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Original Article

Apert syndrome: Cranial procedures and brain malformations in a series of patients

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ABSTRACT

Background: Apert syndrome is one of the most severe craniofacial disorders. This study aims to describe the craniofacial surgeries and central nervous system malformations of a cohort of children with Apert syndrome treated in the past 20 years and to compare these data with previously published data.

Methods: Retrospective analysis of a series of patients with Apert syndrome treated between 1999 and 2019 in our hospital. Information was analyzed regarding craniofacial procedures, hydrocephalus and presence of shunts, Chiari malformation Type 1, and other brain malformations such as corpus callosum and septum pellucidum anomalies.

Results: Thirty-seven patients were studied. Ventriculoperitoneal shunt prevalence was 24.3%, and 8.1% of patients required decompressive surgery for Chiari malformation. All of them needed at least one cranial vault remodeling procedure. The median age for this procedure was 8 months. In 69.7% of patients, the first cranial vault intervention was performed in the fronto-orbital region. In 36.4% of patients, a midface advancement had been performed at the time of this review, although this proportion was very dependent on the follow-up period and the age of the patients. The median age for the midface advancement procedure was 5.25 years. Anomalies of the corpus callosum and the septum pellucidum were reported in 43.2% and 59.5% of patients, respectively.

Conclusion: Apert syndrome is a type of syndromic craniosynostosis, and patients usually require one or more cranial and facial surgeries. In comparison with other syndromic craniosynostosis types, Apert syndrome less frequently requires a VP shunt or treatment for a Chiari malformation.

Keywords: Apert syndrome, Craniosynostosis, Fronto-orbital advancement, Hydrocephalus, Monobloc advancement

INTRODUCTION

Apert syndrome is a severe craniofacial syndrome that was initially described in 1906 by French physician Eugene Apert.[3,17] He described the synostosis of cranial sutures and the severe syndactyly of fingers and toes, a condition that he named acrocephalosyndactyly. It is a rare disease, with an estimated incidence of 1/65.000 births.[3,35] Apert syndrome is an autosomal disorder caused by mutations of the fibroblast growth factor receptor 2 gene (FGFR2) on

chromosome 10q.[35] Nearly, all cases correspond with two genotypes, with mutations identified at either position 252 or position 253 in exon 7.[2] Inheritance is autosomal dominant, with most cases representing new mutations in families without previous history of the disorder.[10] The paternal age at conception is higher than average and has been related to its incidence.[5,16,31]

Patients present with malformations related to the head, face, and limbs. At the skull, it is characteristic of bilateral coronal synostosis, although other sutures may be affected, and coronal sutures are rarely unaffected. Skull base development is abnormal, and the skull shape confers a steep and flattened forehead with a flat occiput. Midfacial hypoplasia and exorbitism are also characteristic of the disorder. Many patients have an associated cleft palate or bifid uvula.[16] All of them present syndactyly of the hands and feet, which is characteristic of the disorder. Patients may also present cardiovascular malformations (about 25%[5]), gastroesophageal reflux, radiohumeral fusion, cervical spine fusions (more than 50%[4,21]), and varying degrees of neurocognitive impairment.[30]

This study seeks to (1) collect and describe the craniofacial procedures performed in our series of Apert patients in the past 20 years; (2) assess the proportion of shunted patients and patients with Chiari malformation type 1 (CM1) needing surgery; and (3) describe a number of brain and cranial malformations that frequently occur in this disorder.

MATERIALS AND METHODS

Patients

We conducted a retrospective analysis of consecutive patients with Apert syndrome treated at Hospital 12 de Octubre, Madrid, Spain; in our Craniofacial Unit, between 1999 and 2019. Informed consents are obtained from parents regarding images and information database. Our database including clinical records and radiological records was examined, and the type, number, and order of surgeries were extracted from the database. The brain malformations associated with this disorder were analyzed using magnetic resonance imaging (MRI), and every patient underwent at least one MRI. The follow-up period was calculated and described as patients still attending the craniofacial clinic or those who were lost to follow-up.

Information of this series of patients was extracted regarding the following:

a. Incidence of hydrocephalus requiring ventriculoperitoneal shunt compared with a normal ventricular size or enlarged ventricular size without shunt (nonprogressive ventriculomegaly). Indications to perform VP shunt procedures were retrieved
b. Incidence of CM1 defined as tonsillar herniation of 5 mm or greater. Proportion of patients requiring surgery and indication of such procedures
c. Cranial and brain malformations detected through MRI studies
d. Craniofacial surgical procedures: number, type, order, and age of the patient at the time of surgery.

Craniofacial surgeries

Various cranial vault procedures are performed in Apert patients and may be divided into surgeries of the anterior half of the skull or the posterior half, although one could even reach two-thirds of the skull. A total cranial vault remodeling or holocranial dismantling is also possible. With regard to the anterior half of the cranium, a remodeling of the frontal region can be performed with or without a supraorbital bandeau. If an advancement of the supraorbital rim and the frontal bones is instead performed, then it is called a fronto-orbital advancement (FOA). The advancement may be static (with absorbable or nonabsorbable miniplates), but it may also be progressive using distractors (osteogenic distraction). Regarding osteogenic distraction, our team has used a technique described by Hirabayashi *et al*.,[18] in which a one-piece craniotomy including a bifrontal craniotomy and bilateral supraorbital rim is performed (without remodeling) and then advanced with distractors in the postoperative period. We have also performed a variant of this technique, in which the bifrontal and bilateral orbital rim craniotomy is elevated, osteotomized, reshaped, and reassembled with absorbable miniplates and then relocated with distractors. Regarding the posterior half of the cranial vault, a similar variety of procedures are accomplished: remodeling without advancement, remodeling with fixed advancement (miniplates), remodeling with osteogenic distractors, fixed advancement without remodeling, or distractors without remodeling. A near-complete craniectomy of the posterior skull is occasionally necessary when the bone is very abnormal and dysplastic.

On the other hand, patients may need surgical procedures affecting the face. Due to midfacial hypoplasia and upper airway obstruction, a midface advancement is often performed. A midfacial advancement may be performed alone (Le Fort III osteotomy) or in combination with a FOA (monobloc advancement).

RESULTS

We identified a total of 44 patients with Apert syndrome from the past two decades in our database. However, seven patients were excluded from analysis since the clinical information was scarce or they were treated mainly in a different hospital. Of the 37 remaining patients, 33 have been treated in our center from birth; thus, we have a complete information and surgical record. The remaining four patients were initially operated on in different centers and subsequently

in ours. We included these four patients for analysis of hydrocephalus and VP shunt, Chiari malformation, and brain malformations (total: 37 patients), since no VP shunts or Chiari decompressions correspond to these four patients. However, we decided to not consider craniofacial surgeries since the indications were made outside our Craniofacial Center (total: 33 patients).

The 37 patients were comprised of 17 females (46%) and 20 males (54%) [Table 1]. The median follow-up time was 127 months (10.5 years), with a minimum of 17 months and maximum of 256 months (21.3 years, a patient initially treated in another hospital and remitted in 1999 at the outset of database and our series). One patient died at the age of 13 years; he corresponds to the group of four patients treated initially in a different hospital.

Hydrocephalus and ventricular size

Nine out of 37 patients (24.3%) required a VP shunt. For the rest, the ventricular size was categorized using the Evans' index, that is, the ratio of maximum width of the frontal horns of the lateral ventricles and the maximal internal diameter of the skull at the same level (where >0.30 is considered ventriculomegaly). In this manner, nonshunted patients were categorized in two groups: those with normal ventricular size and those with ventriculomegaly (referred in the literature as "nonprogressive ventriculomegaly"). Eighteen patients (48.7%) presented a normal ventricular size, with an Evans' index from 0.15 to 0.28. Ten patients (27%) presented nonprogressive ventriculomegaly, with an index oscillating from 0.31 to 0.44, and they did not present clinical findings related to intracranial hypertension and thus were not shunted. The total number of patients with shunt (hydrocephalus) and ventriculomegaly was 19 (51.3%).

Of the nine shunted patients, only one case was the shunt performed before any craniofacial procedure. In this case, the patient presented progressive hydrocephalus from birth and required shunting at 2 months of age. The remaining eight patients required a VP shunt after surgical procedures. The indication was CSF fistula in one patient and progressive hydrocephalus in seven patients. Of these seven patients, cranial vault remodeling surgeries preceded the VP shunt. Four were anterior half remodeling surgeries, two were posterior half remodeling surgeries, and one was a total cranial vault remodeling surgery. This proportion is not informative since the distribution of anterior/posterior/holocranial vault remodeling in the complete series is very similar. Of the nine shunted patients, three patients needed a shunt revision (two patients twice and one patient once); additionally, one patient presented a shunt infection resolved with shunt replacement. In our unit, shunts for Apert-Crouzon-Pfeiffer patients are placed through a posterior (occipital) burr hole to avoid potential contamination of an anterior shunt if they need halo placement for a midfacial advancement.

Table 1: General characteristics of the series.

	Number	Proportion (%)
Total	37	
Gender		
Female	17	46
Male	20	54
Follow-up (median)	127 months (10.5 years)	

Chiari malformation

Cerebellar tonsillar herniation through the foramen magnum or CM1 was present in 8 out of 37 patients of our series (21.6%). Three patients required surgery (8.1%) consisting of a posterior fossa craniectomy with resection of the posterior arch of the C1 vertebrae, plus a wide dural opening and duroplasty. Two patients did not present any attributable symptom at the time of the procedure, and therefore, the indication was made on the basis of very severe radiological tonsillar herniation (>20 mm). One patient was 2 years old at the time, and the other was 3 years old. One patient required Chiari decompression at 9 months of age due to attributable symptoms such as progressive central sleep apneas in a tracheostomized patient. The remaining 5 patients (13.5%), despite presenting radiological diagnosis of Chiari malformation, did not present symptoms, and the tonsillar herniation was not considered sufficiently severe to indicate decompressive surgery. Most of the Apert patients within our series do not present Chiari malformation (29 patients, 78.4%).

Brain and cranial malformations on MRI studies

Thirty-seven patients were included since complete cranial MRI images were available. The majority of brain malformations related to Apert syndrome corresponded to abnormalities of midline development, more specifically involving the olfactory-limbic-septal-callosal structures. Sixteen patients presented corpus callosum malformations: 15 (40.5%) presented segmental or global hypoplasia and 1 (2.7%) presented complete agenesis. Septum pellucidum was analyzed, and complete or partial absence was found in 13 patients (35.2%), whereas 9 patients (24.3%) presented a double septum (cystic septum pellucidum or cavum vergae).

The amygdala and hippocampal region were also scrutinized. Two patients (5.4%) presented verticalized and malrotated hippocampus bilaterally, and one patient presented with intractable epilepsy and an amygdalar tumor that was resected and whose pathology revealed ganglioglioma. The petrous bone was also assessed and revealed nearly constant

malformations in the inner ear. In 33 patients (89.2%), a dilated cystic vestibule was found. Craniocervical junction abnormalities were also common. In 30 patients (81.1%), remodeling of the clivus was confirmed, and 9 patients (24.3%) presented basilar invagination.

Craniofacial surgical procedures

The 33 patients treated from birth in our center were included in this section.

First surgical intervention

The first surgical intervention for 29 patients was a cranial vault procedure, whereas it was mandibular distraction in three patients and VP shunt in one patient. Every patient required a cranial vault surgery at least once. However, the first surgery involved the anterior half (fronto-orbital) in 23 patients (69.7%), the posterior half in 8 patients (24,2%), and a total cranial vault remodeling was carried out in 2 patients (6.1%). The median age for the first cranial vault surgery was 8 months (range 3–15 months), and it was performed before 6 months in 7 patients, between 6 and 12 months in 23 patients, and after 12 months of age in 3 patients.

Type of cranial procedures

A total of 53 cranial vault procedures were performed, including 6 monobloc advancements (frontal and facial). In all 33 patients, a FOA was performed at some point (2 of them as part of holocranial remodeling). Of them, 17 required only one cranial vault surgery. In this subgroup, 15 patients required an FOA, and two patients required a holocranial remodeling.

In 14 patients, two cranial vault procedures were performed. The combinations included FOA and posterior remodeling (7 patients), two FOAs (3 patients), FOA and monobloc advancement (3 patients), and posterior remodeling and monobloc advancement (1 patient). Finally, two patients required more than 2 cranial procedures. One patient underwent three procedures (two FOAs and a posterior remodeling), and another required five cranial vault surgeries (one holocranial remodeling, two FOAs, and two monobloc advancements).

Midfacial advancement and monobloc advancement

Of the 33 patients, at the time of this review, 12 of them required surgical treatment of their midfacial hypoplasia. This proportion was dependent on the age of the patients in the cohort, since nonoperated patients may require these procedures as they age. In fact, in an additional four patients, the midfacial advancement was indicated in outpatient clinic visits and remains pending. Of the 12 operated patients, 9 required only one procedure and 3 required more than 1. Sixteen procedures were undertaken, including 10 midfacial advancements (Le Fort III) and 6 monobloc advancements. The median age for the first procedure was 63 months (5.25 years). In six patients, the procedures were carried out between 5 and 10 years of age. In two patients, they were performed between 10 and 16 years of age, and in four patients, their first procedure was performed when they were <5 years of age.

DISCUSSION

The usual shape of the skull in patients affected of Apert syndrome is brachyturricephaly. Typically, the head width and height are increased, whereas the head length is reduced.[9,21,28] Bicoronal synostosis is the most frequent and characteristic craniosynostosis, which develops in the 1st year of life. A wide and split metopic suture as well as the sagittal suture at presentation are a frequent feature simulating a midline calvarial defect [Figure 1].[3,7,9,16,25] This feature appears to allow for some degree of intracranial decompression.[16] Shallow orbits and consequent proptosis (exorbitism) are common features.[21,24] Cloverleaf skull (*kleeblattschädel*) is not frequent but possible. It represents the most severe form of pansynostosis and has been reported in 4% of patients.[8] Abnormal development of the skull base also occurs[19,26] due to the premature fusion of the sphenofrontal suture and both spheno-occipital and petro-occipital synchondroses.[3] As a consequence, the anterior and middle cranial fossa is shortened. It produces a diminished length of the orbits and upper airway. Furthermore, synostosis at the cranial base may impede CSF flow by reducing venous drainage by stenosis of the basal foramina.[7,11,23,26]

CNS malformations

Apert syndrome is related with brain malformations that may be classified as primary or secondary to the osseous deformity.[29,33] Enlarged ventricles or ventriculomegaly is

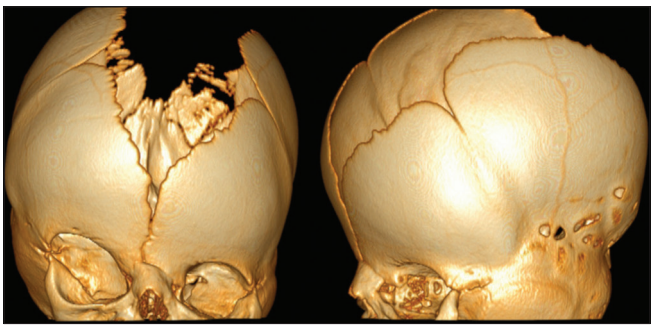

Figure 1: Cranial CT with osseous 3D reconstruction. A 7-month-old patient presented a significant midline defect that included split sagittal suture, enlarged anterior fontanelle, and split metopic suture.

considered a primary malformation.[11,33] In Apert syndrome, some series report up to 60% of ventriculomegaly,[26] and our series presented as much as 51.3% (if we sum the shunted patients and those with ventriculomegaly but not shunted). Nonprogressive ventriculomegaly is more frequent than true hydrocephalus.[4,7,10,11,27] The habitual treatment for hydrocephalus in syndromic craniosynostosis is a VP shunt.[11,20] A high rate of failure has been reported for endoscopic third ventriculostomy (ETV).[16] We reviewed a series of Apert patients, and those requiring a VP shunt [Table 2] varied between 0% and 25%. In our series, shunted patients represent approximately one-fourth of the total patients (24.3%). Regarding the nine shunted patients, in eight of them, the indication was hydrocephalus, but for one, a persistent CSF fistula triggered the procedure. From the series summarized in [Table 2], we very rarely found distinction between the VP shunt indication if it was because of hydrocephalus or CSF fistula. It is well known that patients with Apert syndrome require a VP shunt less frequently when compared to Crouzon or Pfeiffer syndromes.[6,7]

Another type of primary malformations comprises disorders of brain development itself. This type has been described as a greater frequency of abnormalities of midline development (olfactory-limbic-septal-callosal).[14,29,30,33] The usual malformations are corpus callosum anomalies (hypoplasia and agenesis) [Figure 2], septum pellucidum anomalies (hypoplasia, agenesis, duplicity, or cavum vergae) [Figure 3], limbic system abnormalities, anomalies of the olfactory complex (absence of olfactory bulbs and tracts, midline fusion of olfactory tubercles), optic nerve hypoplasia, and septo-optic dysplasia spectrum. The association of these abnormalities and intellectual disability is not clear.[4] In the different series, we reviewed the more common brain abnormalities that correspond with corpus callosum and septum pellucidum anomalies.[37] Corpus callosum abnormalities were reported in 12%–43% of patients, and

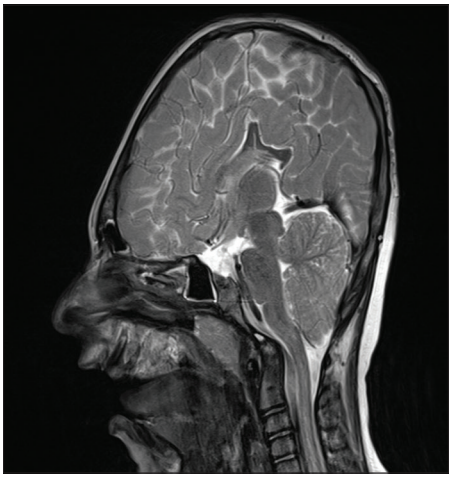

Figure 2: Sagittal T2-weighted MR image. A 5-year-old patient presenting a corpus callosum malformation. A distorted morphology is shown with agenesis of its anterior third.

Table 2: Comparison of different series.

Article	*n* (total)	*n* (with CT or MRI images)	VP shunt	Tonsillar herniation	Corpus callosum anomalies*	Septum pellucidum anomalies†
Hanieh and David[17] (1993, North Adelaide, Australia)	33	13	0% (0/33)	-	-	-
Murovic *et al.*[26] (1993, Toronto, Canada)	44	25	23% (10/44)	-	12% (agenesis) (3/25)	-
Posnick *et al.*[28] (1994, Washington D.C., USA)	8	8	25% (2/8)	-	-	-
Cinalli *et al.*[6] (1995, Paris, France)‡	65	55	6.15% (4/65)	1.9% (1/55)	32.7% (18/55)	50.9% (28/55)
McCarthy *et al.*[24] (1995, New York, USA)	24	24	20.8% (5/24)	-	-	-
Renier *et al.*[30] (1996, Paris, France)‡	70	60	11.7% (7/60)	1.7% (1/60)	30% (18/60)	55% (33/60)
Cinalli *et al.*[7] (1998, Paris, France)‡	77	77	6.5% (5/77)	1.3% (1/77)	-	-
Yacubian-Fernandes *et al.*[37] (2004, Sao Paulo, Brazil)	18	18	0% (0/18)	-	27.8% (5/18)	38.9% (7/18))
Collmann *et al.*[11] (2005, Würzburg, Germany)	45	-	4.4% (2/45)	-	-	-
Marucci *et al.*[23] (2008, London, UK)	24	24	12.5% (3/24	-	-	-
Fearon and Podner[16] (2013, Dallas, USA)	135	135	18.5% (25/135)	29%	12%	24%
Breik *et al.*[4] (2016, North Adelaide, Australia)	94	94	7.45% (7/94)	4% (4/94)	11% (agenesis) (10/94)	13% (12/94)
Munarriz *et al.* (2020, Madrid, Spain)	37	37	24.3% (9/37)	21.6% (8/37)	43.2% (16/37)	59.5% (22/37)

*Corpus callosum anomalies include agenesis and hypoplasia. †Septum pellucidum anomalies include partial absence, complete absence, cavum vergae, or cystic septum. ‡Three papers from the same hospital; thus, they correspond to a series of patients that are very similar to each other

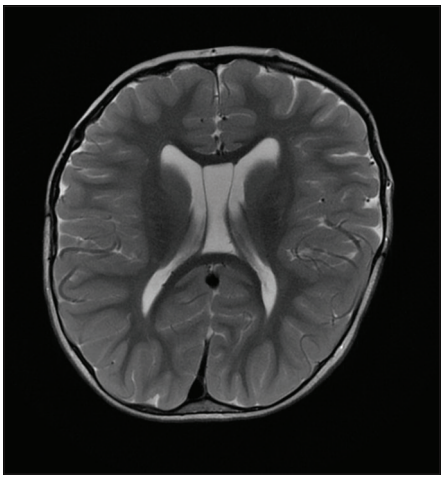

Figure 3: Axial T2-weighted MR image. A 4-year-old patient demonstrating a duplicity of septum pellucidum or cystic septum or cavum vergae.

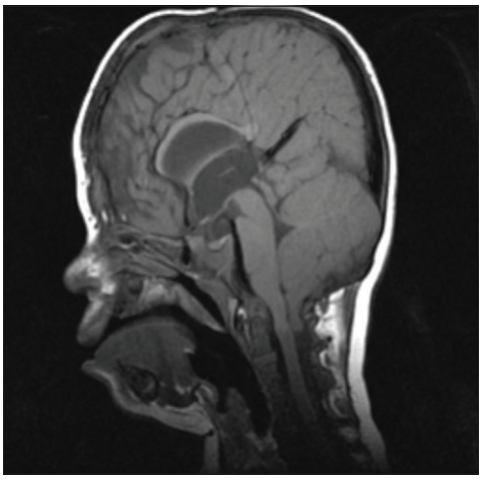

Figure 4: Sagittal T1-weighted MR image. A 17-month-old patient presenting a Chiari malformation with a 9 mm tonsillar herniation through the foramen magnum.

septum pellucidum anomalies were reported in 13%–59% of patients [Table 2].

The main secondary malformation is cerebellar tonsillar herniation through the foramen magnum or Chiari type 1 malformation [Figure 4]. The premature synostosis of the lambdoid sutures is considered to be the main cause of the Chiari malformations secondary to craniofacial syndromes.[6] The tonsillar herniation has been reported in different series as varying between 1.9% and 29% [Table 2], and our study found a prevalence of 21.6%. A less reported aspect is the frequency when patients with tonsillar herniation require decompressive surgery. Even though eight patients in our series (21.6%) exhibit the malformation, only three of them required surgery (8.1%). Similarly, for hydrocephalus, the Chiari malformation is less frequent in Apert syndrome when compared with Crouzon or Pfeiffer syndromes.[6] In the study of Cinalli *et al*.,[6] they ascertained by means of skull X-rays that patients with Crouzon syndrome suffered an earlier fusion of lambdoid and sagittal sutures (median of 20 and 6 months, respectively) when compared with Apert patients (median of 60 and 51 months, respectively), and at the same time, both syndromes presented earlier fusion when compared with the normal population. They postulated that the greater frequency of Chiari malformation in Crouzon syndrome might be due to this finding. From the same study, the bicoronal synostosis, which is common in both syndromes, was found earlier in Apert patients at a median age of 5 months and later in Crouzon patients at 8 months.

Craniofacial surgical procedures

The traditional paradigm of treatment in patients affected with Apert syndrome is to assume that they eventually require at least one surgery of cranial vault expansion or remodeling and thus to proceed with it during the 1st year of life. It is known that a fair number of patients will need more than 1 procedure regarding the skull region.[15,16,31,34,36] In this manner, some Craniofacial Units have proposed protocols of treatment that stage and organize surgeries in a temporal line of action.[12,16]

From the paper of Fearon and Podner from the Craniofacial Center in Dallas,[16] their protocol considers at least two cranial vault expansion surgeries. A completely different approach is that from the study of Marucci *et al*.[23] from London (Great Ormond Street Hospital for Children). In their series of 24 patients, they do not schedule any cranial vault surgery automatically or by default. Instead, they perform the cranial vault expansion only in patients displaying signs of intracranial hypertension. In this way, they report 20 patients (83%) that developed intracranial hypertension and were operated on. Half of these patients presented increased intracranial pressure during the 1st year of life, and all of them before 5 years of age. Seven of the 20 patients required subsequent surgeries after a period of proven normalization of intracranial pressure. Four of the 24 patients (nearly 20%) did not require a cranial vault expansion. They conclude that these data present an accurate picture of the natural history of raised intracranial pressure in Apert syndrome.

In the majority of units, however, the usual management has been to believe that a cranial vault procedure is needed and so to schedule it sometime within the 1st year of life. The controversy for the greater number of authors has been when to perform the first surgery.[13] Nowadays, it is not clear how long the first surgery may be delayed. Some authors suggest that it is beneficial to proceed with it in the first 6 months of life.[1,9,12,22,25] Others, however, advocate to delay

the procedure since a postsurgical skull growth impairment is produced.[16] In the Dallas Unit,[16] the first cranial vault surgery was performed around 12.6 months (median) when compared to ours, which was at 8 months (median). In the same way, this group opines that the midfacial advancement should be delayed when possible as well, since the surgery can impede normal facial growth.[16,22] In the Dallas Unit, when midfacial advancement was first performed, it was performed at approximately 7.5 years (median) compared to 5.25 years (median) in our unit. Thus, earlier cranial or facial surgeries may typically shift the need for a possible second procedure sooner, in the opinion of this group.[16] Another controversial aspect is whether the first cranial expansion must be anterior (FOA) or posterior (occipital advancement), since a greater augmentation of cranial volume has been described after a posterior advancement.[32] Regarding this controversy, in our unit, approximately two-thirds of our first surgeries were anterior advancements and around one-third were posterior advancements.

CONCLUSION

Apert syndrome is one of the most severe craniofacial disorders. Most will require a cranial vault surgical intervention, and many will require more than 1. The need for a midfacial advancement is also very prevalent. The incidence of hydrocephalus and the requirement of a VP shunt – as well as tonsillar herniation – are less common than in syndromes such as Crouzon or Pfeiffer.

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Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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