Expert Opinion on Orphan Drugs

ISSN: (Print) 2167-8707 (Online) Journal homepage: http://www.tandfonline.com/loi/ieod20

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To cite this article: C. Driessen, M. L. C. van Veelen, K. F. M. Joosten, S. L. Versnel, C. A. van Nieuwenhoven, E. B. Wolvius, H. H. Bredero-Boelhouwer, E. Arnaud & I. M. J. Mathijssen (2017) Apert syndrome: the Paris and Rotterdam philosophy, Expert Opinion on Orphan Drugs, 5:7, 599-605, DOI: 10.1080/21678707.2017.1335195

To link to this article: http://dx.doi.org/10.1080/21678707.2017.1335195

Accepted author version posted online: 25 May 2017.
Published online: 05 Jun 2017.

EXPERT OPINION ON ORPHAN DRUGS, 2017
VOL. 5, NO. 7, 599–605
https://doi.org/10.1080/21678707.2017.1335195

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REVIEW

Apert syndrome: the Paris and Rotterdam philosophy

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ABSTRACT

Introduction: Apert syndrome is a rare type of syndromic craniosynostosis. Patients have an explicit phenotype with craniofacial dysmorphologies and severe symmetrical syndactyly of the hands and feet. This review includes background information about the syndrome and several aspects of the treatment.
Areas covered: The cause of Apert syndrome is found in unique mutations in the Fibroblast Growth Factors Receptor (*FGFR*) 2 gene in 99%. It results in cranial suture fusion, craniofacial dysmorphologies and severe symmetrical syndactyly of the hands and feet. Patients with Apert syndrome are at risk for mental retardation, mobility impairment and intracranial hypertension (ICHT). This is the result of a complex interaction between (1) abnormal skull growth, (2) ventriculomegaly, (3) venous outflow obstruction and (4) obstructive sleep apnea (OSA). Mental retardation is mainly determined by the *FGFR*2 mutation and treatment is directed at protecting the intrinsic potential of neurocognition.
Expert Opinion: To prevent ICHT, we prefer an occipital expansion in the first year of life. Screening on ICHT and its underlying causes is necessary at least until the age of ten by means of skull circumference measurements, fundoscopy, optical coherence tomography, MRI and polysomnography. Multicentre studies on long-term outcome are required to validate the rationale of different clinical protocols.

ARTICLE HISTORY
Received 1 March 2017
Accepted 23 May 2017

KEYWORDS
Apert; acrocephalysyndactyly; craniosynostosis; *FGFR2*

1. Introduction

Apert syndrome is a rare type of syndromic craniosynostosis. Children have an explicit phenotype with craniofacial dysmorphologies (Figure 1) and severe symmetrical syndactyly of the hands and feet (Figure 2). These features of acrocephalosyndactyly were first observed and published by the French pediatrician Eugène Charles Apert in 1906 [1,2]. In total, 21% of all cases of craniosynostosis is syndromic, and out of all syndromic cases 4.5% is represented by Apert syndrome [3,4]. The prevalence is estimated to be 1 in 65.000–75.000 live births [5,6]. The highest prevalence is found in Asia, where it is 1 in 45.000 live births. It occurs equally in boys and girls.

Several pioneers have been treating children with Apert syndrome for over half a century [7]. We will discuss where their experiences and research has brought us so far.

2. Genetics

Most cases of Apert syndrome are sporadic, although autosomal dominant inheritance could occur in case of natural propagation of an affected individual. The cause of Apert syndrome is found in unique mutations (Ser252Trp (nucleotide change c.755C>G) and Pro253Arg (nucleotide change c.758C>G)) in the Fibroblast Growth Factors Receptor (*FGFR*) 2 gene in 99% [8]. Besides these mutations, a deletion and insertion in exon IIIc of *FGFR2* have been reported as rare causes of Apert syndrome [9]. All these genetic changes have a gain-of-function effect. It leads to abnormal expression of the altered FGFR2 splice form in the mesoderm-derived mesenchyme of the corona suture [10]. This induces an accelerated proliferation and differentiation of the mesenchymal cells resulting in osteogenesis. Consequently, the coronal suture fails in its function of facilitating skull growth. Instead, synostosis of the frontal bone to the parietal bone occurs [11,12].

Besides affecting the cranial sutures, the *FGFR2* changes are also likely to directly affect the brain, as has been demonstrated in a mouse model. In mice with the Ser252Trp mutation, there is an increase in brain size at post-natal day 0, suggesting that this is a primary rather than a secondary anomaly. Other brain anomalies include cerebral asymmetry and corpus callosum dysmorphology [13]. Regarding the skull base, the rostral regions are affected by primary shape changes. The basio-occipital and parietal regions however are subject to secondary shape changes [11].

Interestingly, there is a positive effect of paternal age on the prevalence of Apert syndrome [14]. New mutations, which are dependent on replication, tend to occur more often with advanced age of the father. This is due to positive selection of mutant spermatogonial progenitor cells in the paternal germ line, resulting in high levels of *FGFR2* mutant sperm [15].

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Article highlights

- Apert syndrome is a rare syndrome with craniofacial dysmorphologies and severe symmetrical syndactylies.
- Multidisciplinary treatment in a specialised center is required to achieve the best mental outcome.
- Patients are at risk for intracranial hypertension.
- To prevent this, we prefer an occipital expansion in the first year of life.
- Screening for intracranial hypertension is strongly recommended at least until the age of ten.

This box summarizes key points contained in the article.

3. Diagnosis

Apert syndrome is primarily a clinical diagnosis, based on the phenotype of head shape (Figure 1), hands, and feet (Figure 2). A newborn is presented most commonly with brachycephaly due to bicoronal synostosis, often accompanied by an enlargement of the anterior fontanel up to the nasal bones. Other features include hypertelorism, exorbitism, midfacial hypoplasia and – to a lesser extent – mandibular hypoplasia.

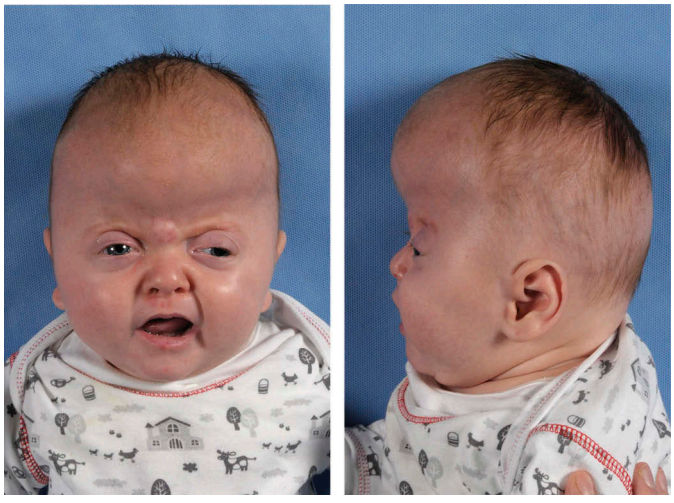

Figure 1. Brachycephaly, exorbitism and midfacial hypoplasia.

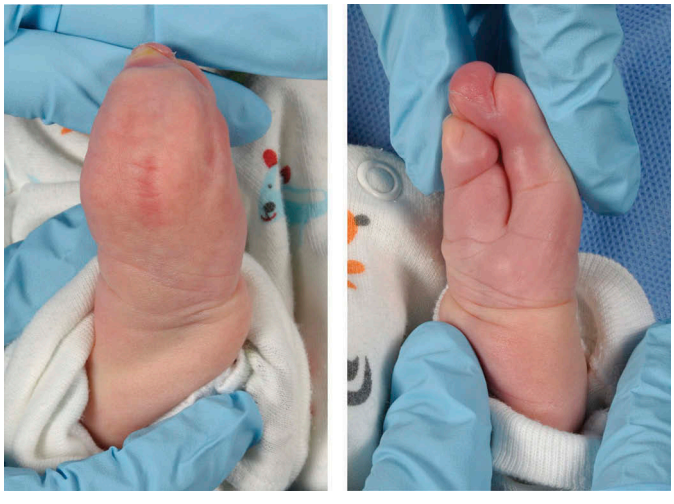

Figure 2. Acrosyndactyly and symphalangism.

It is recommended to first perform a targeted analysis to confirm the pathogenic variants p.Ser252Trp and p.Pro253Arg on the *FGFR2* gene. If these results are negative, one could perform a sequence analysis to detect less common pathogenic variants such as partial gene deletion or insertion [9].

With the improved accuracy of regular antenatal ultrasonic studies, the phenotypic features may be discovered before birth. Retrospective analyses show that craniosynostosis may be diagnosed prenatally in the second trimester due to enlarged ventricles and syndactyly of the extremities or later when the craniofacial deformities become more pronounced. Recent studies show an improvement in antenatal diagnosis using 2D and 3D ultrasound and even MRI [16]. This is an important improvement since early awareness contributes to thorough counseling of the expectant parents. Additionally, delivery in a specialized hospital is urgently recommended because of the increased risk of perinatal complications which consist of traumatic hematomas due to cephalo-pelvic disproportion and an increased risk of unplanned cesarean section [17]. Moreover, severe breathing abnormalities may be present in Apert syndrome and the hospital should be capable of urgent intubation of the child if necessary.

4. Morbidity

The problems that patients with Apert syndrome face can be divided into the craniofacial anomalies, the problems associated with acrosyndactyly and additional congenital anomalies.

4.1. Craniofacial anomalies

The exact shape of the abnormal skull depends on which particular suture is involved. Most often both coronal sutures are closed, the anterior fontanel is enlarged and frontal bossing is obvious. However, also other sutures may be involved resulting in an atypical presentation including metopic suture synostosis [18]. Around the age of one, the biggest concern becomes intracranial hypertension (ICHT). Beforehand, in most of the cases, the anterior fontanel is wide which prevents ICHT until ossification occurs. In initially nonoperated cohorts, 83% of all patients with Apert syndrome develop evident signs of raised intracranial pressure early in life, on an average age of 18 months [19]. Of these patients, 35% developed a second episode of raised intracranial pressure on average 3 years after the initial episode. In a cohort of patients of which 95% was operated primarily (so before ICHT developed), 14% also developed ICHT during follow up [20]. The Australian Craniofacial Unit has reported that only two of 28 adult patients with Apert syndrome had required shunting after initial cranial vault remodeling (mainly frontal-occipital expansion) [21]. A long-term follow-up on nine patients in Los Angeles showed that all but one needed a Monobloc advancement after initial strip craniectomy or frontal-occipital

expansion, but it is unknown if they had a (recurrent) period of ICHT [22].

ICHT is the result of a complex interaction between (1) abnormal skull growth, (2) ventriculomegaly, (3) venous outflow obstruction, and (4) obstructive sleep apnea (OSA).

(1) Deficient skull growth may result in ICHT [23]. It is detected through a fall-off in occipito-frontal head circumference growth, which is closely related to the intracranial volume [24].
(2) Children with Apert syndrome have larger ventricles [25]. The brain volume itself is normal. We observe exaggerated expansion of the ventricles at the site of the most expansive compensatory growth, sometimes accompanied by enlarged subarachnoid spaces in these areas. It usually remains stable over time [25]. The effect of ventriculomegaly on the brain is unknown. The cause of ventriculomegaly is also unclear. It may reflect a primary brain abnormality, overproduction of CSF, reduced absorption, or obstructed outflow of CSF [26]. Although compensatory skull growth results in a larger than normal skull volume, the cerebrum profits only in part from this skull volume due to ventriculomegaly. There might even be a disadvantage to this enlarged volume by the consequent elongation of the white fibers.
(3) Venous outflow obstruction manifests as abnormal venous collaterals and dilated emissary veins, particularly at the occipital area [27]. This appears to be a congenital abnormality of the venous system, and not so much a compensating reaction to ICHT. It is likely that venous hypertension plays an important role in the development of ICHT [28,29].
(4) There is a high prevalence of 70% of OSA in children with Apert syndrome, which is the result of a multilevel upper airway obstruction [30,31]. The spectrum runs from upper airway resistance, without real apneas up to severe obstructed breathing. OSA may result in hypercapnia and subsequent vasodilatation of the cerebral vasculature which contributes to ICHT [32]. As a result of relaxation of the pharyngeal musculature, OSA occurs mainly in rapid eye movement sleep, when the intracranial pressure already rises due to increased blood flow [33]. OSA and intracranial pressure are interrelated and treatment of ICHT should go hand in hand.

Sleep apnea is preferably measured using polysomnography (PSG). This is a multi-parametric test over night that captures electro-encephalography, heart rate, oxygen saturation, respiration movements, and intravenous CO_2 examination. PSG studies have shown a higher respiratory effort-related arousal index, lower sleep efficiency, and less rapid eye movement sleep in patients with syndromic craniosynostosis with moderate or severe OSA [33]. For follow-up, ambulant polygraphy may be considered [34]. Extreme deterioration of OSA for an individual patient is uncommon, which implies that the first PSG produces a good predictive value for expected severity of OSA during the following years. Spontaneous improvement of OSA is unlikely in Apert syndrome [31].

Snoring, persistent upper airway resistance, and mild OSA are not associated to ICHT, but may require treatment if patients are symptomatic, such as tiredness during the day [35]. Central sleep apnea is commonly found in the sleep studies during the first year of life, but appears self-limiting with advancing age [30].

Prolonged ICHT may structurally affect the optic nerve and the brain itself and therefore further visual impairment and neurocognitive delay are feared. Moreover, ICHT may lead to a herniation of the hindbrain. If this herniation is more than 5 mm through the foramen magnum, it is called a Chiari I malformation. Data on the prevalence of the Chiari I malformation among patients with Apert syndrome are variable, differing from 2% to 29% [25,36,37].

4.2. Visual impairment

In addition to the effect of ICHT on the optic nerve, children with Apert can present with severe exorbitism caused by midface hypoplasia. The overexposed cornea is vulnerable due to insufficient eyelid closure, which may cause conjunctivitis and keratitis. Also, amblyopia and visual impairment are more common in patients with the *FGFR*2 Ser252Trp mutation [38,39]. Strabismus is present in as much as 93% of all patients and a refractive error was found in 76% [20].

4.3. Central nervous system malformations

Agenesis of the corpus callosum (12–50%), anomalies of the septum pellucidum (24% PMID) and hydrocephalus (33.3%) may be present [37,40].

4.4. Mental retardation

Most patients exhibit mental retardation and behavioral disabilities. The mean Full Scale IQ score in patients with Apert syndrome was 76.7 ± 13.3 in our cohort. These data are comparable to those in other cohorts in which they vary from 62.0 to 93.8 (range 10–115). Generally, patients with syndromic craniosynostosis have more internalizing, social and attention problems, but not more externalizing problems, as measured by the Child Behavior Checklist. Also, ADHD-any type and ADHD-hyperactive-impulsive type is more common in children who have syndromic craniosynostosis [40].

Generally, for craniosynostosis, there is increasing evidence that the functional and mental outcome is better after early cranial vault expansion. Specifically, for Apert syndrome, it seems that there is a higher risk of mental retardation, regardless of surgery [41], which is related to the *FGFR*2 mutation. Three main associated factors for a better mental outcome are the combination of cranial surgery before the age of one, the absence of brain malformations, and high quality psychosocial environment. A posterior surgical expansion usually with distraction is routinely recommended before the age of one. Long-standing ICHT and sleep apnea should be avoided to preserve the cognitive capacities as much as possible. Finally, there is a correlation between developmental outcome and

treatment at an expertise center from birth on, which is therefore highly recommended [37].

4.5. Acrosyndactyly

Patients with Apert syndrome have acrosyndactyly and symphalangism, involving fingers and toes in mostly a symmetrical manner. The patients with the Pro253Arg mutation are often affected by a more severe syndactyly [42]. The hand deformity is classified into three types (Table 1). As a result of the syndactyly, the thumb is short and radially deviated. Synonychia with paronychia may be present, depending on the type. Additionally, patients have decreased mobility of the shoulder and elbow joint which becomes worse with increasing age. Hips and knees may also be involved, as well as the ankle joints and feet, resulting in an often-overlooked severe functional impairment.

4.6. Other

- Cleft palate; of which there is some evidence that it occurs more often in the patients with a Ser252Trp mutation. A retrospective cohort showed an incidence of palatal abnormalities of 50% [43].
- Hearing loss is present in 72–80% of patients with Apert syndrome [20,44]. 11% needed a hearing aid [20]. In the majority of patients, it concerns a conductive hearing loss. This is explained by the effect of *FGFR2* on the development and function of inner ear and auditory sensory epithelium [44].
- Cervical anomalies were present in 50.8 % in a retrospective cohort. These included fusions of posterior elements of C5/C6 in the majority of patients, C3/4 or multilevel. Other abnormalities were C1 spina bifida occulta and atlanto-axial subluxation [45].
- Heart diseases include septal defects, dextrocardia, and aorta anomalies including tetralogy of Fallot.
- Skin anomalies consist of hyperhidrosis and acneiform lesions. These may become so severe during puberty that treatment by a dermatologist is required and it may have a huge effect on psychosocial well-being of the patient.

Table 1. Acrosyndactyly of the hand in Apert syndrome.

	Thumb	Digit 2, 3, 4	Digit 5
Type I	Brachyclinodactyly Incomplete 1st-web syndactyly	Symphalangism Complex syndactyly	Simple (incomplete) syndactyly of 4th web or separate digit MC 4–5 synostosis possible
Type II	Brachyclinodactyly Simple (incomplete) syndactyly	Symphalangism Complex syndactyly	Complete syndactyly Duplication P3 possible MC 4–5 synostosis possible
Type III	Brachyclinodactyly Complex syndactyly Paronychial infections Skin maceration	Symphalangism Complex syndactyly Paronychial infections Skin maceration	Complete syndactyly Duplication P3 possible MC 4–5 synostosis possible

- Urogenital abnormalities vary between kidney, bladder, and vaginal deformities.
- The presence of diaphragmatic hernia and omphalocele has also been reported on [46,47].

5. Treatment

The treatment of Apert syndrome may vary per unit and child. We present the treatment protocol that is followed in the Dutch Craniofacial Center in Rotterdam.

5.1. Pre- and early postnatal care

In case of antenatal detection of Apert syndrome a consultation at a craniofacial unit to counsel the expectant parents is recommended. After birth, it is important to immediately assess the presence of obstructive breathing and desaturations. In case of OSA, the airway patency can improve with prone or lateral positioning. If closure of the eyelids is incomplete, prescription of lubricating eye ointment may be necessary. A pediatrician should be consulted to analyze the presence of other anomalies.

5.2. Craniofacial surgery

Cranial vault expansion addresses both craniocerebral disproportion as well as venous hypertension [23].

(1) It is our protocol to start with a posterior vault remodeling within the first year of life. The increase in volume is higher after a posterior vault expansion compared to a fronto-orbital advancement [48], and therefore the preferred primary approach, either with the use of springs or distractors. This also leaves the anterior part of the skull untouched for future anterior cranial or facial surgery. Moreover, the flattening of the occiput, commonly present due to hypotonia of the child, is addressed at the same time.
(2) If a child has recurrent eyeball luxations, a monobloc advancement with internal distraction and a transfacial pin is indicated rather than a posterior vault expansion. Sometimes, a tarsoraphy is the only temporarily solution to protect the eyeball when waiting for midface advancement.
(3) If a child has severe OSA, we prefer a tracheal cannula temporarily since a monobloc advancement with internal distraction is safer at the age of 2 or 3 years old. It should be excluded that the problem is based at the level of the tongue base. If so, a monobloc will not resolve OSA and mandibular distraction may be necessary for which we also prefer an age of at least 2–3 years old.
(4) Stable ventriculomegaly does not require shunting. Venous outflow hypertension associated with an absence of true hydrocephalus is a contraindication for neurosurgical shunting.
(5) Hindbrain herniation is not as frequent as in Crouzon syndrome and often not symptomatic. However,

hindbrain herniation may need shunting or suboccipital decompression in case of progressive neurological signs or radiological progression, especially the development of a syrinx.

5.3. OSA

Treatment of OSA in patients with Apert syndrome should be adapted to the outcome of a sleep study and the level of obstruction which is analyzed using upper airway endoscopy [30]. It may vary from tracheostomy, treatment of choanal atresia, nasal corticosteroids, adenotonsillectomy, noninvasive ventilation, palatal split, and midface advancement [21,31]. The disturbed sleep architecture in patients with Apert syndrome was shown to normalize after monobloc surgery [33]. If a cleft palate is present, timing of surgical closure should be critically considered in case of OSA.

5.4. Hand surgery

The aim is to reconstruct a five-fingered hand, although this may be difficult in case of a type III complex syndactyly [49]. Surgery is staged. The early phases include releasing and reconstructing the thumb with desyndactylization of one or more webs. A free thumb is essential to facilitate pinch and large object grasp. This improves neurocognitive development [50,51] and is therefore performed within the first half year of life. The goal is to achieve a pulp-to-pulp pinch to the index finger or little finger [43]. In addition to the reconstruction of the hand, an increase in surgery of the feet is performed in the last decade at our department, with promising results. Recently, the hip, knee, shoulder, and elbow complaints are more often recognized by specialists and treated if necessary. Inclusion of a rehabilitation specialist within the team is essential.

Operations of the hand and feet have to be carefully planned, starting with first stages in the first year of life, depending on the type of hand difference, and the planning of craniofacial-related reconstructions.

5.5. Neurocognition

Screening by a pediatric psychologist is recommended from the age of 3 years old onwards to screen for associated psychopathology. Moreover, the support from a social worker is required to support the parents in how to cope with raising a child with Apert syndrome.

5.6. Follow up

Recurrence of ICHT should be followed up by means of repeated skull circumference measurements, fundoscopy, optical coherence tomography (OCT), MRI, and PSG. If there is a suspicion of a recurrent episode of ICHT, consider invasive ICP monitoring. If ICHT is confirmed, the cause should be analyzed and treated. This may be an insufficient intracranial volume or OSA. Patients could undergo a redo of the occipital expansion or fronto-orbital advancement, which depends on the shape of the skull. Preferably, MRI and CT angiography are then required for surgical planning.

6. Conclusion

Children with Apert syndrome are prone to develop ICHT, functional impairment and mental retardation, which is partially caused by the *FGFR2* mutation. Early release of the thumb is beneficial for childhood development. Mental outcome seems to improve if patients are treated early and preferably by means of occipital expansion. Abnormal skull growth, ventriculomegaly, venous outflow obstruction, and OSA should be monitored closely. Centralizing care in an expert center is of utmost importance for the benefit of the child. Treatment should be individualized but derived from an evidence-based protocol for which multicenter studies of different clinical protocols are required. This includes an analysis of ICHT prevalence, neurocognition, visual outcome, and presence of Chiari with or without syrinx after long-term follow up. By gaining these new insights, treatment can be customized as much as possible to prevent additional harm to a child with Apert syndrome. Our aim is to offer them the best functional and cognitive outcome and achieve an appearance which resembles 'normal' as much as possible.

7. Expert opinion

Our expert opinion is based on the literature that we discussed above and over 40 years of experience in the treatment of patients with Apert syndrome. Traditionally, the preferred initial cranioplasty was a fronto-orbital advancement. Since 2005, we prefer occipital expansion and ever since we perform an occipital expansion first, the incidence of ICHT and Chiari I malformation during follow up has decreased [48,52].

Worldwide, there is a minority who chooses to wait and see if secondary symptoms of ICHT arise instead of performing a cranioplasty regularly [19]. Follow up is performed by means of fundoscopy, optical coherence tomography, or visual evokes potentials scans every few months to study the optic nerve [53]. Opponents of this approach claim that optic nerve abnormalities are a late phenomenon of ICHT, the current ophthalmologic investigations are insufficiently reliable and that mental outcome may be better in the patients operated on early [54].

Some clinics routinely perform a fronto-orbital advancement a year after the occipital expansion. They will later perform a LeFort III osteotomy with distraction to address the midface. We prefer to wait to perform a monobloc advancement, as this can be done with internal distractors instead of an external frame and because it preserves the frontonasal angle, while a Le Fort III elongates the nose. If there is no severe exorbitism, OSA or ICHT, we wait until the age of seven. A facial bipartition is preferred if hypertelorism needs to be addressed simultaneously. This procedure requires the use of an external frame for the initial distraction, while the consolidation period can be managed with the internal distractors only. An external frame might be contraindicated in Apert patients with significant behavioral issues. The age for these midface procedures varies among different leading centers from 2 to 10 years old, but could also be postponed until adulthood. The potential downside of midface advancement is velopharyngeal insufficiency. These odds appear to be higher if there is, or has been, a cleft palate. Recognition, speech analyses, and therapy is then recommended. Sometimes it is indicated to surgically widen the narrow maxilla.

Table 2. Timing of follow up.

Timing	SC[a]	X ray	Fundo[b]	CT angiography[c]	MRI[d]	Brouillette score	PSG	ENT[e]
At presentation	•		•	•	•	•	•	
At surgery								UAE[f]
1 year	•	•	•			•		HT[g]
1+3 months	•					•		
1+6 months	•		•			•	•	
1+9 months	•					•		
2 years	•	•	• + orthoptist		•	•	•	SE[h]
2+6 months	•					•		
3 years	•		•			•	•	
3+6 months	•					•		
4 years	•	•	•		•	•	•	
5 years	•		•			•	•	
6 years	•	•	•			•	•	
7 years	•	•				•		
8 years	•	•				•		
9 years	•	•				•		
10.5 years	•	•				•		
12 years	•	•				•		
15 years	•	•				•		
18 years	•	•				•		
21 years	•	•				•		

[a]SC: skull circumference.
[b]Fundo: fundoscopy; to assess the presence of papilledema. From the age of six years onwards only when clinically indicated. Optical coherence tomography may be used as an alternative.
[c]CT angiography; to assess venous collaterals and dilated emissary veins.
[d]MRI; to assess ventricle size, hindbrain herniation, and other brain anomalies.
[e]ENT: ear nose and throat.
[f]UAE: upper airway endoscopy; repeated whenever moderate or severe OSAS is detected.
[g]HT: hearing test.
[h]SE: speech evaluation.
PSG: polysomnography; repeated whenever the Brouillette score is abnormal.

In our experience, additional orthognathic surgery is indicated at the age of 18, when skeletal maturity is reached, to correct open bite and remaining skeletal dysbalance. This is preceded by orthodontic treatment. Other procedures include repositioning of the zygoma and nasal septum correction.

In our expertise center there is a narrow collaboration of plastic surgeons, neurosurgeons, maxillofacial surgeons, specialized intensive care pediatricians, ENT surgeons, ophthalmologists, orthodontics, speech therapists, social workers, medical psychologists, and a dedicated nurse practitioner to facilitate optimal care. There is a craniofacial outpatient team meeting at the age of 4, 6, 9, 12, 15, and 18 years old. The current work up and follow up of our children with Apert syndrome is listed in Table 2. We have an ongoing prospective study that enables us to continuously update our treatment protocol with the latest scientific conclusions to provide the best care possible.

Funding

This paper was not funded

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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