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ORIGINAL PAPER

Central nervous system and cervical spine abnormalities in Apert syndrome

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Abstract
Purpose Apert syndrome characterized by acrocephalosyndactyly is a rare autosomal dominant congenital malformation with a prevalence of 1/65,000 births. With an extensive range of phenotypic and developmental manifestations, its management requires a multidisciplinary approach. A variety of craniofacial, central nervous system (CNS), and cervical spine abnormalities have been reported in these patients. This study aimed to determine the incidence of these CNS abnormalities in our case series.
Methods Retrospective review of Australian Craniofacial Unit (ACFU) database for Apert patients was performed. Data collected that included demographics, place of origin, age at presentation, imaging performed, and images were reviewed and recorded. Where available, developmental data was also recorded.
Results Ninety-four patients seen and managed at the ACFU had their CNS and cervical spine abnormalities documented. The main CNS abnormalities were prominent convolutional markings (67 %), ventriculomegaly (48 %), crowded foramen magnum (36 %), deficient septum pellucidum (13 %), and corpus callosum agenesis in 11 %. Major C-spine findings were present in 50.8 % of patients and included fusion of posterior elements of C5/C6 (50 %) and C3/4 (27 %). Multilevel fusion was seen in 20 %. Other abnormalities were C1 spina bifida occulta (7 %) and atlanto-axial subluxation (7 %).
Conclusion Multiple CNS and cervical spine (c-spine) abnormalities are common in Apert syndrome. The significance of these abnormalities remains largely unknown. Further research is needed to better understand the impact of these findings on growth, development, and treatment outcomes.

Keywords Apert syndrome · Abnormalities · CNS · Cervical spine · Craniosynostosis

Introduction

Abnormal skull shapes were known in antiquity; they were later described by both Hippocrates and Galen. Virchow was the first to associate abnormal skull shape to premature fusion of cranial sutures in 1851 [1].

In 1906, Dr. Eugene Apert, a French physician described nine cases with a condition he named acrocephalosyndactyly, all having acrocephaly and severe syndactyly of all limbs. The syndrome was eponymously named Apert syndrome [2].

This rare syndrome (1/65,000 births) characterized by bilateral coronal suture fusion, abnormal cranial base development, syndactyly of the hands and feet, symphalangism (fusion of digital phalanges), radio-humeral fusion, and varying degrees of neurocognitive impairment is autosomal dominant with 98 % of cases due to de novo mutations [3]. Up to 75 % of patients have an associated cleft palate or bifid uvula [4].

Genetic mutations discovered in 1995 by Wilkie et al. identified two adjacent mutations (S252W or P253R) of the FGFR2 gene on chromosome 10q in all patients with Apert syndrome [5]. Further research has identified two other de novo insertion mutations in the

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same gene. These four mutations transmitted in the paternal chromosome are causative in this condition, [6] thus the theory of advanced paternal age being a risk factor in Apert syndrome [7]. The significant phenotypic variability observed in Apert syndrome is thought to be due to environmental or supplemental genetic factors.

The craniofacial findings of Apert syndrome have been described in detail [8]. The skull is hyperacrobrachycephalic—a steep, wide, and flattened forehead with a flat occiput [8]. The skull's asymmetry at birth is due to premature intrauterine fusion of the coronal suture; unilateral or bilateral lambdoid suture fusion in infancy or early childhood further establishes the shape.

Patency of other calvarial sutures overlying the expanding underlying brain results in the developing skull shape being constrained and deformed during intrauterine life. The forehead bulges with widening around the temporal region; overt clover leafing of the skull however is rare [9]. A midline calvarial defect is usually found at birth, this closing progressively over the first 2 years or more.

Abnormal skull base development occurs with the sphenofrontal suture being fused at birth; subsequent premature closure of both spheno-occipital and petro-occipital synchondroses in early infancy with associated bicoronal synostosis results in a shortened skull base [8]. A shortened anterior fossa has a widened cribriform plate and a steeply ascending lesser wing of the sphenoid resulting in shallow orbits with various degrees of proptosis. The middle cranial fossa is also shortened with marked elevation and bowing of the greater wings of the sphenoid. The underlying growing brain results in deformity with lateral bowing of the squamous temporal bone [10]. The posterior cranial fossa is unusually small and asymmetric with crowded contents.

Multiple abnormalities of the central nervous system (CNS) have been reported in Apert syndrome. Abnormalities commonly reported include ventriculomegaly, hydrocephalus, deficient or absent septum pellucidum, abnormalities of the corpus callosum, and limbic structures [11]. Their clinical significance remains unknown. Their true incidence is difficult to ascertain due to the small sample size of most published reviews [11].

Study

This study reviews Apert cases treated by the Australian Craniofacial Unit and Neurosurgical Unit at the Women's and Children's Hospital in Adelaide, Australia, and documents the incidence of CNS abnormalities and cervical spine abnormalities in Apert syndrome in a large case series evaluated by an experienced multidisciplinary team.

Materials and methods

Inclusion criteria

Patients with complete medical records in both datasets (ACFU and Central Medical Records Department) were included.

Exclusion criteria

Any patient whose records were incomplete or only available on one dataset was excluded.

After permission from the hospital medical ethics department, a retrospective review of all patient records with a diagnosis of Apert syndrome assessed and managed by the ACFU from 1985 to 2013 was conducted. Patient records were retrieved from two databases, the Central Medical Records Department and the Australian Craniofacial Unit's database (collected prospectively) enabling cross-reference and internal validation of data. Consent for inclusion in approved ethical study is collected prospectively from patients or carers at admission. Of the distinct patients with Apert syndrome, 118 were identified from both databases.

Fourteen patients' records could not be located in the Central Medical Records and these were excluded. They had been assessed or treated in South East Asia by visiting surgeons from the ACFU and included in the unit's database. Nine other patients were excluded due to inadequate medical records.

Both databases had 94 complete patient records, which comprise this review; their demographic data, nationality, radiographic findings of various CNS anomalies, and cervical spine abnormalities were recorded.

Results

Ninety-four patients are included in this study. There were near-equal numbers of male and female patients (49 males and 45 females). Fifty-one patients presented before 12 months of age while 43 presented after the age of 12 months. A significant number of patients came from neighboring countries for treatment.

All patients underwent pre-operative 3-D computerized tomography (CT) scanning. CNS malformations identified are outlined in Table 1 below. Other CNS abnormalities found included occipital encephaloceles (three patients) and one patient with a temporal encephalocele (Table 2). One patient had cerebral hemiatrophy with severe intellectual disability.

Fifty-seven patients had adequate imaging of the cervical spine, and 50.8 % had cervical spine (c-spine) abnormalities. The commonest abnormality (50 %) was fusion of the

Table 1 Frequency of common CNS abnormalities in Apert syndrome

Abnormality	Number affected	Percentage
Convolutional markings	63	67 %
Ventriculomegaly	45	48 %
C-spine abnormalities	33	35 %
Crowding of foramen magnum	34	36 %
Absent/deficient septum pellucidum	12	13 %
Corpus callosum agenesis	10	11 %
Chiari 1 malformation	4	4 %

posterior elements of C5/6. Fusion of C3/4 was seen in 27 % of patients while 20 % had multilevel fusion (Table 3).

Discussion

This study elucidates the CNS and cervical spine abnormalities found in Apert syndrome patients treated in a large clinical series in the ACFU. Previous publications have been made from this unit [12, 13].

CNS abnormalities

The commonest structural CNS abnormality was ventriculomegaly, found in 48 % of patients (Fig. 1). This is consistent with the literature [11], with a reported frequency of up to 60 % in some case series [14]. This was mostly a non-progressive ventriculomegaly consistent with previous documentation in the literature [11, 12, 15]. All patients presenting after 5 years of age with no previous surgical intervention had normal-sized ventricles, suggesting that ventriculomegaly became less apparent with progressive brain growth. Different mechanisms likely contribute to the non-progressive ventriculomegaly. Most authors believe that it may reflect primary brain parenchymal maldevelopment or a compensated state of increased CSF outflow resistance [16]. The presence of significant cerebral abnormalities in Apert syndrome suggests that the ventriculomegaly may be related to primary structural maldevelopment. This form of ventriculomegaly has been called "distortion ventriculomegaly" by Cohen and Kreiborg [11] to emphasize the malformative nature of the ventricular enlargement. However, shunt-independent ventriculomegaly has also been observed in Crouzon syndrome, which is usually associated with normal cerebral development. Therefore, some authors favor the idea of a compensated hydrocephalic state due to venous hypertension in Apert syndrome [15]. Venous hypertension induced by jugular foramen stenosis [17] and abnormalities in venous drainage results in a higher CSF pressure required for CSF outflow balance, and this is an important cause of increased intracranial pressure (ICP) [18]. In children with open sutures, this leads to progressive head enlargement, resulting in dilatation of ventricles and subarachnoid spaces as seen in achondroplasia [19]. This mechanism is believed to contribute to the progressive hydrocephalus seen in Crouzon syndrome. Why does this not cause progressive hydrocephalus in Apert syndrome? In Apert syndrome, although the bicoronal synostosis may be severe and develops early, sagittal and lambdoid suture involvement is rare and late. Additionally, fusion of the cranial base synostoses occurs later in life, and jugular foramen stenosis is less common in Apert compared to Crouzon [15, 17]. This venous hypertension in the setting of large open sutures may explain why ventriculomegaly in Apert syndrome is rarely progressive. In addition, our finding that ventriculomegaly is no longer apparent in our patients greater than 5 years of age may be explained by the development of collateral venous pathways with age. A similar phenomenon is seen in achondroplasia, and this explains why patients with achondroplasia rarely need shunting [19].

Table 2 Other less frequent CNS abnormalities reported

CNS abnormalities	Number affected
Occipital encephaloceles	3
Temporal encephaloceles	1
Bilateral colpocephaly	2
Choroidal fissure cyst	1
Cerebral hemiatrophy	1
Vermian hypoplasia	1

The skull base in Apert syndrome demonstrates a shortened antero-posterior dimension in all (anterior, middle, and posterior) cranial fossae [8]. Although some studies have reported a normal-sized posterior fossa [20], the middle and posterior cranial fossae subsequently increase in height to accommodate the growing brain with resultant turribrachicephaly. The incidence of Chiari malformation in these patients ranges from 1.8 [20] to 29 % [21] (Fig. 2). In this study, the incidence of Chiari malformation was 4 % with approximately 36 % of patients having a crowded foramen magnum (FM), which is a common finding in Apert and other syndromic craniosynostosis [22]. The reason for the low incidence of Chiari malformation in Apert syndrome may be associated with the pattern of sutural fusion. In one study comparing Crouzon and Apert syndromes, the incidence of Chiari malformation was 72.7 % and 1.9 %, respectively [20]. The authors also compared the patterns of sutural closure in these patients and found that although bicoronal sutural fusion was at around the same age (5 months in Apert and 8 months in Crouzon), the fusion of sagittal and lambdoid sutures

Table 3 Identified C-spine abnormalities

C-spine abnormality	Number affected	Percentage of c-spine abnormalities
C5/C6 fusion of posterior elements ± vertebral body	15	50 %
C3/C4 fusion of posterior elements ± body	8	27 %
C1 spina bifida occulta	2	7 %
Atlanto-axial subluxation	2	7 %
C1 occipital fusion	1	3 %
C3/4 subluxation	1	3 %
Multiple segments of fusion	6	20 %

differed significantly [20]. The sagittal suture closed very early in Crouzon (median 6 months) and later in Apert (median 51 months). The lambdoid suture closed at a median age of 20 months in Crouzon and 60 months in Apert [20]. This difference in suture closure may explain why the incidence of Chiari malformation differs so much between the two syndromes. The delayed closure of the lambdoid suture (although it closes earlier than normal children) allows the posterior fossa to adapt more to cerebellar growth in Apert than Crouzon syndrome.

Parenchymal abnormalities included absence/deficiency of the septum pellucidum (13 %) and corpus callosum agenesis (11 %). Half of the patients with corpus callosum agenesis exhibited concurrent absence of the septum pellucidum. Given their common embryological origin from the commissural plate during the sixth to seventh week of gestation [23], this finding suggests primary maldevelopment of this region. Renier et al. (1996) showed that septal abnormalities in Apert syndrome were associated with an intelligence quotient (IQ) of less than 70 while corpus callosum malformations and ventricular size appeared not to affect IQ [24]. Other studies have found no association between intracranial anomalies and development [21, 25]. The significance of these abnormalities remains unknown. One study found that mental development did not correlate with brain malformation but found that mental development was related to the family environment and parental education. [25]

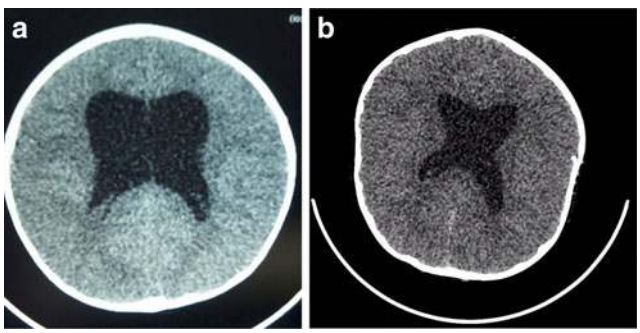

Fig. 1 **a** Axial CT scan showing ventriculomegaly, deficient septum pellucidum, and significant increased intracranial pressure in a male who presented at the age of 3 with Apert syndrome. **b** Axial CT scan showing ventriculomegaly and an absent septum pellucidum

Skull inner table convolutional markings when pronounced and extensive (copper-beaten skull) are suggestive of raised ICP. However, they have a low sensitivity for raised ICP [26]. It remains unclear what role, if any, increased ICP plays in development of convolutional markings [27]. Radiographic evidence of convolutional markings before the age of 18 months in healthy children is uncommon; it is seen in children older than 18 months due to the rapid brain growth from this age up to 8 years. [28] Convolutional markings in craniosynostosis however are more extensive compared to healthy subjects [26]. The presence of convolutional markings at an early age appears to have no significant long-term effect on intelligence levels [28]. Extensive convolutional markings were present in 67 % of CT scans; 57 % of patients presenting before the age of 1 year had them. In patients older than 1 year with no previous intervention, this increased to 75 %. The presence of prominent convolutional markings may represent a generalized disturbance of normal brain development or be a normal consequence of rapid brain growth in constrained surroundings and a malleable cranium [28].

Other CNS abnormalities found are included in Table 3. Four patients were found to have encephaloceles, three occipital and one temporal. Frontal and temporal encephaloceles have previously been reported in Apert syndrome [11, 29]. Two previous cases of occipital encephaloceles have been reported in literature, and this to our knowledge is the third report with more cases (Fig. 3) [30, 31].

C-spine abnormalities are reported in Apert syndrome with up to 65 % incidence [32, 33]. In this review, the incidence of c-spine abnormalities was 50.8 %. The slightly lower frequency may be due to the large number of younger patients in our cohort, who at the time of imaging may not display obvious c-spine abnormalities. This may be representative of progressive fusion phenomenon which has been demonstrated in previous studies [32, 33]. Thompson et al. (1996) in an analysis of sequential radiographs in 17 patients demonstrated progressive fusion occurring over time in 10 patients [33]. The

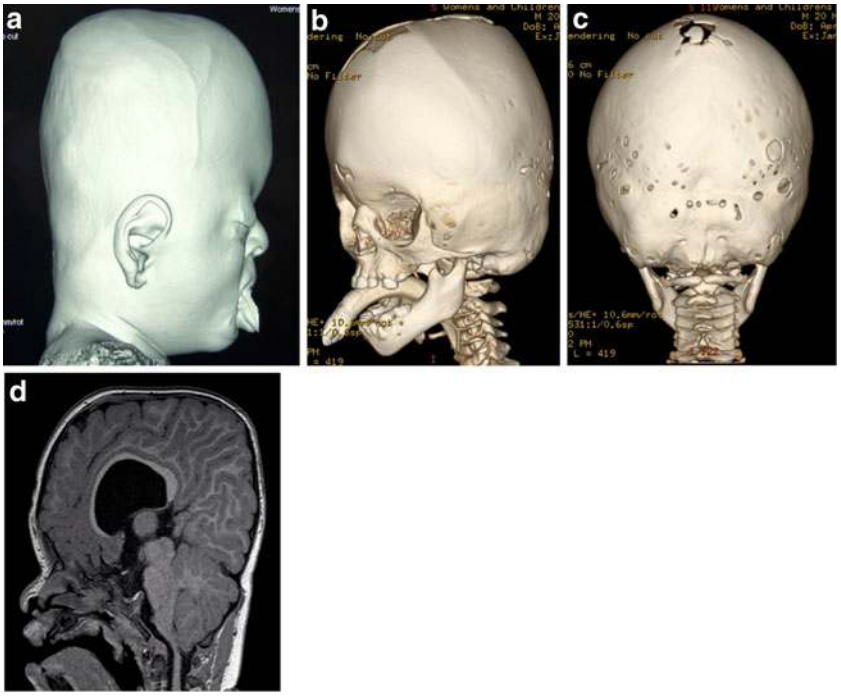

Fig. 2 Images of a child presenting at the age of 2 with Apert syndrome. **a** Soft tissue CT reconstruction demonstrating turribrachicephaly, orbital proptosis, and midfacial hypoplasia. **b** 3-D CT reconstruction demonstrating turribrachicephaly, bilateral coronal suture synostosis, midfacial hypoplasia, and shallow orbit. **c** 3-D CT reconstruction from posteriorly demonstrating bilateral lambdoid suture synostosis, convolutional markings, and C5/C6 fusion of posterior elements. **d** Sagittal T1-weighted MRI scan of child with Apert syndrome. Abnormalities present include the turribrachycephalic shape of the skull, the narrow cranial base, thin corpus callosum, crowding of foramen magnum, and a Chiari 1 malformation

authors believed that the fusions might occur at the site of subtle congenital vertebral anomalies that may not be apparent as a congenital feature.

Majority of patients in this series had fusion of the C5/6 posterior elements (50 %) consistent with the literature (Fig. 2).[32, 33] Twenty percent of cases had multiple levels of fusion. C-spine abnormalities may complicate intubation of an already compromised airway adding to the complexity of anesthesia for reconstructive surgery. An appropriate evaluation of the C-spine in Apert syndrome patients is imperative.

C-spine abnormalities correspond to the areas of maximal contribution to the brachial plexus. This may represent a primary abnormality of neural fetal development with the resultant forearm and hand findings. Data from lumbar imaging would have been important to test this hypothesis with respect to the lumbar plexus and the attendant syndactyly of the lower limbs. The lumbar region was not imaged regularly in our center, and this data could not be compiled. An extensive literature search also failed to find any studies reporting on this. Further research is required to determine if associated brachial and lumbar plexal developmental abnormalities explain the syndactyly found in Apert syndrome.

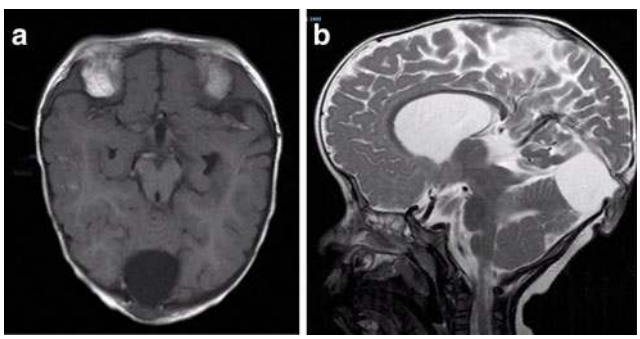

Fig. 3 Patient with Apert syndrome with occipital encephalocele. **a** Axial T1-weighted MRI scan and **b** sagittal T2-weighted MRI scan demonstrating encephalocele

The main limitation of our study relates to the fact that the CNS abnormalities reported were seen on CT imaging only. Few patients underwent magnetic resonance imaging (MRI) in our unit as this is an expensive test and often does not alter management. An MRI however would be more accurate in identifying brain parenchymal abnormalities [10]. Another limitation in this study was the lack of developmental data available to determine the significance of different CNS abnormalities to overall development and growth. This data is difficult to collect in a unit like the ACFS because a significant number of our patients are from countries other than the home country of the unit. This makes long-term follow-up of development and standardization of tools for assessing development very difficult.

Future studies should aim to determine which of these abnormalities correlate most with developmental

abnormalities or intellectual disability. Measuring IQ and thoroughly evaluating development during growth in Apert syndrome patients with specific CNS abnormalities may guide parental and clinician expectations of treatment and guide neurocognitive training required for these children as they grow.

Conclusion

Apert syndrome is associated with a wide array of parenchymal CNS and cervical spine abnormalities. The significance of these parenchymal abnormalities remain unclear but are likely surrogate markers of functional brain defects with a greater number of abnormalities, potentially resulting in further reduced executive function. Being aware and understanding the significance of these abnormalities and the natural history of these anomalies is vital for the treating multidisciplinary team.

Further research is needed to determine the significance of specific abnormalities on the growth and development of these patients and which patients benefit most from treatment.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest to declare.

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