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ETIOLOGY, SYMPTOMS AND TREATMENT OF APERT SYNDROME, A CONGENITAL DISORDER: AN OVERVIEW

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ABSTRACT

Apert syndrome is a genetic disorder characterized by the premature fusion of certain skull bones (craniosynostosis). This early fusion prevents the skull from growing normally and affects the shape of the head and face. In addition, a varied number of fingers and toes are fused together (syndactyly).Many of the characteristic facial features of Apert syndrome result from the premature fusion of the skull bones. The head is unable to grow normally, which leads to a sunken appearance in the middle of the face, bulging and wide-set eyes, a beaked nose, and an underdeveloped upper jaw leading to crowded teeth and other dental problems. Shallow eye sockets can cause vision problems. Early fusion of the skull bones also affects the development of the brain, which can disrupt intellectual development. Cognitive abilities in people with Apert syndrome range from normal to mild or moderate intellectual disability.

Individuals with Apert syndrome have webbed or fused fingers and toes. The severity of the fusion varies; at a minimum, three digits on each hand and foot are fused together. In the most severe cases, all of the fingers and toes are fused. In the present article, we have concentrated on etiology, causes, symptoms, pathophysiology and treatment of Apert syndrome.

KEYWORDS

Apert syndrome, Apert's syndactyly, acrocephalosyndactyly, malocclusion and congenital disorder.

INTRODUCTON

Apert syndrome is a congenital condition marked by a peaked head, webbed fingers and toes. Oral manifestations include cleft palate or uvula, a prognathic mandible, and maxillary hypoplasia, resulting in extreme malocclusion[1]. Apert syndrome is a form of acrocephalosyndactyly, a congenital disorder characterized by malformations of the skull, face, hands and feet. It is classified as a branchial arch syndrome, affecting the first branchial (or pharyngeal) arch, the precursor of the maxilla and mandible.

Disturbances in the development of the branchial arches in fetal development create lasting and widespread effects.In 1906, Eugène Apert, a French physician, described nine people sharing similar attributes and characteristics[2, 3]. Linguistically, “acro” is Greek for “peak,” referring to the “peaked” head that is common in the syndrome. “Cephalo”, also from Greek, is a combining form meaning “head”. “Syndactyly” refers to webbing of fingers and toes. In embryology, the hands and feet have selective cells that die, called selective cell death or apoptosis, causing separation of the digits. In the case of acrocephalosyndactyly, selective cell death does not occur and skin, and rarely bone, between the fingers and toes fuses. Apert syndrome occurs in approximately 1 per 160,000 to 1 per 200,000 live births[4]. Prevalence is estimated at 1 in 65,000 (approximately 15.5 in 1,000,000) live births[5, 6, 7]. Apert syndrome accounts for 4.5% of all cases of craniosynostosis.

ETIOLOGY AND CAUSES OF APERT SYNDROME

Acrocephalosyndactyly may be an autosomal dominant disorder. Males and females are affected equally; however research is yet to determine an exact cause. Nonetheless, almost all cases are Sporadic, signifying fresh mutations or environmental insult to the genome. The offspring of a parent with Apert syndrome has a 50% chance of inheriting the condition. In 1995, A.O.M. Wilkie Published a paper showing evidence that acrocephalosyndactyly is caused by a defect on the fibroblast growth factor receptor 2 gene, on chromosome 10 [8].More than 98% of cases with Apert syndrome are caused by specific missense substitution mutations, involving adjacent amino acids (i.e., Ser252Trp, Ser252Phe, Pro253Arg) in the linker between the second and third extra cellular immunoglobulin domains of *FGFR2*, which maps to chromosome bands 10q26. The remaining cases are due to Alu-element insertion mutations in or near exon 9 of *FGFR2*. Most cases are sporadic, resulting from new mutations with a paternal age effect. The incidence of *FGFR2* mutations increases exponentially with paternal age, probably due to an increase in the frequency of these mutations and a selective advantage in the male germ line[9, 10]. Most new mutations, estimated at 1 per 65,000 live births, imply that germ line transversion rates at these 2 positions are currently the highest known in the human genome. The rarity of familial cases can be explained by reduced genetic fitness of individuals because of severe malformations and the presence of mental retardation in many cases.

PATHOPHYSIOLOGY OF APERT SYNDROME

During early infancy (<3 month), the coronal suture area is prematurely closed. A bony condensation line beginning at the cranial base and extending upward with a characteristic posterior convexity represents this occurrence. Anterior and posterior fontanelles are widely patent. The midline of the calvaria has a gaping defect, extending from the glabellar area to the posterior fontanelle via the metopic suture area, anterior fontanelle, and sagittal suture area. The skull with a gaping midline defect appears to permit adequate accommodation of the growing brain. The lambdoidal sutures appear normal in all cases[11].

During the first 2-4 years of life, the midline defect is obliterated by coalescence of the enlarging bony islands without evidence of any proper formation of sutures. An extreme short squama and orbital part of the frontal bone together with the posterior convexity of the coronal bone condensation line suggest that growth inhibition in the sphenofrontal and coronal suture area has its onset very early in fetal life.

Unique fibroblast growth factor receptor 2 (*FGFR2*) mutations lead to an increase in the

number of precursor cells that enter the osteogenic pathway. Ultimately, this leads to increased subperiosteal bone matrix formation and premature calvaria ossification during fetal development. The order and rate of suture fusion determine the degree of deformity and disability. Once a suture becomes fused, growth perpendicular to that suture becomes restricted, and the fused bones act as a single bony structure. Compensatory growth occurs at the remaining open sutures to allow continued brain growth; however, complex, multiple sutural 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[12] .

The first genetic evidence that syndactyly in Apert syndrome is a keratinocyte growth factor receptor (*KGFR*)-mediated effect was provided by the observation of the correlation between *KGFR* expression in fibroblasts and severity of syndactyly. Patients with Ser252Trp and those with Pro253Arg have different phenotypic expression. The syndactyly is more severe with Pro253Arg mutation for both hands and feet, whereas cleft palate is significantly more common with Ser252Trp mutation.

Amblyopia and strabismus is more common in patients with the *FGFR2* Ser252Trp mutation, and optic disc pallor is more frequent in patients with the *FGFR2* Pro253Arg mutation. Patients with *FGR2* Ser252Trp mutations have a significantly greater prevalence of visual impairment compared with patients with the *FGFR2* Pro253Arg mutation [13].

CLINICAL FEATURES, SIGNS AND SYMPTOMS OF APERT SYNDROME

The spectrum of abnormalities in Apert syndrome has recently been described along with current recommendations for orthodontic treatment[14]. Many of the characteristic facial features of Apert syndrome result from the premature fusion of the skull bones. The head is unable to grow normally, which leads to a sunken appearance in the middle of the face, bulging and wide-set eyes, a beaked nose, and an underdeveloped upper jaw leading to crowded teeth and other dental problems. Shallow eye sockets can cause vision problems. Early fusion of the skull bones also affects the development of the brain, which can disrupt intellectual development. Cognitive abilities in people with Apert syndrome range from normal to mild or moderate mental retardation.

Individuals with Apert syndrome have webbed or fused fingers and toes. The severity of the fusion varies; at a minimum, three digits on each hand and foot are fused together. In the most severe cases, all of the fingers and toes are fused. Less commonly, people with this condition may have extra fingers or toes (polydactyly). Additional signs and symptoms of Apert syndrome can include hearing loss, unusually heavy sweating (hyperhidrosis), oily skin with severe acne, patches of missing hair in the eyebrows, fusion of spinal bones in the neck (cervical vertebrae), and recurrent ear infections that may be associated with an opening in the roof of the mouth (a cleft palate). Apert syndrome patients also have characteristic abnormalities in other bones, including the shoulders, elbows, hips, knees, and ribs[15]. Some symptoms of Apert syndrome may be summarized in Table1.

Table 1:- Symptoms of Apert syndrome

- Early closure of sutures between bones of the skull, noted by ridging along sutures
- Frequent ear infections
- Fusion or severe webbing of the 2nd, 3rd, and 4th fingers, often called "mitten hands"
- Hearing loss
- Large or late-closing soft spot on a baby's skull
- Possible, slow intellectual development (varies from person to person)
- Prominent or bulging eyes
- Severe under-development of the mid-face
- Skeletal (limb) abnormalities
- Short height
- Webbing or fusion of the toes

TREATMENT OF APERT SYNDROME

MEDICAL CARE

- Medical management of Apert syndrome includes the following[16, 17, 18].
  - Protection of the cornea
    - Instill lubricating bland ointments in the eyes at bedtime to protect corneas from desiccation
    - Artificial teardrops during the day
  - Upper airway obstruction during the neonatal period
    - Remove excessive nasal secretions
    - Treat upper airway infection
    - Humidification with added oxygen
    - Judicious use of topic nasal decongestants
  - Sleep apnea
    - Polysomography (a sleep recording of multiple physiologic variables), currently the most reliable method for determining the presence of sleep apnea
    - Continuous positive pressure
  - Chronic middle ear effusion associated with bilateral conductive hearing deficit - Antimicrobial therapy
  - Psychological and social challenges confronted by individuals with Apert syndrome
    - Emotional adjustment
    - Body image development
    - Impact of surgery and hospitalization on children with Apert syndrome.

SURGICAL CARE

- Surgical management[19] of Apert syndrome includes the following:

- Protection of the cornea: Lateral or medial tarsorrhaphy is performed in severe cases to narrow the palpebral fissure cosmetically and to protect the corneas and the vision.
- Upper airway obstruction during the neonatal period: This rarely requires orotracheal intubation.
- Sleep apnea: Tracheostomy is indicated in severely affected children.
- Chronic middle ear effusion associated with bilateral conductive hearing deficit: Bilateral myringotomy and placement of ventilation tubes are the most effective treatment.
- Cranial surgery
  - Removes synostotic sutures
  - Reshapes the calvaria
  - Allows more normal cranial development to proceed with respect to shape, volume, and bone quality
  - Relieves increased intracranial pressure
- Orbital surgery
  - Correction of ocular proptosis
  - Reduction of increased interorbital distance (hypertelorism)
  - Correction of increased interior malrotation
- Nasal surgery
  - Infants and children: Nasal reconstruction focuses on correction of the excessively obtuse nasofrontal angle, flat nasal dorsum, and ptotic nasal tip.
  - Teenagers and adults: Reduction of the nasal tip bulk is indicated.
- Midfacial surgery
  - Normalization of midface appearance
  - Expansion of the inferior orbit
  - Volumetric expansion of the nasal and nasopharyngeal airways
  - Establishment of a normal dentoskeletal relationship
- Mandibular surgery: Mandibular osteotomies are performed to improve dentoskeletal relations for masticatory and aesthetic benefit.

- Other surgical approaches
  - Surgical care involves early release of the coronal suture and fronto-orbital advancement and reshaping to reduce dysmorphic and unwanted skull growth changes. Craniosynostosis requires multistaged operative procedures. A significant cosmetic improvement is possible. Initial surgery is often performed as early as age 3 months.
  - Facial cosmetic reconstruction for dysmorphisms is indicated.
  - A new technique of craniofacial disjunction, followed by gradual bone distraction (Ilizarov procedure), has been reported to produce complete correction of exophthalmos and improvement in the functional and aesthetic aspects of the middle third of the face without the need for bone graft in patients aged 6-11 years.
  - Surgical separation of digits (mitten-glove syndactyly) provides relatively little functional improvement
  - Shunting procedure reduces intracranial pressure[20].
  - For orthodontic treatment, most patients require 2-jaw surgery (bilateral sagittal split osteotomy with mandibular setback and distraction in the maxilla). During the period of distraction, the orthodontist guides the maxilla into final position using bite planes and intermaxillary elastics

CONCLUSION

It may be concluded that Apert syndrome is a rare autosomal dominant disorder characterized by craniosynostosis, craniofacial anomalies, and severe symmetrical syndactyly (cutaneous and bony fusion) of the hands and feet. It is an inherited disorder of the bones and connective tissues that leads to a characteristic pattern of deformities in the head, hands, and feet, which consequentially impact many aspects of normal development. There is an effective therapy both medically & surgically; further consultations of Neurosurgeon, Plastic surgeon, Oromaxillofacial surgeon, Craniofacial anesthesiologist, Radiologist ,Otorhinolaryngologist, Orthodontist, Dentist, Orthopedist, Ophthalmologist, Clinical geneticist, Developmental pediatrician, Neurologist, Psychiatrist, Psychologist, Audiologist, Speech pathologist and Physical and occupational therapy specialist may be required time to time. Family members of people with Apert syndrome will also need help in coping with the stresses of the disease. Social and psychiatric support can help with family relationships and antisocial behavior. Family therapy and genetic counseling are often useful for alleviating family conflict and stressors related to relationship losses. For patient suffering from Apert syndrome, behavioral treatment is likewise a useful strategy for minimizing social isolation and lack of social stimulation.

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