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Original Article

Shape analysis of the sphenoid bone in Apert syndrome using 3D CT scans

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Abstract Apert syndrome is a rare acrocephalosyndactyly syndrome characterised by craniosynostosis, midface hypoplasia and syndactyly of the hands and feet. The majority of cases arise as the result of one of two mutations of the fibroblast growth factor receptor 2 gene (FGFR2). Due to the involvement of both the cranial and the facial sutures, the keystone of the craniofacial skeleton, the sphenoid bone, is affected by the disease process and as a result is dysmorphic. This may significantly affect craniofacial morphology but it is recognised that there are marked variations in this between different affected individuals. This is a retrospective study examining the morphology of the sphenoid bone using three dimensional reconstructions of computed tomography (CT) scan data. Shape analysis was performed using generalised Procrustes analysis and principal component analysis (GPA/PCA). Comparisons were made between the individuals with Apert syndrome and a group of normal individuals, and between the two genotypic groups. The sphenoid bone in those with Apert syndrome showed marked differences in morphology compared to the normal individuals with a restriction in height and increased angulation of the lesser wings; however, there were no consistent differences between the two genotypic groups. It is possible that fronto-orbital advancement (FOA) surgery indirectly releases the sphenoid bone and allows compensatory growth in this direction.

Keywords: Apert syndrome, FGFR2, GPA/PCA.

Introduction

Apert syndrome is one of the rare acrocephalosyndactyly syndromes and is characterised by craniosynostosis, midface hypoplasia and syndactyly of the hands and feet (David *et al.,* 1982; Tessier, 1985; Cohen and MacLean, 2000). Almost all cases of Apert syndrome occur as the result of one of two mutations of the fibroblast growth factor receptor 2 gene (FGFR2) resulting in an amino acid substitution of either S252W or P253R, both of which are in the linker region between immunoglobulin-like domains II and III of the extracellular component of the molecule (Wilkie *et al.*, 1995; Oldridge *et al.*, 1997). The S252W mutation is the most common and has been reported to occur in sixty-three to seventy-one percent of individuals with Apert syndrome and the P253R mutation in twenty-six to thirty-seven percent (Park *et al*., 1995; Wilkie *et al.*, 1995; Slaney *et al*., 1996; Lajeunie *et al*., 1999; von Gernet *et al*., 2000). In the majority of cases of newborn Apert syndrome the craniofacial morphology is characterised by bicoronal synostosis with patent metopic and sagittal sutures (David *et al.,* 1982; Cohen and MacLean, 2000). Suture fusion is progressive during childhood with the sagittal and lambdoid sutures subsequently fusing and also squamosal synostosis may rarely occur (David *et al.,* 1982). In most cases, the pattern of cranial suture involvement results in hyperbrachycephaly with a low wide face or hyperacrocephaly (David *et al.,* 1982; Tessier, 1985; Marsh *et al*., 1991). The maxilla is hypoplastic in three dimensions and consequently short, narrow and retruded (Tessier, 1985; Ferraro, 1991; Kaplan, 1991).

The anterior cranial fossa in Apert syndrome is shortened and the sphenoid ridges are increased in length and abnormally shaped which may be a result of bicoronal synostosis; there is also abnormal protrusion of the greater wings of the sphenoid (Marsh *et al*., 1991; Cohen and MacLean, 2000). The sella turcica may be larger than normal and the clivus shorter and more vertical with an excessively lordotic nasion-sella-basion angle (David *et al.,* 1982; Tessier, 1985; Marsh *et al*., 1991). It has been postulated that synostosis of the sphenoid bone both anteriorly and posteriorly may be one of the main causative factors in the craniofacial anomalies seen within Apert syndrome (Tessier, 1985). To investigate hypothesis, we wished to investigate the morphology of the sphenoid bone in detail.

Materials and methods

This was a retrospective study undertaken at the Australian Craniofacial Unit (ACFU) of the Women's and Children's Hospital in Adelaide, Australia. Ethical approval for this study was granted by the Human Research Ethics Committee of the Women's and Children's Hospital, Adelaide, dated 1st March 2004 (Ref: WCHZ74). The study comprised twenty-two patients with a diagnosis of Apert syndrome who had been genotyped and had available computed tomography (CT) scan data. Comparisons were made between the sphenoid bone morphology of these patients and a group of normal individuals, and between the two genotypic groups.

Genetic sequencing was performed at South Eastern Area Laboratory Services (SEALS) based at the Prince of Wales Hospital in Randwick, New South Wales, Australia.

Pre-operative CT scan data of the craniofacial skeleton were reconstructed and on each scan twenty-eight osseous landmarks were determined on the sphenoid bone using the Persona software package developed at the ACFU. A subset of these landmarks can be seen in Fig. 1.

The growth of the sphenoid bone was examined in four patients with the same set of osseous landmarks being determined on consecutive CT scans. The time of closure of the spheno-occipital synchondrosis within those with Apert syndrome was compared to the time of closure within the group of normal individuals.

Shape analysis was performed using generalised Procrustes analysis and principal component analysis (GPA/PCA). There were several steps required in performing the GPA/PCA. Standardisation was achieved by translating the landmark configuration of each sphenoid bone to its centroid and scaling to unit centroid size, that is, the sum of the squared distances from each landmark to the centroid was equal to one. Procrustes registration of the landmarks of each patient was undertaken and the mean landmark configuration was established as the mean of the three dimensional positions of the registered corresponding landmarks. Principal component analysis was then performed to express each patient's landmark configuration in terms of a sum of scaled standardised principal component vectors. The scale factors are the standardised principal component scores and are in units of standard deviations. The standardised principal component vectors have magnitude equal to the square root of their contribution to the total variance and are ordered in descending contribution to the total variance. GPA/PCA was performed using the Visualisation Tool Kit (VTK) and the "R" statistical package (http://cran.us.r-program.org). The growth of the sphenoid bone was also examined using GPA/PCA; however, there were insufficient data to perform an analysis based on genotype.

Description on the shape difference is based on the two Principle components (PC) (Smith, 2002). Principle component One, PC1, describes a shape difference that is due to age effects, that is as an infant changes into an adult. Principle component Two, PC2, describes shape difference associated with Apert syndrome, the turricephaly, midface hypoplasia and brachycephaly.

Finally, in all scans the speno-occipital synchondrosis was studied to assess whether it was patent or closed, to investigate if this could be a contributory factor affecting craniofacial growth.

Table 1 Landmark definitions of paired structures (left and right) in Fig. 1 from superior to inferior.

Landmark	Definition
spa	the most anterior on the posterior margin of the lesser wing of sphenoid.
sobf	the most lateral point on the margin of the superior orbital fissure.
ofam	the medial margin of of the anterior opening of the optic canal.
ac	the most posterior point on the anterior clinoid of the lesser wing of sphenoid.
gwl	the point located at the junction of inferior orbital fissure and the suture between the greater wing of sphenoid and the zygomatic bone.
pc	the most superior-lateral point on the posterior clinoid.
gwm	the most inferior point of the superior orbital fissure.
peta	the most anterior part on the crest of the petrous temporal bone.
hn	the deepest point of the hamular notch.
ptl	the most lateral point on the lateral pterygoid plate.
hp	the tip of the hamular process of the medial pterygoid plate.

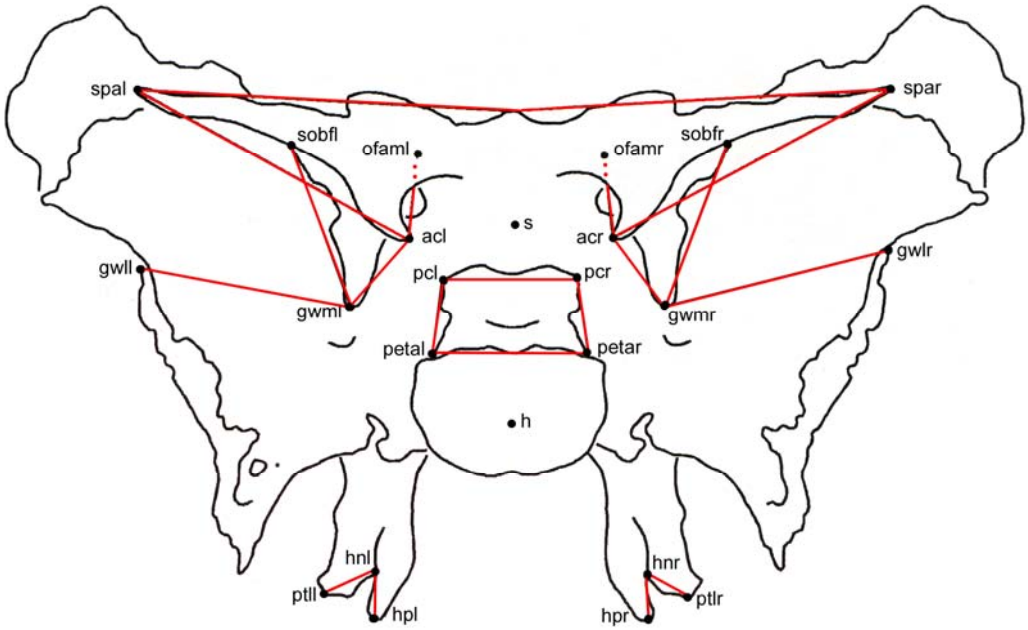

Fig. 1 A diagram demonstrating the positions of a subset of the osseous landmarks on the posterior aspect of the sphenoid bone.

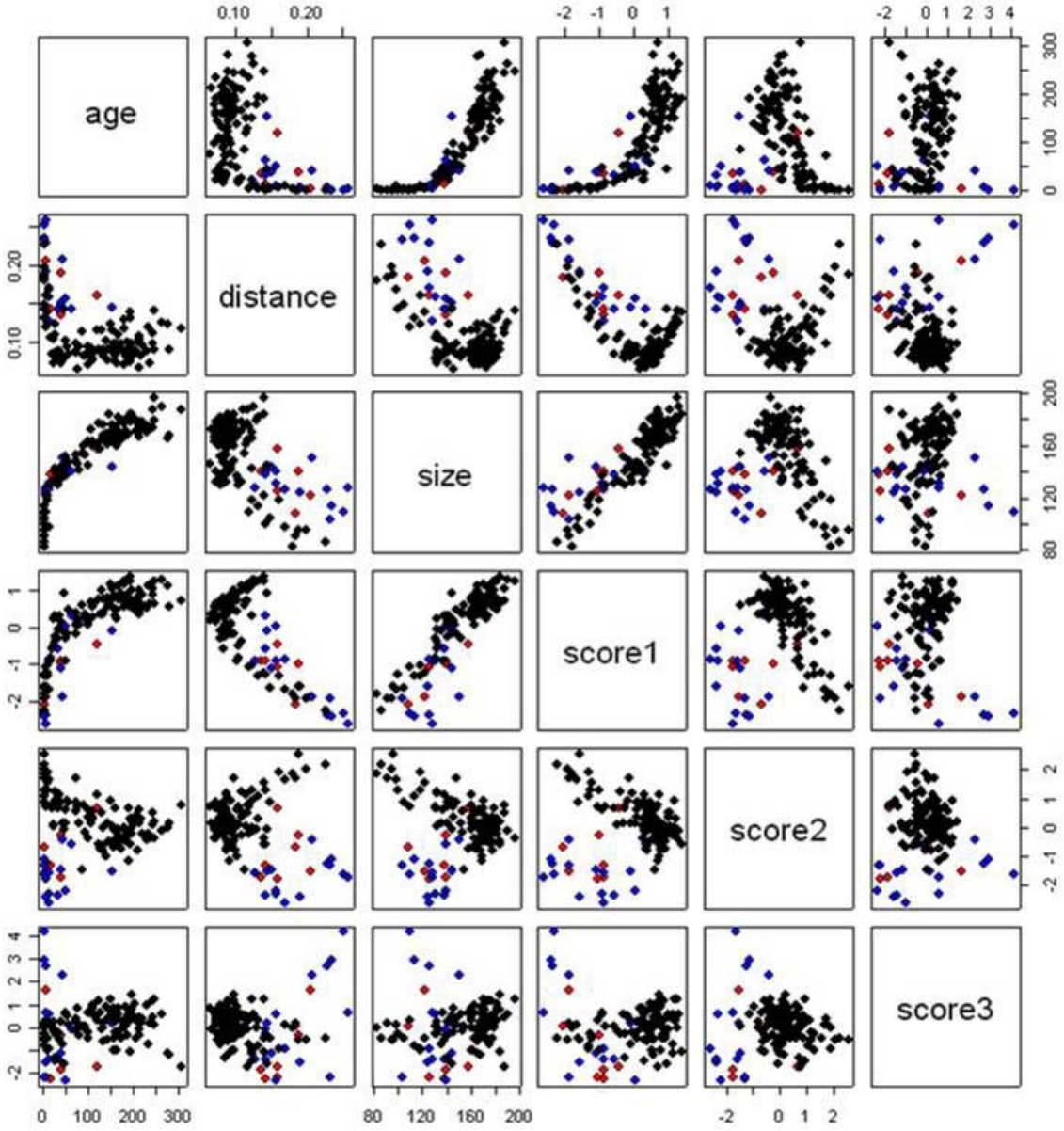

Fig. 2 GPA/PCA of sphenoid bone morphology. Patients with the S252W mutation are represented in red, those with the P253R mutation in blue and normal individuals in black.

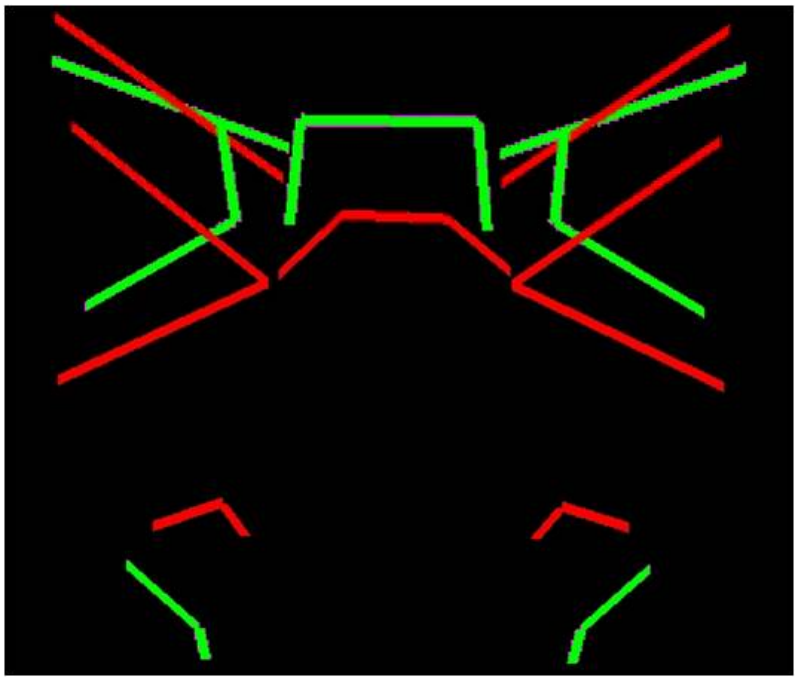

Fig. 3 PC1 of the GPA/PCA. The wireframe in red shows minus two standard deviations and the wireframe in green plus two standard deviations.

Results

Fifteen of the patients within this series were shown to harbour the S252W mutation and seven the P253R mutation. The patients ranged in age at the time of imaging from one month to up to thirteen years of age. Assessment of sphenoid bone morphology using GPA/PCA demonstrated obvious differences in the shape of the pre-operative sphenoid bone between those patients with Apert syndrome and the normal individuals. It can be seen from the GPA/PCA (Fig. 2) that the patients with Apert syndrome separate from the normal individuals when both principal component 1 (PC1) and PC2 are examined; however, there is no separation of the two genotypic groups.

PC1 largely describes a change in the height of the sphenoid bone (Fig. 3), which is partly related to growth. However, it appears that the patients with Apert syndrome have a restriction in the growth of the sphenoid bone in the inferior-superior plane. The patients with Apert syndrome also have increased angulation of the lesser wings of the sphenoid compared to the normal individuals, possibly a result of bicoronal synostosis. PC2 also describes an angulation in the lesser wings of the sphenoid.

A further GPA/PCA of sphenoid bone morphology was performed for the normal individuals and four patients with Apert syndrome who had consecutive CT scans available in order to examine the growth of the sphenoid bone in three-dimensions. The first CT scan of each of these four patients was their pre-operative scan and the remainder were post-operative and therefore the changes in shape were partly the result of growth and partly indirect effects of surgery. When PC1 against PC2 is examined more closely, it can be seen that three of the four points representing the pre-operative CT scans are clustered together. Therefore three of the four pre-operative scans are separated from the remaining pre-operative and the post-operative scans largely based on the height of the sphenoid bone, with these three pre-operative scans showing a sphenoid bone considerably reduced in height. Hence,

post-operatively the sphenoid bone appears to have undergone compensatory growth in the inferior-superior direction. There was insufficient data to enable a comparison based on genotype in respect to the growth of the sphenoid bone.

The time of closure of the spheno-occipital synchondrosis was examined also using the three-dimensional CT scan reconstructions. Within the group of normal individuals the earliest age at which the synchondrosis was found to be closed was twelve years in the females and fifteen in the males. In all of the normal individuals the spheno-occipital synchondrosis was closed by 16.5 years of age. The synchondrosis was closed in five of the twenty-two patients with Apert syndrome examined in this respect. Four of these patients were younger than twelve years of age, the youngest 2.6 years of age. Hence, there was premature closure of the spheno-occipital synchondrosis in four patients in this series (eighteen percent).

Discussion

GPA/PCA of the osseous landmarks on the sphenoid bone of those individuals with Apert syndrome showed marked differences in morphology compared to the normal individuals. The sphenoid bone morphology of individuals with Apert syndrome largely separates from the normal individuals when examining the height of the sphenoid bone and the angulation of the lesser wings. Within Apert syndrome there is a restriction in the height of the sphenoid bone in the inferior-superior plane and the lesser wings show increased angulation. There were no consistent differences in the morphology of the sphenoid bone between the two genotypic groups.

Although growth of the sphenoid bone was only examined in a small number of cases, it was interesting to note that the fronto-orbital advancement (FOA) procedure that these patients had undergone appears to have released the sphenoid bone through indirect effects enabling compensatory growth in the inferior-superior direction. Although the restriction to the growth of the sphenoid bone was greatest in the inferior-superior direction we postulate that premature fusion of the spheno-occipital synchondrosis, as seen within four patients within this series, may also impact on craniofacial morphology as a result of early fusion of the cranial base.

Conclusions

The morphology of the sphenoid bone in Apert syndrome is markedly different to that seen within normal individuals. However there are no consistent differences between the two genotypic groups. The patients with Apert syndrome within this series showed a significant restriction in the growth of the sphenoid bone in the inferior-superior plane and increased angulation of the lesser wings. In a small number of cases examined fronto-orbital advancement appeared to release the sphenoid bone allowing compensatory growth in this direction. Early closure of the spheno-occipital synchondrosis may also contribute to craniofacial anomalies. Further investigation of the sphenoid bone in Apert syndrome including the spheno-occipital synchondrosis is warranted to develop a greater understanding of the causal relationships of craniofacial dysmorphology in Apert syndrome.

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