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Abstract

Craniofacial microsomia (CFM) is the result of a disturbance in embryologic development and is characterised by an asymmetric, mostly unilateral facial underdevelopment. The aim of this study is to understand the midfacial involvement in CFM using principal component analysis (PCA). Pre-operative data from 19 CFM and 23 control patients were collected. A set of 71 landmarks was placed on 3D reconstructions of all skulls to compare both populations. PCA visualised variation within both groups and calculated the vector of change. Linear measurements were taken to compare ratios between the populations and between the affected and unaffected side in CFM patients. PCA defined a vector that described shape changes between both populations. Videos showed the variation within the control and CFM group and the transformation from a mean CFM skull into a normal phenotype. Linear measurements showed a significant difference between the affected and unaffected side in CFM patients. PCA has not been applied on asymmetrical data before but has proved to be a useful method to describe CFM. The virtual normalisation of a mean CFM skull enables visualisation of the bony shape changes, which is promising to delineate and plan surgical correction and could be used as an outcome measure.

Keywords	hemifacial microsomia; craniofacial abnormalities; principal component analysis; skull; midface

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ABSTRACT

Craniofacial microsomia (CFM) is the result of a disturbance in embryologic development and is characterised by an asymmetric, mostly unilateral facial underdevelopment. The aim of this study is to understand the midfacial involvement in CFM using principal component analysis (PCA).

Pre-operative data from 19 CFM and 23 control patients were collected. A set of 71 landmarks was placed on 3D reconstructions of all skulls to compare both populations. PCA visualised variation within both groups and calculated the vector of change. Linear measurements were taken to compare ratios between the populations and between the affected and unaffected side in CFM patients.

PCA defined a vector that described shape changes between both populations. Videos showed the variation within the control and CFM group and the transformation from a mean CFM skull into a normal phenotype. Linear measurements showed a significant difference between the affected and unaffected side in CFM patients.

PCA has not been applied on asymmetrical data before but has proved to be a useful method to describe CFM. The virtual normalisation of a mean CFM skull enables visualisation of the bony shape changes, which is promising to delineate and plan surgical correction and could be used as an outcome measure.

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INTRODUCTION

Craniofacial microsomia (CFM) is a congenital deformity regarded to be the result of a disturbance in the embryologic development of the first- and second branchial arches(*Grabb*, 1965) (*Converse et al.*, 1973). The most often suggested pathoetiology hypotheses are local haemorrhage of the stapedial artery(*Poswillo*, 1975) and disturbed migration of cranial neural crest cells(*Converse et al.*, 1973) (*Johnston* and *Bronsky*, 1995) (*Tuin et al.*, 2015) (*Stark* and *Saunders*, 1962). Following cleft lip and palate, CFM is commonly regarded as the most common facial birth defect(*Murray et al.*, 1984) with an incidence varying from 1:3500(*Poswillo*, 1974) to 1:5600(*Grabb*, 1965) births. CFM has a heterogeneous presentation. The most commonly used classification system was provided by Pruzansky(*Pruzansky S.*, 1969), later modified by Kaban et al.(*Kaban et al.*, 1988) The most recent classification system is the PAT-CFM based on the OMENS-plus(*Vento et al.*, 1991) (*Horgan et al*., 1995) (*Birgfeld et al.*, 2011). Orbital, mandibular, auricular and soft tissue malformations as classified in the PAT-CFM system are common(*Caron et al.*, 2017). Furthermore, zygomatic deformities such as flattening or hypoplasia of the cheekbone and maxillary hypoplasia are frequently observed in CFM(*Santler et al.*, 2003) (*Keogh et al.*, 2007) (*Cousley* and *Calvert*, 1997) (*Gorlin* and *Cohen*, 2001).

A great amount has been written on the correction of the mandibular asymmetry(*Pluijmers et al.*, 2014) (*Wan et al.*, 2011) (*McCarthy et al.*, 1992). Fewer reports focus on the correction of midfacial asymmetry. Treatment options include maxillary distraction osteogenesis and maxillary, orbital and

zygomatic osteotomies(*Santler et al.*, 2003) (*McCarthy et al.*, 1992). Additional volume can be created by overlying grafts, including autologous and alloplastic implants(*Staal et al.*, 2016). Assessment of the pathology and monitoring of growth in CFM is mostly done by standard radiographs(*Sant'Anna et al.*, 2015) (*Ongkosuwito et al.*, 2013). In order to plan the optimal surgical correction, there should not only be an understanding of the deformity but also a comparison to the anatomy of a normal skull. Therefore, 3D computed tomography (CT) is used (*Shibazaki-Yorozuya et al.*, 2014). A technique used to analyse the size and shape of surfaces as the craniofacial skeleton is geometric morphometrics(*Bookstein*, 1997). In order to compare biological shapes, landmarks are required to be placed on biologically homologous points. Not only should there be enough landmarks to represent the specific shape, they must be repeatable and reliable. In practise, these tend to be intersections of sutures, foramina and recognisable ridges. Landmarks represent the coordinates of specific points on the surfaces and the space between them is interpolated. Principal component analysis (PCA) can then be applied to landmarks placed on the craniofacial skeleton to evaluate the variation in shape change between the control population and patients with CFM. This method of 3D shape analysis allows for a better understanding of CFM deformities in a holistic fashion in order to plan surgical treatment.

The purpose of this study is to analyse the differences in shape of the midface within patients with CFM and between patients with CFM and control patients to gain a better perception of the variance of the specific deformations in order to

make surgical planning more accurate and to see if it can be used as a surgical outcome measure.

MATERIAL AND METHODS

Data collection

Patients diagnosed with unilateral CFM, between the age of 7 and 12, without any history of bony facial surgery and with suitable preoperative 3D-CT scans, were included. All patients with missing essential anatomical features due to severe CFM were excluded, as analysis of missing parts is impossible. Bilateral CFM scans were excluded, as the affected sides would cancel out each other. Anatomical control paediatric data was collected from a series of trauma patients undergoing diagnostic CT scans from Erasmus MC, Rotterdam (EMC) and from a series of epileptic patients undergoing CT scans for surgical planning from GOSH. Inclusion criteria of the control group were patients with an unaffected facial skeleton and ages between 7 and 12 for age matching purposes. Scans at GOSH were taken using a 16-slice Siemens Somatom Sensation spiral CT scanner set to 0.75mm collimation (Siemens Medical Solutions, Malvern, PA, USA). Scans at the EMC were taken using a 6-slice Siemens Emotion spiral CT scanner (Siemens, Munich, Germany) with a slice thickness of 0.8 mm. All scans were saved as Digital Imaging and Communications in Medicine (DICOM) files. The DICOM files were then converted into University College London (UCL) proprietary format and loaded into 3D voxel-imaging software (Robins 3D 2006). The CT images of both control and affected patients were edited for analysis of the hard tissue surface and a Hounsfield Unit (HU) from 223 to 271 was used to represent the bony surface. Polyglon mesh surfaces (stl) representing bone were extracted from all scans for landmark placement.

Landmarks

Scans were landmarked using 3D voxel imaging software (Robins 3D 2006). To compare the control and affected patient scans, a reliable set of landmarks needed to be determined. The first set of 52 landmarks was partly based on a previous study(*Staal et al.*, 2015), and expanded to 71 landmarks to fully capture the orbital, maxillary, zygomatic and mastoid region (Table 1, Fig. 1).

The software allowed visualisation of changes between the landmarks of two scans by creating a thin-plate spline warp. Discrepancies between different skull shapes were made visible by warping the surface of the skull to the position of corresponding landmarks of a different skull, those differences in surface were visualised in a colour-coded map (Fig. 2).

Data analysis

PCA is a statistical method based on eigenvector multivariate analysis of, in this study, variations in shape within a population. It allows describing a large amount of high dimensional data with a smaller number of relevant variables. Instead of comparing single linear measurements, this morphometric analysis makes it possible to capture skull surface as a whole. A Point Distribution Model (PDM) is created of the landmarks. A PDM is a model that describes the mean shape and the allowed variability within a population. Eigenvectors are extracted from the landmark data which are the principal components of variation in shape(*Bookstein*, 1997) (*Cootes et al.*, 1992) (*O 'higgins*, 2000). The first principal component describes the largest variation within the

population. The second and third principal components describe the second and third largest variation. The thin-plate splines (TPS) can interpolate changes between landmarks and are using minimum bending energy to estimate the surface between landmarks(*Bookstein*, 1997). This method was used to visualise the bone shape changes and to create videos that showed the variation in the control and affected population and between the populations.

To define the repeatability of the landmarks, a randomly chosen control skull and affected skull were landmarked ten times in different sittings, which allowed determining the intra-observer reliability.

Since our cohort consisted of both right- and left-sided CFM patients, creating a representative unilateral CFM model was impossible. Therefore, all the paired landmarks of the left-sided skulls were flipped to the right side and registered to the same coordinate system. This enabled creating a right-sided CFM data set. To emphasize the outcomes of the videos, linear measurements of the skulls were taken. Using Robins 3D software, distances between coherent landmarks from the original landmark set were calculated and were defined as linear measurements to ratify the visual changes seen in the PCA model and in addition to the limitation of PCA. As it was impossible to define landmarks on partly missing anatomy, PCA was not able to describe the shape changes. Therefore, we used linear measurements from for example the origin of the zygoma to the zygomatic angle to describe changes in length of the expected zygomatic length. When videos did not show large differences, linear measurements were used to verify these assumptions. The left and right side in

and between CFM skulls and control skulls were compared and ratios of the orbits were calculated for a better comparison of orbital size (Table 2).

The Wilcoxon signed-rank test was used to analyse differences within CFM and control group. To compare between the two groups, an independent two-tailed t-test for unequal sample sizes was used after determining the data to be normally distributed with the Lilliefors test. To allow comparison of the orbital ratios between the total amount of normal orbital ratios and right or left CFM ratios, the Mann-Whitney test was performed. A p-value of ≤ 0.05 was chosen for significance level.

RESULTS

Of 19 patients an adequate CT-scan was available for analysis. These included 11 right-sided CFM. All patient scans were classified using Pruzansky-Kaban classification (table 3). A total of 23 ‘normal’ patient scans were included as a control group.

Landmark reliability

The mean standard deviation (SD) of each landmark was calculated using univariate statistical analysis (Table 4). All landmarks used were within a SD value of 2mm.

Control population

Out of 71 landmarks, 11 had a SD between 1mm and 2mm. 60 landmarks had a SD <1mm. Therefore, 85% (60/71) of the landmarks was regarded highly accurate and 100% was within a 2mm.

CFM population

Out of 71 landmarks, 4 had a SD between 1mm and 2mm. 67 landmarks had a SD <1mm. Therefore, 94% (67/71) of the landmarks was regarded highly accurate and 100% was within a 2mm range.

Variation within the populations

The morphometric analysis on each group of skulls showed the variation within the two groups.

Control population

In the control group the first principal component of variation showed allometric growth in a horizontal vector (Video 1+2). The frontal face shows widening, in particular the zygomatic body and the maxilla. Also the space between the mastoid region and the frontal face increases with growth.

The second mode showed predominantly allometric growth in the vertical vector (Video 3+4). The alveolar bone and the change in orbital height both contribute to variation in lengthening of the frontal face. The mastoid region gets longer with growth.

CFM population

The first component of variation in the CFM population shows the variability in severity of CFM (Fig. 3) (Video 5+6). From the zygomaticotemporal suture a down bending zygoma is displayed on the affected side. The zygomatic body appears to be shorter and decreased in length. The orbit shows an increase in width and decrease in length and the frontotemporal region moves down. The distance between the mastoid and the lateral dorsal zygomatic ridge decreases. The maxilla shows a decreased length.

The second mode of variation shows predominantly allometric growth (Video 7+8). The affected side demonstrates a flattening of the lower part of the zygoma.

The third component in the CFM population shows most variation in the oblique vector (Video 9+10). The more the maxilla shifts to the affected side the

more the zygomatic body moves upwards. This causes a flattening of the caudal lateral orbital arc and a reduction in length.

Variation between the populations

PCA was also performed between control and CFM skulls resulting in an average vector between all the warps. This averaged vector describes shape changes between the CFM and control skulls and represents a model for normalization of a CFM skull. Resulting TPS-videos of the principal components showed how a mean CFM skull transformed into its predicted normal phenotype (Fig. 4) (Video 11 + 12). As most allometric growth is cancelled out, it mainly shows the shape changes between a CFM and control skull. Normalisation of the affected side shows a lengthening of the maxilla and of the zygomatic body. The length of the orbit increases, mostly due to of a downshift of the inferior orbital margin. The frontotemporal region becomes longer and the distance between the mastoid and the lateral dorsal zygomatical ridge increases. The lateral orbital and zygomatic region of the unaffected side seems to show a slight reaction to the deformity on the contralateral side by a little torsion downwards.

Linear measurements

Euclidean distances were calculated (Table 5) for a total of 13 measurements. When comparing the affected (right) side to the unaffected (left) side within the CFM population, it is evident the affected side is significantly different (Fig. 5-7)

except for the nasiozygomatic length (Fig. 8). No differences between the right and left side were found within the control population.

Comparing both populations with each other, the affected (right) side in CFM was significantly different from the right side in the control group (Fig. 6-7). Both the right and left CFM orbital ratios were compared to the total of normal orbital ratios. This showed a significant different orbital ratio on the affected side in the CFM skulls (Fig. 5). There was no difference in facial width between the populations (Fig. 9).

DISCUSSION

PCA allows a mathematical analysis of a unique skull as a whole rather than comparison of average values taken from samples of a control population. Earlier analysis of Noonan(*Hammond et al.*, 2004), Apert(*Pluijmers et al.*, 2012) and Crouzon and Pfeiffer(*Staal et al.*, 2015) has been done. These syndromes affect the skull symmetrically. This was the first time PCA was performed on asymmetrical skulls with underdeveloped and missing parts (*Netherway et al.*, 2006). Previously our study group showed the skull base to be asymmetrical in patients with CFM (*Schaal et al.*, 2017). Defining a reliable set of landmarks was challenging though analysing the intra-observer errors confirmed the chosen landmarks are reproducible.

The PCA model showed the variation within the populations. The fact the mathematical model shows allometric growth in the first and second principal component of the control population means the model appears to mirror growth in the control population. The largest variation in controls seems to be allometric growth, for the CFM population this seems to be a visualisation of the spread in severity. Concurrent with other studies, we also noticed unequal orbital sizes(*Santler et al.*, 2003), a more hypoplastic zygoma(*Cousley* and *Calvert*, 1997) and a decrease in height of the maxilla(*Wink et al.*, 2014). Furthermore, we found a decreased length of the lateral part of the upper face and a bending down of the zygomatic body. The fact allometric growth in the CFM population is seen in the second principal component means the variability in craniofacial phenotype has more effect on the model than changes in age.

Besides hypoplasia also aplasia of derivatives of the first and second arch is seen in patients with CFM. It is impossible to place landmarks on missing elements and therefore, the bony shape changes in the often partly missing zygomatic arch could not be described reliably. Additional linear measurements showed a significant decrease in length from the lateral orbital rim to the origin of the zygoma. This could relate to the frequently underdeveloped temporomandibular joint and the frequently seen microtia. Orbital measurements showed a decreased orbital size on the affected side when compared to normal and to the unaffected side. This is caused by an increased orbital width, when taking ratios of length and width, rather than a variation in length.

The model demonstrated the deformities of CFM and defined a vector between the populations. This enabled transforming a CFM skull to its unique normalised skull. Depending on the direction of the vector, it can either normalise a CFM skull or construct a CFM skull from a control patient. Because of the large phenotypic variation in CFM, the average normal vector might not be adequate for all patients to create a skull within normal boundaries. A skull with a severe phenotype will need to be moved further along the normal vector to appear normal than a mild one. Normalizing the skull of a patient and visualizing the differences in a colour-coded map will point out where surgery is needed to improve the facial appearance in an individual patient.

Age range is limited due to available CT-scans, which are only made of patients pre-operatively i.e. in younger patients there is no indication for surgery yet and in older patients surgery already has been performed. Furthermore,

when there is too much variability between the sizes of the skulls due to growth, PCA will show that growth is the biggest change in shape because growth can outweigh the subtle changes of CFM.

This study is different from other studies in the way it uses morphometric geometrics to analyse the variation of shape in a group of patients with craniofacial microsomia, an asymmetrical disorder with frequently missing parts of the skull. It includes the analysis of the midface from the upper orbital rim to the alveolar bone of the maxilla and from the one mastoid bone to the other. Previous studies on CFM mainly focused on mandibular growth so little was known of the changes in size and especially shape of the midface. This method is an excellent way to describe variation in shape by analysing the skull as a whole with a visual approach. The images and videos make this study more visual. The linear measurements are an addition to the principal component analysis and give extra information and confirmation about particular parts of the craniofacial skeleton. This study shows a technique to transform an affected skull to its unique normalised skull, which will be important for an individual surgical approach.

As a continuation of this study, more CFM specific landmark sets of other craniofacial regions (e.g. mandible, cranial base) should be defined to analyse the skull as a whole. Outcome of craniofacial surgery on CFM can be measured by comparing the normalised skull with the postoperative scan. Also a more extensive study with collaboration between international craniofacial centres to increase the numbers of patients is recommended, which would increase the sensitivity of PCA.

CONCLUSION

The skull of a patient with craniofacial microsomia differs in many ways from a ‘normal’ skull. It was already known that orbital, zygomatic and maxillary size was different in the affected side of patients with CFM. The exact changes in shape like the increased orbital width, the bending down of the zygoma and the frontotemporal region were not described yet. These findings are helpful for a better understanding of the deformity. The developed vector between the populations, which is able to transform a CFM skull into its normalised skull, is a promising tool for reconstructive surgery and could be used as a surgical outcome measurement tool.

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CAPTIONS TO ILLUSTRATIONS

Figure 1. Landmarks projected on the skull in frontal (left) and 40° (right) view, showing where the 71 landmarks from are placed on the skull

Figure 2. Colour-coded map showing the predicted (warped) skull compared to its actual counterpart. A frontal view, 40° view and lateral view showing the positive and negative surface differences. Areas of light blue and green show good correspondence between the two scans, showing that the landmarks capture most of the skull shape.

Figure 3. First principal component of the CFM group in 40° left, frontal and 40° right. Plus 2SD (top) and minus 2SD (bottom). Showing the shape variation on the affected (right) side. At the bottom: the zygoma bends down and the zygomatic body is shorter. The orbit is smaller and the frontotemporal region moves down.

Figure 4. Mean CFM skull transforming into a normalized skull using the PCA model. From left to right: CFM skull transforming into its (unique) predicted normalized skull.

Figure 5. Comparison of the orbital ratios between the control group and the CFM group (right and left). * = $p \leq 0.05$

Figure 6. Comparison of the zygomatic height between right and left in the control group and in the CFM group. * = p≤0.05

Figure 7. Comparison of the expected zygomatical length between right and left in the control group and the CFM group. * = p≤0.05

Figure 8. Comparison of the nasiozygomatic length between right and left in the control group and the CFM group. * = p≤0.05

Figure 9. Comparison of the facial width between the control group and the CFM group. * = p≤0.05