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Apert syndrome: Surgical outcomes and perspectives

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ABSTRACT

Purpose: Apert syndrome is a rare congenital malformation with severe craniofacial anomalies. The aim of this study was to review the outcomes of craniofacial and neurosurgical interventions in Apert syndrome patients treated at a single institution.

Materials and methods: A retrospective review of all patient records with a diagnosis of Apert syndrome assessed and managed in the Australian Craniofacial Unit (ACFU) from 1985 to 2013 was conducted.

Results: A total of 94 patients were identified, and 130 transcranial procedures were performed. Of the patients, 83 underwent a fronto-orbital advancement (FOA) as their primary procedure, and 18 patients also underwent a posterior vault procedure. Twenty patients underwent a fronto-facial monobloc advancement. Overall, 70% of patients underwent at least 2 transcranial procedures. Shunts were inserted in 2 patients preoperatively and in 5 patients postoperatively for cerebrospinal fluid (CSF) leaks or acute hydrocephalus. Re-do FOAs were performed in 8 patients. Patients who underwent an FOA at the age of more than 18 months had no recurrence of raised intracranial pressure (ICP). Of 18 patients who also underwent a posterior vault procedure, 1 patient had recurrence of raised ICP. Midfacial surgery was performed early if there was evidence of obstructive sleep apnoea (OSA), but delayed midfacial surgery was preferred. Complications were reported in 18% of procedures. The most common complications were CSF leaks and acute hydrocephalus.

Conclusion: Shunting is rarely required in Apert syndrome patients, confirming a predominantly nonprogressive ventriculomegaly. FOA appears to be a more stable procedure when performed at an age of more than 18 months. Undergoing a posterior vault procedure may reduce the risk of recurrent raised ICP and lead to fewer transcranial procedures needed in childhood. Midfacial surgery should be delayed until adolescence where there is no evidence of OSA, psychological disturbance, or complications of exorbitism. Complications are rare when these patients are treated by an experienced craniofacial team.

1. Introduction

In 1906, Dr Eugene Apert, a French physician, described 9 patients with a condition that he named acrocephalosyndactyly, all having acrocephaly and severe syndactyly of all limbs. The syndrome, thereafter eponymously named Apert syndrome (Apert, 1906), is rare (1/65,000 births). It is characterized by craniosynostosis, midfacial hypoplasia with exorbitism, syndactyly of the hands and feet, symphalangism (fusion of digital phalanges), radiohumeral fusion, and varying degrees of neurocognitive impairment. Up to 75% of patients also have an associated cleft palate or bifid uvula (Kreiborg and Cohen, 1992). Apert syndrome is an autosomal disorder, with the majority (98%) of cases arising due to gain-of-function mutations of the fibroblast growth factor receptor 2 gene (FGFR2) (Cohen et al., 1992; Ibrahimi et al., 2005). Genetic mutations discovered in 1995 by Wilkie et al. identified 2 adjacent mutations (S252W or P253R) of the FGFR2 gene on chromosome 10q in all patients with Apert syndrome (Wilkie et al., 1995).

The cranial deformity, primarily due to premature fusion of the coronal suture (with various other sutures usually involved) and abnormal skull base development is described as hyperacrobrachycephalic—a steep, wide, and flattened forehead with a flat occiput (Cohen and Kreiborg, 1996). Patency of other calvarial sutures overlying the expanding underlying brain results in the developing skull shape being deformed during intrauterine life. The

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forehead bulges with widening around the temporal region; overt clover-leafing of the skull is, however, rare (Cohen and Kreiborg, 1994). A midline calvarial defect is usually present at birth. Bony islands form and coalesce, closing both the defect and the anterior fontanelle. The age at which this occurs is variable.

The skull base develops abnormally with the sphenofrontal suture fused at birth; subsequent premature closure of both spheno-occipital and petro-occipital synchondroses in early infancy with associated bicoronal synostosis shortens the skull base (Cohen and Kreiborg, 1996). The shortened anterior fossa, widened cribriform plate, and steeply ascending lesser wing of the sphenoid result in shallow orbits with various degrees of exorbitism. The middle cranial fossa is shortened with marked elevation and bowing of the greater wing of the sphenoid. The enlarging growing brain deforms the overlying calvarium with lateral bowing of the squamous temporal bone (Tokumaru et al., 1996). The posterior cranial fossa remains unusually small and asymmetric with crowded contents. The main surgical focus is the expansion of the cranial vault to accommodate the growing brain, with cosmesis as an important albeit secondary consideration.

The background of constant development and ongoing changes in the bony abnormalities with an underlying expanding brain presents surgeons with perhaps their greatest challenge in the management of Apert syndrome: the type of operation, the timing of the operation (when to operate), and, as always, when not to operate. Our paper intends to add to the Apert syndrome literature, stimulate further research, and contribute to better the management of this complex syndrome.

Due to the rarity of the syndrome, many questions still remain as to the ideal surgical management of Apert syndrome, with various competing and differing opinions. Most reports are based on small case series (Marsh et al., 1991; Allam et al., 2011). Other perspectives and protocols are based on publications by experienced craniofacial units that have reviewed their outcomes and outlined important questions about the care of these patients (McCarthy et al., 1995; Fearon and Podner, 2013). Timing of surgery, stability of results, and need for adjunctive neurosurgical procedures such as shunting are currently controversial topics.

The aim of achieving an aesthetically normal head shape to remove the stigma of disease in Apert syndrome requires a focus on the *entire* cranial vault; the traditional focus on anterior vault procedures may well need to be revisited (Mulliken and Bruneteau, 1991; McCarthy et al., 1995). Correction of the facial deformity has also been made possible by the work of Paul Tessier (Raulo and Tessier, 1981). Fronto-facial advancements, Le Fort advancements, and orthognathic surgery are considered in Apert syndrome patients to try to resolve obstructive sleep apoea, to deepen the orbits to reduce the complications of exorbitism, and to normalize facial appearance for psychosocial development. Due to the variety of surgical options available and the phenotypical variability of the syndrome, there are a wide variety of reported outcomes and protocols for the management of the facial deformity in Apert syndrome (Posnick et al., 2004).

Recent studies in animals and children have also shown neurocognitive delays of the developing brain associated with exposure to general anaesthetics (Loepke and Soriano, 2008; McCann and Soriano, 2012). Thus, an important surgical aim must include stable surgical interventions that reduce the total number of operations needed in the management of these patients.

The Australian Craniofacial Unit provides a unique environment for the management of rare craniofacial anomalies. The ACFU has a patient catchment that extends internationally, especially into Southeast Asia and the Middle East. Some patients are referred at infancy, but others are referred late; hence, sequelae of untreated or late treated Apert syndrome are seen. Management challenges are common, providing an environment for constant critical interrogation and modification of our management protocols.

The purpose of this study was to evaluate the surgical interventions and resultant outcomes of Apert syndrome patients treated at the ACFU, with the aim of identifying correlations that result in improved treatment outcomes for our patients or that have subsequently altered our unit's operative practices.

The main factors considered in this study were as follows: 1) the incidences of adjunctive neurosurgical procedures such as shunting; 2) the incidences of repeat operations, and factors associated with them; 3) comparison of outcomes from patients treated exclusively with anterior vault procedures with those who had both anterior and posterior vault procedures; and 4) the overall incidence of complications from surgical interventions in Apert syndrome.

2. Materials and methods

To address the research questions, the investigators designed and implemented a retrospective case series. This study was undertaken following approval from the ethics committee of the Women's and Children's Hospital of Adelaide. The study population was composed of all patients with Apert syndrome managed by the Australian Craniofacial Unit (ACFU) between January 1985 and September 2013 inclusive. This study was conducted in accordance with the ethical guidelines approved by the Women's and Children's Hospital ethics committee.

To be included in the study sample, patients had to have Apert syndrome confirmed by clinical assessment by experienced clinicians or genetic analysis (which has been used in later years). The patients needed to have complete medical records. Patients were excluded if there was uncertainty about which syndrome the patient had, and if their medical records were incomplete.

Study participants were identified from records within the ACFU department internal records and from the Women's and Children's Hospital Central medical records department. Patient records were retrieved from both databases, as this enabled cross-reference and internal validation of data. The data were checked and validated by 2 independent reviewers (O.B. and A.M.). Consent for inclusion in approved ethical studies is collected prospectively from patients or carers/caregivers at admission.

The data collected included basic demographic data (age at presentation, gender, country of origin), initial clinical and radiographic assessments, surgical interventions offered, and reasons for surgery. In regard to the surgical details, the operations performed, reasons for surgery, age at time of different operations, and operative and postoperative complications as well as management of complications were collected.

3. Results

A total of 118 distinct patients with Apert syndrome were identified from both databases. Fourteen patients' records could not be located in the Central Medical Records, and these patients were excluded. They had been assessed and/or treated in Southeast Asia (Indonesia, Malaysia, Singapore, and China) by visiting surgeons from the ACFU and included in the unit's database. Ten other patients were excluded due to inadequate medical records.

A total of 94 patients were included in this study, with near equal numbers of male and female patients (49 males, 45 females). Of the patients, 51 presented before 12 months of age, whereas 43 presented afterwards (mean age of presentation was 33.2 months; range, birth to 39 years of age). A significant percentage (76.5%) of patients came from neighbouring countries for treatment, most commonly Indonesia (Table 1).