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CLINICAL CASE

Apert Syndrome: Acrocephalosyndactyly, Clinical Case

Irina Suley Tirado-Pérez[1*], Ulfran de Jesús Castro Salas[1], María Camila Durán Martínez[2], Andrea Carolina Zárate-Vergara[1]

https://orcid.org/0000-0003-3036-2494
https://orcid.org/0000-0002-0170-3643
https://orcid.org/0000-0001-8716-7097

1. Faculty of Medical Sciences, Universidad de Santander, Bucaramanga, Colombia.
2. Pediatric Service, Fundación Cardiovascular de Colombia, Bucaramanga, Colombia.

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ABSTRACT

Introduction: Apert Syndrome has a variable incidence. A prevalence of 1: 160 thousand births has been estimated. It is autosomal-dominant, and some related factors have been found, such as advanced paternal age.

Case: Girl, newborn at term, with respiratory distress, hypotonia, syndactyly and neurodevelopmental delay. Upon paranasal sinus tomography, a malformation of the lateral semicircular canal and the bilateral vestibule was reported, and the presence of a right nasal stenosis with septal deviation to the right and the presence of bilateral choanal stenosis were confirmed. Following CT of the skull, left unilateral plagiocephaly and the presence of craniosynostosis were reported.

Evolution: During hospitalization, the withdrawal of supplemental oxygen was achieved, and she received myofunctional therapy, with which she tolerated oral feeding adequately. The correction of choanal stenosis was scheduled on an outpatient basis, which was performed at 14 months. At 18 months, craniosynostosis correction surgery was performed with a fronto-orbital advance. During the postoperative period, the patient developed pneumonia that was treated with antibiotics. When the picture was resolved, she was discharged.

Conclusion: Apert Syndrome is a congenital disorder characterized by coronal craniosynostosis, symmetric syndactyly in all four limbs, and craniofacial malformations. The diagnosis is clinical. Treatment is symptomatic, related to the different associated malformations, and interdisciplinary management must be carried out.

Key Words: Acrocephalosyndactylia, Apert Syndrome, Pediatrics.

* Corresponding autor:

Email: itirado@unab.edu.co (Irina Suley Tirado Pérez) / Phone: +314 5598697 El Bosque, Sector F, Apartamento 302, Torre 9. Floridablanca, Santander, Colombia

INTRODUCTION

Apert Syndrome is named after the French pediatrician Eugene Apert, who first described the main signs in 1906. It is a congenital disease that is a type of acrocephalosyndactyly and is characterized by malformations of the skull, hands, feet, and face. It is an autosomal-dominant disorder; most cases involve sporadic mutations of the FGFR-2 gene that are associated with paternal age greater than 40 years. The main manifestations are bicoronal synostosis and maxillary hypoplasia, strabismus, syndactyly, and hearing loss. Cognitive delay can occur in up to 50% of cases. The treatment of these patients is multidisciplinary.[1]

The usual treatment consists of surgical interventions, such as craniosynostosis release; fronto-orbital advancement usually occurs at approximately 6 to 8 months of age. At the level of the midface, correction of brachycephaly, orbital dystopia or hypoplasia of the midface are addressed. Hypertelorism correction involves resection of the interorbital bone. Mandibular and maxillary orthodontics are usually performed after cranial maturation to improve cosmetic appearance.[2,3]

CLINICAL CASE

A full-term newborn girl was referred to the institution with suspected Apert Syndrome with signs of respiratory distress, hypotonia and syndactyly. She had a history of continuous failure in the procedure of "inserting a nasogastric tube" into the nostrils on a recurring basis in the neonatal period. The patient was referred with oxygen to this hospital. She was the product of a second pregnancy from nonelderly parents. She has a four-year-old brother who is clinically normal. During her hospital stay, she was assessed in an interdisciplinary manner.

In the Otorhinolaryngology service, the specialists requested a computerized axial tomography (CT) of the paranasal sinuses with extension to the ears, in which the presence of a malformation of the lateral semicircular canal and the bilateral vestibule was reported, with normal-appearing cochlea, an aqueduct with bilateral dilated vestibular stenosis, the presence of a right nasal stenosis with septal deviation to the right and the presence of bilateral choanal stenosis, which was more severe on the right side. Surgical correction was indicated in the medium term.

In the Pediatric Neurology Service, the specialists established the presence of neurodevelopmental delay. The auditory evoked potentials test was performed, which showed complete waves, with a displacement of waves I and II bilaterally, findings that could be normal at the age at which the study was performed, for which a control was recommended after three months, and a new performance of auditory evoked potentials in six months and physical and speech therapies (myofunctional therapy) were prescribed.

In the Neurosurgery service, the specialists requested a skull CT with 3D reconstruction, in which left unilateral plagiocephaly, asymmetry of the lateral ventricles as an anatomical variant, and the presence of craniosynostosis were reported. Surgical correction was indicated in the medium term.

In the Pediatric Pneumology Service, the specialists determined the absence of pulmonary pathology and warned that the patient was at risk of microaspirations and recurrent pneumonia due to the presence of hypotonia that predisposed her to the presence of a recurrent broncho-obstructive syndrome.

In the Plastic Surgery Service, the specialists assessed the syndactyly alteration and determined that a surgical procedure was not indicated. A six-month follow-up appointment was recommended for a new evaluation.

In the Genetics Service, the specialists considered that she met the clinical criteria to establish the diagnosis of Apert Syndrome. A genetic study was not carried out (**Figure 1**).

Evolution:

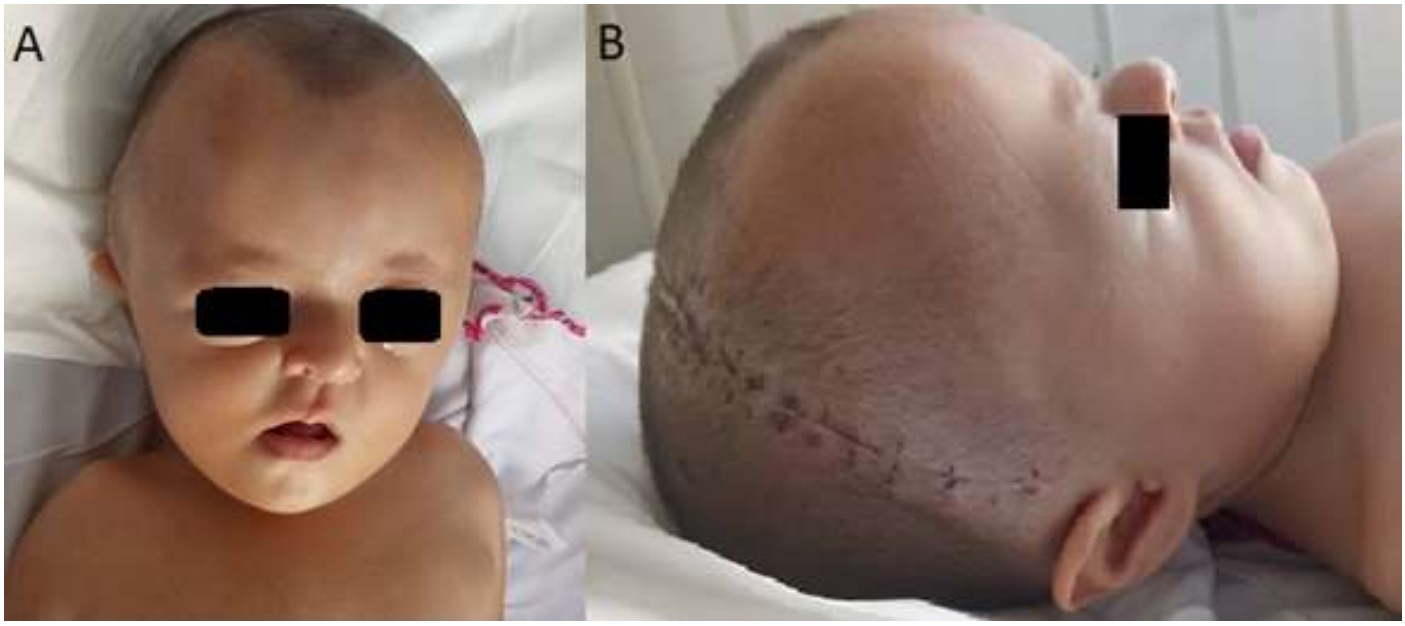
During hospitalization, the patient was weaned from supplemental oxygen, and she received myofunctional therapy with which she adequately tolerated oral feeding. Choanal stenosis correction was scheduled on an outpatient basis.

Two months after hospital discharge, the bilateral choanal stenosis was corrected with outpatient surgery.

At 18 months of age, with planned surgery with hospitalization, the craniosynostosis was corrected with a fronto-orbital advance, without intraoperative complications.

During the postoperative period, the patient developed a respiratory clinical picture related to left basal pneumonia, which was treated with antibiotics. When the picture was resolved, she was discharged.

Figure 1 Descriptive photograph of the clinical case



A: Frontal view, acrocephaly, prominent forehead, proptosis and broad nasal bridge are evident.
B: Side view, craniosynostosis surgery suture scar.

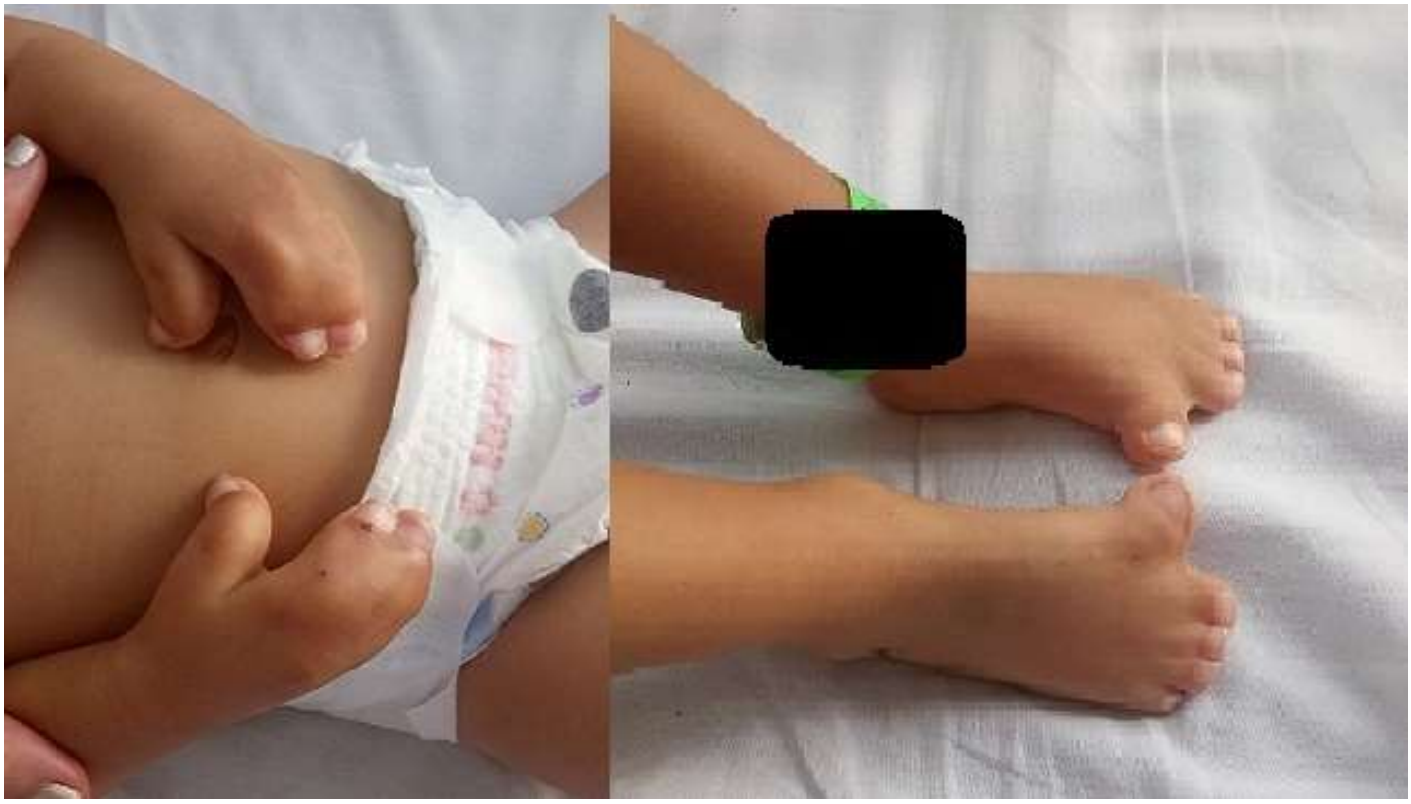
DISCUSSION

Apert Syndrome (SA) has an estimated incidence of 1/100,000 to 1/160,000 live births. Also called acrocephalosyndactyly type I, it is a congenital disorder characterized by coronal craniosynostosis, symmetric syndactyly in all four limbs, and craniofacial malformations and was first described in 1906. It is one of the most common causes of craniosynostosis. The main clinical manifestations are acrocephaly, hypoplasia of the midface (Figure 1) and symmetric syndactyly in the hands and feet with the presence of synonychia in the hands, where the severity of syndactyly is greater, as evidenced in **Figure 2**.

Apert Syndrome is a form of acrocephalosyndactyly and a rare congenital disease that has a specific molecular mechanism. The syndrome is characterized by craniosynostosis in utero, syndactyly, and abnormalities in the skin, brain, and viscera, with a higher prevalence estimated among the Asian population. Decades of study reports have focused on identifying the underlying genetic mutations and defect signaling mechanisms that contribute to their development. However, due to the condition's low prevalence, human studies have not provided sufficient data to elucidate the genotype-phenotype continuum.

The affected chromosome is believed to be chromosome 10 and there are two main identified genetic defects that affect the fibroblast growth factor receptor 2 (FGFR-2) gene. The resulting abnormal receptor prevents apoptosis of cells; therefore, in the case of those affected by Apert Syndrome, the fingers on both hands and feet can fuse. These fusions can involve skin or bone. Receptors in the skull are also affected, causing premature fusion of the sutures, leading to craniosynostosis. Apert Syndrome is always evident at birth, as in the case described. This is due to the characteristic deformities of the hands and feet, although the facial deformity may be less obvious in some cases. [4,5]

Figure 2. Descriptive photograph of syndactyly in the clinical case



Symmetric syndactyly in upper and lower limbs

Patients generally have extensive structural and functional impairments related to limb and cranial deformities. Craniosynostosis can cause acrobrachycephaly or turribrachycephaly with delayed closure of the fontanelles and possible impacts on brain growth and neurodevelopment. Macrocephaly is also found. Limb malformations mainly consist of soft tissue involvement and bony syndactyly of the fingers and toes, occasional rhizomelic shortening, and ankylosis of the elbow, with functional alterations and restricted mobility.

Facial findings include midface hypoplasia, which is generally moderate to severe, with maxillary hypoplasia, shallow orbits, strabismus, hypertelorism, downward sloping palpebral fissures, and proptosis, as well as a depressed nasal bridge and a deviated nasal septum. Dental findings include delayed eruption, impaction, crowding, thick gingival swelling, and missing teeth, along with a high risk of cavities. A summary of the main affectations and their clinical manifestations is shown in Table 1.[5,6]

Table 1. Diseases by systems in Apert Syndrome

System Affected	Condition	Symptoms	Signs	Test
Central Nervous System	Ventriculus enlargement, Hydrocephalus, Elevated intracranial pressure	Nausea, vomiting, headache	Papilledema Cognitive and developmental delay Thermoregulatory disorders	CT/MRI
Craniofacial	Craniosynostosis, midface hypoplasia, nasopharyngeal and palatal anomalies	Dyspnea, difficulty phonation	Early fusion of cranial sutures Hypertelorism Cleft or V-shaped palate	Radiological studies
Cardiovascular	Atrial Septal Defect, Ventricular Septal Defect, Persistent Foramen Ovale, Aortic Defects	Dyspnea Lethargy	Heart murmur	Echocardiogram
Respiratory	Central or obstructive sleep apnea Aspiration Bronchospasm, Increased airway secretions	Daytime sleepiness Snoring, Apnea witnessed, Cough, Wheezing	Wheezing, Respiratory aggregates, Increased oral secretions	Sleep study
Musculoskeletal	Cervical spine abnormalities (usually C5-C6 fusion) Syndactyly	Limb abnormalities	Decreased range of motion	Radiographic studies

Common associated complications include chronic otitis media, hearing loss, and increased pressure in the eye that can cause blindness. Moderate to severe intellectual disability and variable developmental delay are also common in Apert Syndrome (more than 50% of cases). Some patients are also reported to have agenesis of the corpus callosum, ventriculomegaly, hydrocephalus, fused cervical vertebrae (usually C5-C6), and occasionally heart and gastrointestinal defects, radiohumeral synostosis, or cleft veil (see this term). Common associated complications include chronic otitis media, hearing loss, and increased pressure in the eye, which can cause blindness. Moderate to severe intellectual disability and variable delay in development are also common (more than 50% of cases). Some patients are also reported to have agenesis of the corpus callosum, ventriculomegaly, hydrocephalus, fused cervical vertebrae (usually C5-C6), and occasionally heart and gastrointestinal defects, radiohumeral synostosis, or cleft veil (see this term). Common associated complications include chronic otitis media, hearing loss, and increased pressure in the eye that can cause blindness. The diagnosis is based on the clinical findings that can be evidenced from birth in most cases. Some cases can be identified prenatally. The diagnosis can be

confirmed by molecular genetic testing.[7,8] The differential diagnosis includes other syndromic craniosynostosis syndromes, such as the Pfeiffer, Crouzon, Saethre-Chotzen, Muenke, and Jackson-Weiss syndromes.[9]

A mutation in the FGFR2 gene (10q25.3-10q26) involved in cell signaling during embryonic development is the cause of this syndrome. Advanced paternal age has been associated with de novo mutations that are found in most cases.[9,10]

Regarding management and treatment, a multidisciplinary approach with lifelong follow-up is necessary. Treatment mainly involves the release of craniosynostosis, followed by surgical intervention for midface hypoplasia and cosmetic or reparative treatment for other malformations. Successful treatment focuses on improving aesthetics and functional performance (breathing, chewing, oral and eye health). The psychosocial aspects of the syndrome should also be taken into account.[2, 7]

The forecast is reserved. Some patients have life-threatening complications, including those related to the airways and central nervous system involvement. Others may progress well with proper medical and surgical management, but intellectual limitations are still very common. Life expectancy varies among Apert Syndrome patients due to the variable clinical severity of their multiple malformations and the success of treatment.[2,8]

CONCLUSIONS

Apert Syndrome is associated with multiple classic phenotypic findings, among which are coronal craniosynostosis, dysmorphic facial involvement, acral alterations with symmetric syndactyly in the hands and feet, and visceral involvement. Its diagnosis is clinical, and its treatment requires minimal neurosurgical procedures apart from the remodeling procedures of the cranial vault such as fronto-orbital interventions and fronto-facial advancement. Despite the frequent presence of ventriculomegaly, shunt is rarely required and is usually not progressive. Comprehensive management in an interdisciplinary manner is essential for its treatment.

ARTICLE ADMINISTRATIVE INFORMATION

Abbreviations

FGFR2: fibroblast growth factor receptor 2.
CT: computed axial tomography
NMR: nuclear magnetic resonance

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The authors declare that the procedures followed were in accordance with the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki.

Confidentiality of the data:

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Publication consent:

The authors have obtained the informed consent of the guardians of the patient referred to in the article. This document is in the possession of the corresponding author. The authorization for publication of this case has been signed by the parents.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Authors' contributions

ISTP: Research idea, article writing, critical analysis, editorial corrections.

UDJCS: Data compilation, bibliographic review.

MCDM: Research Idea, article writing, critical analysis

ACZV: Critical analysis, editorial corrections.

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AUTHORS INFORMATION

Irina Suley Tirado-Pérez. Epidemiologist, Master in Pediatric Palliative Care, Pediatric Intensive Care Resident, University of Santander; mail: irinasuley@gmail.com

https://orcid.org/0000-0002-9995-3287

Ulfran de Jesús Castro Salas, Pediatrician, Professor, University of Santander

María Camila Durán Martínez, General Physician, Fundación Cardiovascular de Colombia.

Andrea Carolina Zárate-Vergara, Epidemiologist, Pediatric Intensive Care Resident, University of Santander: email: andreacarolinazaratevergara@gmail.com

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