

Apert Syndrome with Combination of Synostosis: A Case Report



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ABSTRACT: Apert syndrome is a rare condition affecting the skull, face, hands and feet due to premature closure of cranial sutures. This case report describes a 6-month-old boy with Apert syndrome presenting with an abnormal head shape. A CT scan revealed craniosynostosis (fused sutures) of both the coronal and lambdoid sutures. Surgery involved removing a 1-2 cm section of the fused sutures along the coronal suture and across the lambdoid suture. After 4 months, the boy showed improvement in both clinical appearance and imaging scans. While Apert syndrome is typically classified based on the suture involved, the specific timing of surgery depends on various factors. This case demonstrates that minimally invasive surgery can be effective with minimal complications. Even though unilateral coronal and lambdoid suture fusion in Apert syndrome is uncommon, it can still be successfully treated with surgery.

KEYWORDS: Apert Syndrome; Syndromic Craniosynostosis; Case Report

I. INTRODUCTION

Apert syndrome, also known as acrocephalosyndactyly type 1, is a rare genetic disorder characterized by a combination of craniosynostosis, midfacial hypoplasia, and complex syndactyly of the hands and feet (1). This condition is considered a severe craniofacial syndrome, with a prevalence at birth estimated at 15 per million (2). The classic features of Apert syndrome include craniosynostosis, severe syndactyly, and dysmorphic facial features (3). Individuals with Apert syndrome typically exhibit craniofacial dysmorphism, syndactyly of the hands and feet, and other brain malformations (4). The syndrome is associated with premature fusion of one or more cranial and facial sutures, leading to a range of congenital deformities (1).

One of the hallmarks of Apert syndrome is craniosynostosis, which involves the premature fusion of cranial sutures (5). Specifically, individuals with Apert syndrome often present with bilateral coronal synostosis, which is the most common type found in these patients (6). The fusion of cranial sutures in Apert syndrome can lead to various craniofacial anomalies, including midfacial hypoplasia and dysmorphic facial features (1). The syndrome is also associated with symmetrical syndactyly of the hands and feet, further contributing to the complex presentation of this condition (7). In addition to the craniofacial manifestations, individuals with Apert syndrome may experience complications such as elevated intracranial pressure (ICP) (8). Elevated ICP occurs preoperatively in a significant percentage of Apert syndrome patients, highlighting the importance of monitoring and managing this complication in clinical practice (8). Furthermore, Apert syndrome patients may require multiple surgical interventions due to the complex nature of the condition, including operations to address hand and feet syndactyly, upper and lower airway obstruction, and congenital cardiac malformations (9).

The genetic basis of Apert syndrome involves mutations in the fibroblast growth factor receptor 2 (FGFR2) gene, with specific mutations such as Ser252Trp and Pro253Arg commonly associated with the syndrome (10). These mutations play a crucial role in the pathogenesis of Apert syndrome, contributing to the characteristic craniofacial and limb abnormalities observed in affected individuals (10). The molecular mechanisms involved in craniosynostosis, including those seen in Apert syndrome, are complex and involve various signaling pathways such as the Wnt/ β -catenin pathway (11). Dysregulation of these pathways can lead to aberrant osteoblast differentiation and cranial suture fusion, contributing to the pathophysiology of craniosynostosis syndromes like Apert syndrome (11).

A rare congenital abnormality, known as Apert syndrome, also called acrocephalosyndactyly, is defined by the early fusing of the cranial sutures (craniosynostosis), as well as abnormalities of the hands, feet, face, hands, and skull (12). It is estimated that 1 in every 45,000 live births, regardless of gender, are affected by this condition, with the Asian population reporting the highest

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frequency at roughly 65,000–75,000 live births (13). One of the signs of the apert syndrome is craniosynostosis. 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. The incidence increased with older fathers, whereas there was no difference in incidence between males and females (14).

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. In this syndrome, a defect in the coronal suture is found. Presenting with midface hypoplasia, hypertelorism (bulging and wide-set eyes), beaked nose, underdeveloped jaw (that leads to crowded teeth), syndactyly of hands and feet, hearing loss. They can have mild to moderate intellectual disabilities (14,15). Apert syndrome combined with the second suture of craniosynostosis is a rare condition, according to the literature the percentage were 10% from all apert syndrome (16). In this case, after 4 months of suturotomy, sutura coronary and lambdoid right and left have a better clinical outcome. Here we present a rare case of Apert Syndrome with combination of synostosis.

II. CASE PRESENTATION

Case Report

History and Examination.

A 6 month old child was taken to our hospital due to abnormal head shape (Fig.1) complaints of symmetric syndactyly of both hands and feet (Fig.2)



Fig. 1 The child's characteristics include a turribrachycephalic (tall and reduced AP dimension) skull, frontal bossing with FOC 38 centimeters, a depressed nasal bridge, an antimongoloid slope to the eyes, and a lack of the midface. Taken on March, 2022 before operation



Fig. 2 Bilateral symmetrical syndactyly of both the feet with deformation of the great toes. Taken on March, 2022 before operation

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The parent were not have history of illness during the pregnancy and also had a normal delivery with no history of trauma, infection. There were no family history of similar complaints or any other congenital abnormality was reported. Examination revealed abnormal turribrachycephalic head contour, flat occiput and a protuberant frontal region. Ocular proptosis, strabism, hypertelorism, down sliding lateral palpebral fissures were present. He had depressed nasal bridge and a thick nose with a bulbous tip and cross bow-shaped lips. Bilateral symmetrical syndactyly with complete fusion of all the five digits of both hands with inwardly placed thumb was present,also syndactyly was present with both feet with deformationof the great toe. Radiologic evaluation with Head CT Scan without contrast we came across craniosynostosis of the coronal and lambdoid suture (Fig. 3).

The operation procedure was peromed with a 1-2 cm wide suturectomy was performed along the closed bilateral coronal suture across the anterior fontanel and the lambdoid suture using Kerrison rongeurs and bone rongeurs. The bleeding from the bone was controlled by bone wax. There were no complication after surgery. After 4 months of suturectomy, sutura coronary right and left and lambdoid, the patient have a better clinical and imaging outcome (Fig. 4 and Fig. 5).

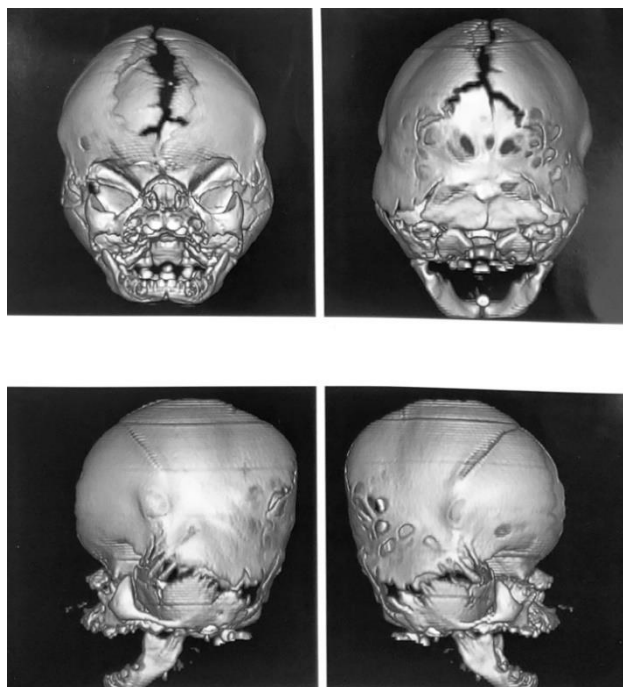


Fig. 3 Three-dimensional CT performed before surgery showing a midline defect extending from glabella to posterior fontanelle with abnormally wide anterior and posterior fontanelle

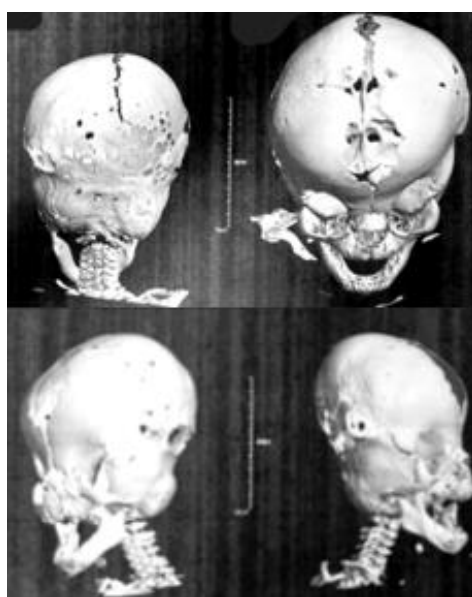


Fig. 4 Three-dimensional CT performed after surgery showing a midline defect extending from glabella to posterior fontanelle reduced

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Fig. 5 Durante operation with Suturotomy of Sutura Coronaria + Lambdoid (R) performing on April 25th 2022

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Fig. 6 Taken on September, 2022 (4 months after operation) Dome-shaped protruberance in anterior parietal region and increased height of the skull

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Fig. 7 Taken on September, 2022.

DISCUSSION

Apert syndrome with a genetic mutation in FGFR2 is one of the 5 most common syndromes underlying craniosynostosis (17). Apert syndrome has an incidence rate of 1.5 per 100,000 per year. The prevalence of births with Apert syndrome ranges from 15.5 out of 1 million births and is associated with 4.5% of all cases of craniosynostosis. In a study conducted the prevalence of births with Apert syndrome is quite uniform in different populations (18).

Holten and colleagues came to the conclusion that a genetic abnormality, specifically in the distal limb bud and craniofacial skeleton, is responsible for the varied and uncoordinated differentiation of the mesenchyme at the time of embryologic division into separate skeletal components. Postnatally, the disease process continues, particularly in endochondral bone development. The fibroblast growth factor receptor 2 gene, located on chromosome 10, was found to be defective in acrocephalosyndactyly in 1995, according to a report written by A.O.M. Wilkie. The linker between the second and third extracellular immunoglobulin domains of FGFR2, which maps to chromosome bands 10q26, is where specific missense substitution mutations involving adjacent amino acids (i.e. Ser 252Trp, Ser 252Phe, and Pro 253Arg) are responsible for more than 98% of cases of Apert syndrome.

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 occasionally upper airway obstruction. Compensatory growth occurs at the remaining open sutures to allow continued brain growth (12).

The finding that the degree of syndactyly is correlated with KGFR expression in fibroblasts served as the first genetic proof that syndactyly in Apert syndrome is a keratinocyte growth factor receptor (KGFR)-mediated impact. Ser252Trp and Pro253Arg patients have various phenotypic expressions. In contrast, cleft palate is substantially more prevalent with Ser252Trp mutation, even if our patient does not have it. Syndactyly is more severe with Pro253Arg mutation for both hands and feet, such in this patient who has type III ("hoof or rosebud") syndactyly in both the hands and feet.

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 FGFR2 Ser252Trp mutation have a significantly greater prevalence of visual impairment compared with patients with the FGFR2 Pro253Arg mutation (12).

Cardiovascular and genitourinary anomalies occurred in 10% and 9.6% of cases, respectively. Intelligence varied from normal to mental deficiency, even though fewer numbers were reported to have good integration into the society with normal social life. In patient with Apert syndrome, webbed or fused fingers and toes (syndactyly) are characteristic, and the severity of fusion varies from three digits on each hand and foot is fused together. In the most severe form, all of the fingers and toes are fused; this is the case of this patient we are reporting, because our patient has type III (hoof or rosebud) syndactyly which was well corroborated by the X-ray of the hands and feet showing fusion of the bones of the digits.

Apert syndrome is one of the several genetic syndromes associated with craniosynostosis, a condition that includes premature fusion of one or multiple cranial sutures. There has been significant clinical variation among different sutural synostoses and also within particular suture synostosis (19). Apert syndrome was classified into 3 types classification of Subtypes of Apert Syndrome, Based on the Type of Vault Suture Synostosis (16). The first type is Bilateral coronal synostosis, the second type is Pansynostosis, and the third type have 3 subtype, the first one is unilateral coronal and metopic synostosis, the second one is sagittal and bilateral/unilateral coronal synostosis, and the third one is other type of perpendicular combination of synostosis (16).

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Table 1. Type of Synostosis

TYPE	SYNOSTOSIS CHARACTERISTICS	PERCENTAGE (%)
TYPE I	BILATERAL CORONAL SYNOSTOSIS	55
TYPE II	PERPENDICULAR COMBINATION OF SYNOSTOSIS	19
TYPE III	a. PERPENDICULAR COMBINATION OF SYNOSTOSIS	19
	b. SAGITTAL + BILATERAL / UNILATERAL CORONAL	19
	c. OTHERS	6
TOTAL		100

In radiological studies, CT Scan with 3D reconstruction is the most accurate method and is able to provide a very good picture of the entire suture, compared to plain X-ray and MRI, although the disadvantage of the patient is exposed to greater radiation. The newest modality in radiology uses GRASE (gradient-and-spin-echo), a type of MRI, which enhances bone-soft tissue boundaries showing the cranial sutures as hyperintense (20). Genetic testing is highly recommended, especially in cases of craniosynostosis at two or more sutures. genetic examination focused on abnormalities of FGFR 3, FGFR 3, transcription factor TWIST and MSX2 (21,22). The unilateral coronal-lambdoid suture synostosis cases shared the common morphological features of upward deviation of the ipsilateral orbital rim, nasal ridge deviation, ipsilateral frontal flattening, ipsilateral occipitotomastoid bulging, and contralateral parietal bulging (23). Over time, surgical treatment for craniosynostosis has advanced dramatically. Suturectomy or strip craniectomies were the first treatment for craniosynostosis to be documented. By eliminating the fused suture, it was intended to allow the constrained region to expand along with the developing brain. To create a normal head shape, cranial vault reconstructions were developed. These procedures involve removing cranial bone, reshaping it, and securing the relocated bony segmen. Although the outcome of this treatment is great, it is a lengthy surgical procedure that results in higher blood loss and requires extended anesthesia (19). New methods and applications have been created for less invasive surgical procedures to accomplish the same results, with the benefits of less blood loss and smaller scars. however a lot depends on the surgeon's abilities and the accessibility of the endoscopic tool. The purpose of surgical treatment for craniosynostosis is to repair the cranial deformity's atypical head shape and avoid secondary complications including raised intracranial pressure, visual impairment, and other detrimental effects on neurocognitive development (24). Syndromic forms that require urgent surgical intervention due to the involvement of the airway, ophthalmologic, and neurological system. Open craniotomy: done in patients older than six months because the bones are more rigid and cannot be manipulated as well with an endoscope. This modality allows for a better remodeling of the skull and decreases the need for helmet use postoperatively (20,25). The main goal of surgery is to create enough space in the cranial vault for the brain to grow and develop properly as well as to provide the child with a more decent-looking appearance (26). Unilateral coronal-lambdoid suture synostosis suturectomy followed by helmet therapy and in favorable outcomes, although the correction of frontal flattening was less satisfactory than the other measures. Considering the minimal invasiveness of the treatment, suturectomy may be a viable option for these patients (23). The timing of surgical management depends on several factors such as the type and severity of synostosis, surgical technique, comorbidities, and surgeon preference. In the literature the optimal timing of surgery is 3 to 6 months of age. Some authors also divided the timing of surgery into early surgical intervention which occurs between 2 to 3 months of age and later surgical intervention occurs 6 to 12 months old. Early intervention has advantage of early decompression of elevated intracranial pressure and increase the intracranial volume to allow the brain to grow (24).

The current study demonstrates that the complication rate with the minimally invasive approach is comparable with other minimally invasive reports as well with other open-approach reports. There was no statistical difference in complication rates between the minimally invasive and the open groups (14.9% versus 7.1%). However, the microscopic group tended to have a higher major reoperation rate, although this was not statistically significantly different. The microscopic unicoronal patients had a statistically significant higher reoperation rate (58.3%). The microscopic metopic patients also had a higher reoperation rate, although this was not statistically significant (27). While there are relatively few complications immediately following surgical correction of craniosynostosis, there is a sub-stantial risk of delayed complications. Rapid postoperative bone growth, called

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resynostosis, can cause additional cranio- facial deformities and/or increased intracranial pressure. Resynostosis can require additional cranial vault reconstruction, which has a 13% incidence of life-threatening complications, including dura tears, subdural hemorrhages, tearing of the cranial sinuses, stroke, encephalitis, meningitis, and seizures (28). In Apert and Crouzon syndrome and multisuture craniosynostosis involving at least both lambdoid sutures, occipital expansion with distraction is preferred due to the high risk of increased ICP and tonsillar herniation. Leaving the fronto-orbital region undisturbed during the first operation reduces the risk of complications in a later monobloc (29). The need for additional intervention can always arise and is more bound to occur in syndromic cases (25). The incidence and morbidity of complications related to resynostosis are so severe that it is a major factor in deciding the timing of surgical intervention. Children <6 mo of age at the time of surgery have >3 times the risk of developing resyn- ostosis when compared with children who are between 6 mo and 2 y old. In addition to the age-dependent risk, resynostosis risk increases in certain syndromic forms of craniosynostosis, with up to a 40% incidence of resynostosis. The incidence and morbidity of complications related to resynostosis are so severe that it is a major factor in deciding the timing of surgical intervention. Children <6 mo of age at the time of surgery have >3 times the risk of developing resyn- ostosis when compared with children who are between 6 mo and 2 y old. In addition to the age-dependent risk, resynostosis risk increases in certain syndromic forms of craniosynostosis, with up to a 40% incidence of resynostosis (25).

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