Apert Syndrome- A Review

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Abstract

Apert syndrome, also called acrocephalosyndactyly, is a genetic syndrome characterized by anomalies of the skull, face and limbs. Gene mutations are responsible for causing the early fusion of the skull, hand and feet bones.Apert syndrome is a genetic disorder that causes abnormal development of the skull. Babies with Apert syndrome are born with a distorted shape of the head and face. Many children with Apert syndrome also have other birth defects. Apert syndrome has no cure, but surgery can help correct some of the problems that result.

Key words: Apert syndrome, Craniosynostosis, Acrocephalosyndactyly, Fibroblast Growth Factor Receptor 2

Introduction

Apert syndrome is another genetically inherited syndrome characterized by craniosynostosis (premature fusion of coronal sutures) resulting in skull and facial deformities and syndactyly. The syndrome was first described in 1906 by French physician Eugene Apert when he described nine people with similar facial and extremity characteristics.[1]Syndromiccraniosynostoses such as Crouzon, Apert, Pfeiffer syndromes not only affect multiple sutures, but are also associated with the presence of additional clinical symptoms, including hand and feet malformations, skeletal and cardiac defects, developmental delay, and others.The cranial malformations are the most apparent effects of acrocephalosyndactyly. Craniosynostosis occurs, in which the cranial sutures close too soon, though the child's brain is still growing and expanding. Brachycephaly is the common pattern of growth, where the coronal sutures close prematurely, preventing the skull from expanding frontward or backward and causing the brain to expand the skull to the sides and upwards. This results in another common characteristic, a high, prominent forehead with a flat back of the skull. Due to the premature closing of the coronal sutures, increased cranial pressure can develop, leading to mental deficiency. A flat or concave face may develop as a result of deficient growth in the mid-facial bones, leading to a condition known as pseudo mandibular prognathism. Other features of acrocephalosyndactyly may include shallow bony orbits and broadly spaced eyes. Low-set ears are also a typical characteristic of branchial arch syndromes.

Etiology

Apert syndrome is an autosomal dominant inherited craniosynostosis syndrome. It is due to gain-of-function missense mutation of fibroblast growth factor receptor(FGFR2)-2 on chromosome 10q.[2]The etiology of craniosynostosis may involve genetic (also somatic mosaicism and regulatory mutations) and epigenetic factors, as well as environmental factors.Apert syndrome is caused by a rare mutation on a single gene. This mutated gene is normally responsible for guiding bones to join together at the right time during development. In almost all cases, the Apert syndrome gene mutation seems to be random. Only about one in 65,000 babies is born with Apert syndrome.

Epidemiology

Apert syndrome is a rare disease and is estimated to occur in 1 in 65,000 to 200,000 births depending on the study cited.[3] Both genders are equally affected. The incidence of the disease significantly increases with paternal age and is felt to provide a selective advantage within the male spermatogonial cells.[4]The syndrome has complete

penetrance but variable expressivity resulting in phenotypically unaffected to severe deformities within the same family.Observed mutation rates in humans appear higher in male than female gametes and often increase with paternal age. This bias, usually attributed to the accumulation of replication errors or inefficient repair processes, has been difficult to study directly.

Frequency and Inheritance

Apert syndrome is an extremely rare condition. The number of people who have it is not known, and estimates vary between sources.The U.S. National Library of Medicine estimate that it affects 1 in 65,000 to 88,000 newborns, and the National Organization for Rare Disorders (NORD) estimate that the figure is closer to 1 in 165,000 to 200,000 births.Most cases of Apert syndrome appear with no previous family history of the disorder. However, the NORD also report that when one parent has the disorder, the child will have a 50 percent chance of developing it. This statistic applies to each pregnancy.This syndrome appears to affect males and females equally.[2]

Pathophysiology

Two-thirds of cases of Apert syndrome are due to a specific cysteine to guanine mutation at position 755 of the Fibroblast Growth Factor Receptor 2 (FGFR2) gene resulting in a serine to tryptophan amino acid change on the paternally derived allele.[5]The incidence of the disease increases with the age of the father. Unfortunately, there are only hypotheses as to why both the extremities and cranial sutures are affected, and some data from a single mouse model. In mice, the FGFR2 receptor loses its specificity and can bind other fibroblast growth factors thereby suppressing apoptosis of osteoblasts resulting in syndactyly and craniosynostosis. The underlying mechanism is still not clear even in this mouse model, but it is linked to a specific FGF.[6]Apert syndrome (AS) is a severe congenital disease caused by mutations in fibroblast growth factor receptor-2 (FGFR2), and characterised by craniofacial, limb, visceral, and neural abnormalities.

History

The family history of patients suspected of having Apert syndrome is crucial due to its autosomal dominant inheritance. A lack of family history does not rule out the diagnosis due to the possibility of de novo mutations; however, a positive family history makes the diagnosis much more likely.Patients with Apert syndrome have craniosynostosis, midface hypoplasia, and symmetric syndactyly of the hands and feet. The craniosynostosis is more severe than that found in Crouzon syndrome, and the additional finding of syndactyly helps confirm the diagnosis between multiple, similar syndromes in regard to their phenotype. However, features of hypertelorism (wide-set eyes), proptosis (bulging eyes), and down-slanting palpebral fissures are facial features found in several of the craniosynostosis that cannot be used to differentiate the syndromes but are helpful.

Clinical Features

The defective gene in babies with Apert syndrome allows the skull bones to fuse together prematurely, a process called craniosynostosis. The brain continues to grow inside the abnormal skull, putting pressure on the bones in the skull and face.

The abnormal skull and facial growth in Apert syndrome produce its main signs and symptoms:

- A head that is long, with a high forehead
- Wide-set, bulging eyes, often with poorly closing eyelids
- A sunken middle face

Other Apert syndrome symptoms also result from the abnormal skull growth:

- Children often get sick.
- Poor intellectual development (in some children with Apert syndrome)
- Obstructive sleep apnea
- Repeated ear or sinus infections
- Hearing loss
- Crowded teeth due to underdevelopment of the jaw

- Abnormal fusion of the bones of the hands and feet (syndactyly) -- with webbed or mitten-like hands or feet -- are also common. Some children with Apert syndrome also have heart, gastrointestinal, or urinary system problems.[4,5,6]

Evaluation

The evaluation for Apert syndrome is a clinical one as the characteristic physical examination findings confirm the diagnosis. In cases where the clinical presentation is not clear and no family history to support the diagnosis, additional tests such as advanced imaging techniques can help. Magnetic resonance imaging (MRI) and computed tomographic (CT) imaging of the brain are used to detect craniosynostosis or other skeletal abnormalities (perisutural sclerosis, reduced serration, and bony bridging and/or the absence of the suture altogether). These same imaging techniques can be helpful in detecting complications related to the syndrome such as increased intracranial pressure. The history, physical, and imaging findings are used to confirm the specific craniosynostosis but can be difficult due to significant overlap amongst the craniofacial syndromes.Much like that discussed with Crouzon syndrome in which there is an unclear diagnosis, or the syndrome has atypical features, genetic and molecular testing can be pursued. Unfortunately, the underlying mechanism of multiple craniosynostosis syndromes is related to FGFR mutations and abnormal signalling. Prenatal genetic testing, MRI, and ultrasounds can be utilized to confirm the diagnosis before the birth of the child.[7]

Treatment

Apert syndrome has no known cure. Surgery to correct the abnormal connections between bones is the main treatment for Apert syndrome.[8]

In general, surgery for Apert syndrome takes place in three steps:

1. Release of skull bone fusion (craniosynostosis release). A surgeon separates the abnormally fused skull bones and partially rearranges some of them. This surgery is usually performed when a child is between ages 6 and 8 months.
2. Midface advancement. As the child with Apert syndrome grows, the facial bones again become misaligned. A surgeon cuts the bones in the jaw and cheeks and brings them forward into a more normal position. This surgery may be done at any time between ages 4 and 12. Additional corrective surgery may be needed, especially when midface advancement is done at a young age.
3. Correction of wide-set eyes (hypertelorism correction). A surgeon removes a wedge of bone in the skull between the eyes. The surgeon brings the eye sockets closer together, and may adjust the jaw, too.

Other Apert syndrome treatments include:

Eyedrops during the day, with lubricating eye ointment at night; these drops can prevent the dangerous eye drying that can occur in Apert syndrome.

Continuous positive airway pressure (CPAP); a child with Apert syndrome and obstructive sleep apnea may wear a mask at night, attached to a small machine. The machine delivers pressure that keeps the child's airways open during sleep.

Antibiotics. Children with Apert syndrome are prone to ear and sinus infections caused by bacteria, requiring antibiotic therapy.

Surgical tracheostomy, or placement of a breathing tube in the neck; this surgery may be done for children with severe obstructive sleep apnea due to Apert syndrome.

Surgical placement of ear tubes (myringotomy), for children with repeated ear infections due to Apert syndrome

Other surgeries may be beneficial for certain children with Apert syndrome, depending on their individual pattern of facial bone formation problems.

Prognosis

Children with Apert syndrome usually require surgery for release of the skull bones to allow a chance for the brain to develop normally. The older a child is before this surgery is performed, the lower the chance for reaching normal intellectual ability. Even with early surgery, certain brain structures may remain poorly developed, however. In

general, children who are raised by their parents have a better chance of achieving normal intellectual ability. About four in 10 children with Apert syndrome who are raised in a healthy family environment reach a normal intelligence quotient (IQ). Children with Apert syndrome and other similar conditions who have normal IQs do not seem to have an increased risk of behavioral or emotional problems.[9,10] However, they may require additional social and emotional support to help cope with their condition. Children with Apert syndrome with lower IQs often do have behavioral and emotional problems. Life expectancy also varies between children with Apert syndrome. Those with Apert syndrome who survive past childhood and don't have heart problems likely have a normal or near-normal life expectancy.

Complications

The main complications likely to occur in patients with Apert syndrome include:
Increased intracranial pressure that can cause papilledema and cognitive impairment.
Exposure keratopathy and corneal scarring
Respiratory complications
Spinal cord injury and neurologic deficits in patients with cervical spine anomalies.
Aspiration pneumonia and further chronic lung disease.

Conclusions

Apert syndrome is the rare acrocephalosyndactyly syndrome type 1, characterized by craniosynostosis, severe syndactyly of hands and feet, and dysmorphic facial features. It demonstrates autosomal dominant inheritance assigned to mutations in the fibroblast growth factor receptor gene. Diagnosisof Apert syndrome is based on acrocephaly, prominent forehead, ocular hypertelorism, proptosis, short and broad nose, pseudoprognathism, dental crowding and ectopia, maxillar hypoplasia, low hairline, webbed neck, pectus excavatum, and severe, bilateral syndactyly of hands and feet. The multiple phenotypic signs of Apert syndrome make multidisciplinary team, including dentist, neurosurgeon, plastic surgeon, physiatrist, ophthalmologist, perinatalogist and geneticist, essential for successful management.

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