52,55].

There is a logical and rational sequence of the surgical plan of these patients, which can be organized into different stages: (i) correction of craniofacial changes, which aims to perform surgical decompression for normal brain growth; (ii) advancement of the middle third of the face to improve air-nasal flow; (iii) and orthognathic surgery, which allows functional and aesthetic correction [23,51,52,55].

**Conclusion**

Based on the data presented in this study, it can be concluded that the dentist plays a relevant role in the treatment of patients with Apert syndrome, considering the impact that its maxillofacial and oral manifestations have on patient’s health, significantly affecting their quality of life.

The dentist needs to understand the importance of oral disorders associated with Apert syndrome and be able to propose a treatment plan appropriate to the needs of individuals affected by this pathology.

**Conflict of Interest**

The authors and planners have disclosed no potential conflicts of interest, financial or otherwise.

**References**


