Does the Mutation Type Affect the Response to Cranial Vault Expansion in Children With Apert Syndrome?

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Abstract

Most cases of Apert syndrome are caused by mutations in the FGFR2 gene, either Ser252Trp or Pro253Arg. In these patients, over the last decades, spring-assisted posterior vault expansion (SA-PVE) has been the technique of choice for cranial vault expansion in the Craniofacial Unit of Great Ormond Street Hospital for Children (GOSH), London. The aim of this study was to investigate if there is a difference in preoperative intracranial volume (ICV) in patients with Apert syndrome with Ser252Trp or Pro253Arg mutation and whether these mutations affect the change in ICV achieved by SA-PVE. The GOSH craniofacial SA-PVE database was used to select patients with complete genetic testing and preoperative and postoperative computed tomography scans. ICV was calculated using FSL (FMRIB Analysis Group, Oxford) and adjusted based on Apert-specific growth curves. Sixteen patients were included with 8 having Ser252Trp mutation and 8 having Pro253Arg mutation. The mean preoperative adjusted computed tomography volume for patients in the Ser252Trp group was 1137.7 cm3 and in the Pro253Arg group was 1115.8 cm3 (P=1.00). There was a significant increase in ICV following SA-PVE in all patients (P<0.001) with no difference in mean change in ICV between the groups (P=0.51). Four (50%) patients with Ser252Trp mutation and 3 (37.5%) with Pro253Arg mutations required a second operation after primary SA-PVE. The results demonstrate that regardless of the mutation present, SA-PVE was successful in increasing ICV in patients with Apert syndrome and that a repeat volume expanding procedure was required by a similar number of patients in the 2 groups.

Introduction

Apert syndrome, which affects around 1 in 100,000 live births, was named after French physician Eugene Apert who described its clinical features in the 1906 publication De l'acrocephalosyndactylies.1 The phenotype of patients with Apert syndrome is characterized by turribrachycephaly, mid-face hypoplasia and a symmetrical syndactyly of both feet and hands. During the development of the skull, many factors contribute to the Apert hyperacrobrachycephalic head shape.2 Although synostosis occurs at multiple sutures, the cranial malformation is primarily due to coronal suture synostosis. This is combined with abnormal fusion of the skull base sutures, namely the sphenofrontal, spheno-occipital, and petro-occipital, to leave a shortened skull base and a small, crowded posterior fossa.

Apert syndrome is an autosomal disorder, with gain-of-function mutations of FGFR2 being responsible in 98% of cases.2,3 The majority of Apert syndrome cases are caused by missense mutations of FGFR2, either Ser252Trp (66%) or Pro253Arg (32%).4 The Ser252Trp substitution is associated with a higher frequency of cleft palate, but milder syndactyly, and the Pro253Arg substitution with a more severe syndactyly.3 The phenotype of Ser252Trp and Pro253Arg are displayed in Figures 1 and 2, respectively. Both Ser252Trp and Pro253Arg mutations result in enhanced binding to FGFR2. Ser252Trp mutation displays a greater increase in affinity over the Pro253Arg mutation for most FGF ligands.3 Furthermore, Apert syndrome mutations appear to cause a loss of ligand binding specificity (Pro253Arg more so than Ser252Trp), with the greater loss of ligand binding specificity mirroring the severity of syndactyly in patients with Apert syndrome. This explains the genotype-phenotype correlation seen in these patients.3

Craniosynostosis associated with Apert syndrome was traditionally treated with cranial vault expansion undertaken via the anterior route.5 However, since the introduction of posterior vault expansion (PVE) by the Birmingham Craniofacial Team in 1996,6 this route has become increasingly favored, as it avoids disturbance of the fronto-orbital region, thereby preserving it should a subsequent frontofacial procedure be required. Spring-assisted PVE (SA-PVE) has been the surgical technique of choice at the Craniofacial Unit, Great Ormond Street Hospital for Children (GOSH), London, UK, since 2008, with a set of removable, implanted springs which result in skeletal distraction followed by osteogenesis whilst allowing for ease of closure and gentle stretching of the overlying soft tissues.7

This study aims to investigate if there is a difference in the preoperative intracranial volume (ICV) in patients with Apert syndrome with Ser252Trp or Pro253Arg mutation, and whether these mutations can be used as predictors of change in ICV achieved by SA-PVE.

Methods

Study Population

The GOSH Craniofacial Unit SA-PVE database, consisting of 172 patients, was assessed. This study was approved by the Joint Research and Development Office (R&D number 14DS25). All Apert syndrome cases with available preoperative and postoperative computed tomography (CT) scans with 1 mm slice thickness were included. The slice thickness limit would allow for sufficient quality for 3D segmentation. Patients with any type of preceding craniofacial surgery were excluded. Data on demographics, indication, diagnosis and age at time of preoperative CT scan, spring insertion, and postoperative CT scan were collected.

ICV was calculated using FSL (FMRIB Analysis Group, Oxford, UK).8,9 As time between the preoperative CT scan, spring insertion, and postoperative CT scans varies between patients, the preoperative ICVs were adjusted to the expected values for a patient of that age and syndrome (unoperated Apert-specific growth curves previously published10) to the day of surgery in order to calculate the ICVs at the time of surgery between patients accurately. In addition, the change in ICV between time of postoperative CT scan and time of surgery was also adjusted for growth using the same Apert growth curves to calculate the ICV change (Fig. 3 ΔICVsprings) due to the SA-PVE independently of individual growth.10

SPSS version 25.0 (IBM SPSS Inc., Chicago, IL) was used for statistical analysis. Descriptive statistics were performed to describe the study population. The Shapiro-Wilk test was used to assess for normality of data. Preoperative and postoperative ICV measurements as well as SA-PVE ICV increases were investigated using the Mann-Whitney U test to compare the ICV differences within groups. The change in ICV in all patients was assessed using a one sample t test. A P value <0.05 was considered to be statistically significant.

Results

Thirty patients were included from the craniofacial SA-PVE database with a diagnosis of Apert syndrome. Fourteen of these patients were excluded due to absence of genetic testing or incomplete ICV data. Of the 16 remaining patients (10 male), 8 were identified as having Ser252Trp (S252W) mutation and 8 had Pro253Arg (P253R) mutation. Indication for SA-PVE was raised intracranial pressure in 13 patients, shape for 2 patients, and a combination of raised intracranial pressure and shape for 1 patient. The age at operation was 421.5 days (range: 152–1175); there was no significant difference in age between the 2 groups (P=0.41). 4 (50%) of S252W patients and 3 P253R (37.5%) of patients required a second operation after primary SA-PVE. There was no association between mutation and likelihood of reoperation (P=1.0). ICV data was not available for these procedures.

The adjusted ICV at time of surgery was 1126.7±310.6 cm3 and postoperatively 1339.0±260.0 cm3, resulting in a significant increase in ICV due to SA-PVE in the overall population (198.7±134.2 cm3, P<0.001). The adjusted preoperative ICV for S252W patients was 1137.7±379.3 and 1115.8±250.0 cm3 for P253R patients (P=1.00). The adjusted postoperative ICV was 1311.7±294.5 cm3 for S252W and 1339.1±240.0 cm3 for P253R patients (P=0.645). Thus, the spring ICV increase was 174.1±152.8 and 223.4±117.6 cm3 for S252W and P253R patients, respectively (P=0.51). Supplemental Table 1, Supplemental Digital Content 1, https://links.lww.com/SCS/E680 demonstrates the preoperative and postoperative CT volume in all 16 patients.

Discussion

The old adage of “bad hands, good airway and face” and “good hands, bad airway and face” in Apert syndrome has been shown to be related to genetic mutations as the Pro253Arg mutation presents with more severe syndactyly, whereas the Ser252Trp mutation confers milder hand abnormalities and an increased incidence of cleft palate.11 This study aimed to investigate if these mutations also had a relationship to ICV and whether they could act as predictors of outcome following SA-PVE. Raised ICP was the predominant driver for SA-PVE in this study cohort. Craniofacial centers worldwide have differing protocols as to when and how cranial vault expansion should be undertaken. The majority advocate a prophylactic, posterior approach, undertaken before the age of 1 year in an attempt to prevent the development of raised ICP. At GOSH, the practice differs in that an expectant approach is taken, with cranial vault expansion being undertaken as and when raised ICP occurs.12–14 A significant step increase was achieved in ICV following SA-PVE independent of diagnosis. There were no significant differences in absolute ICV change or percentage ICV change between patients with Ser252Trp and Pro253Arg mutation. Although, the type of mutation in patients with Apert correlates with facial appearance, the data from this study suggests that it does not relate to ICV and the change in ICV following SA-PVE. Therefore, the adage of “band hands, good head” does not relate to ICV. As in most craniofacial institutions, at Great Ormond Street Hospital, exposure to ionizing radiation is kept to a minimum. CT scans are taken preoperatively to aid clinical assessment and surgical planning, but in the immediate follow-up period CT scans are not routinely undertaken. Some patients might have CT scans taken post SA-PVE for further assessment and for surgical planning for further frontofacial surgery. This meant there was limited availability of coupled preoperative and postoperative CT scan, resulting in 16 patients eligible for analysis. This invariably adds a degree of bias to the data presented.

The use of growth curves to adjust for growth during preoperative and postoperative CT scans was useful in this study. Two patients had minimal adjusted ICV increases: both had a considerable time lag between their preoperative and postoperative imaging. Error may be introduced in cases with long time lags between scans and time of surgery as ICV change attributable to growth or to the SA-PVE becomes confused. This may be explained by the understandably low number of data points in the growth curves that represent older unoperated children with Apert syndrome, because the majority have needed surgical intervention by this age.

The small sample size for this research was related in part to having limited patients due to the requirement for both preoperative and postoperative CT scans despite obtaining data from a specialized center for craniofacial syndromes, highlighting the difficulty of performing research in rare disease cohorts such as Apert syndrome. Nevertheless, these findings are helpful when considering surgical planning and counseling of parents of children with Apert syndrome for SA-PVE. Regardless of the mutation profile of the patient, the increases in ICV following SA-PVE are in the same range. This finding has not previously been reported in the literature and suggests that variations in outcome may be related to other factors such as cranial stiffness or surgical strategy (such as spring position and type). The results demonstrate that SA-PVE was successful in increasing ICV in patients with Apert syndrome and that a repeat volume expanding procedure was required by a similar number of patients following SA-PVE. This information can be used to reassure patents when counseling for SA-PVE.

List of References

1. Apert E. De l'acrocephalosyndactalie. Bull Soc Med Hop Paris 1906;23:1310–1330
2. Cohen MM, Kreiborg S, Lammer EJ, et al. Birth prevalence study of the apert syndrome. Am J Med Genet 1992;42:655–659
3. Ibrahimi OA, Chui ES, McCarthy JG, et al. Understanding the molecular basis of Apert syndrome. Plastic Reconstr Surg 2005;115:264–270
4. Johnson D, Wilkie AOM. Craniosynostosis. Eur J Hum Genet 2011;19:369–376
5. Choi M, Flores RL, Havlik RJ. Volumetric analysis of anterior versus posterior cranial vault expansion in patients with syndromic craniosynostosis. J Craniofac Surg 2012;23:455–458
6. Sgouros S, Goldin J, Hockley A, et al. Posterior skull surgery in craniosynostosis. Childs Nerv Syst 1996;12:727–733
7. Breakey RWF, van de Lande LS, Sidpra J, et al. Spring-assisted posterior vault expansion—a single-centre experience of 200 cases. Childs Nerv Syst 2021;37:3189–3197
8. Muschelli J, Ullman NL, Mould WA, et al. Validated automatic brain extraction of head CT images. NeuroImage 2015;114:379–385
9. Breakey RWF, Knoops PGM, Borghi A, et al. Intracranial volume measurement: a systematic review and comparison of different techniques. J Craniofac Surg 2017;28:1746–1751
10. Breakey RWF, Knoops PGM, Borghi A, et al. Intracranial volume and head circumference in children with unoperated syndromic craniosynostosis. Plast Reconst Surg 2018;142:708e–717e
11. O'Hara J, Ruggiero F, Wilson L, et al. Syndromic craniosynostosis: complexities of clinical care. Mol Syndromol 2019;10:83–97
12. Forrest CR, Hopper RA. Craniofacial syndromes and surgery. Plast Reconst Surg 2013;131:86e–109e
13. Marucci DD, Dunaway DJ, Jones BM, et al. Raised intracranial pressure in Apert syndrome. Plast Reconst Surg 2008;122:1162–1168
14. Spruijt B, Rijken BF, Joosten KF, et al. Atypical presentation of a newborn with Apert syndrome. Childs Nerv Syst 2015;31:481–486

Supplement material

Table 1: Summary of all patients undergoing SA-PVE

Study Number	Mutation	Pre-op ICV (cm^3)	Post op ICV (cm^3)	Mean change in ICV	
				cm^3	%
1	S252W	902.50	1121.69	219.2	24.3
2	S252W	941.10	1109.13	168.1	17.9
3	S252W	702.70	1061.42	358.7	51.0
4	S252W	1196.70	1197.58	0.9	0.07
5	S252W	710.59	1098.97	388.4	54.7
6	S252W	1499.30	1650.70	151.4	10.1
7	S252W	1460.20	1409.50	-50.7	-3.47
8	S252W	1688.50	1845.06	156.6	9.27
9	P253R	900.60	1232.49	331.9	36.8
10	P253R	1038.10	1177.12	139.0	13.4
11	P253R	1013.90	1468.78	454.9	44.9
12	P253R	823.70	1048.55	224.8	27.3
13	P253R	1080.10	1268.52	188.4	17.4
14	P253R	1458.00	1636.17	178.2	12.2
15	P253R	1083.40	1166.00	82.6	7.62
16	P253R	1528.20	1715.25	187.0	12.2

Figure Legend

Figure 1: Phenotype associated with SerTrp mutation.

Figure 2: Phenotype associated with ProArg mutation.

Figure 3: A stylized graph showing intracranial volume (ICV) change adjustments for growth to calculate ICV change due to springs alone. CT indicates computed tomography.

Figures

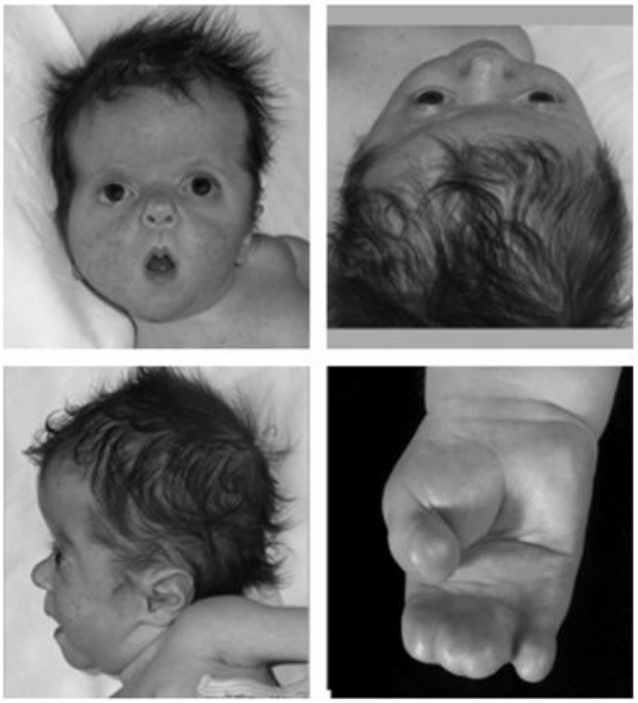

Figure 1.

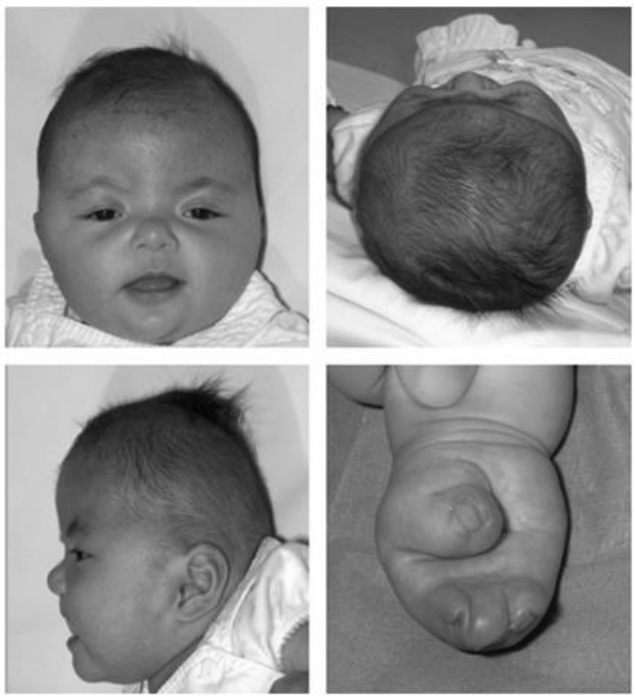

Figure 2.

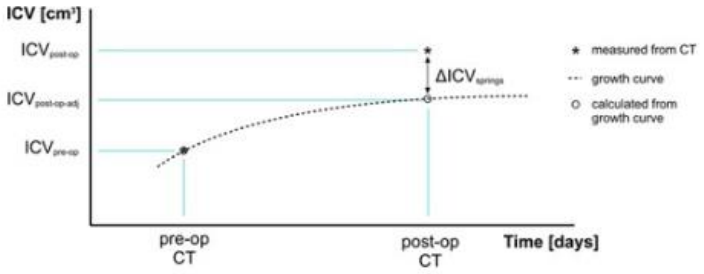
ICV [cm³]
ICV post-op
ICV post-op-adj
ICV pre-op
ΔICV springs
measured from CT
growth curve
calculated from growth curve
pre-op CT
post-op CT
Time [days]

Figure 3.