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Understanding the heterogenicity of unicoronal synostosis – A morphometric analysis of cases compared to controls

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KEYWORDS
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Summary *Background:* Preoperative severity of unicoronal synostosis varies greatly and involves the frontal bone, skull base and orbits. Degree of deformity affects long-term morphological and functional outcomes after surgery. The aim of this study was to describe the morphological heterogenicity and investigate its relation to patient-specific factors.

Abbreviations: Dice, Dice similarity coefficient; DO, distraction osteogenesis; FOA, fronto-orbital advancement; FS, fronto-sphenoidal suture; HC, head circumference; HD, Harlequin deformity; IOI, improved orbital index; SP, spheno-parietal suture; SZ, spheno-zygomatic suture; UCS, unicoronal synostosis

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coefficient;
Symmetry;
Severity

Materials and methods: In this retrospective cohort study, non-syndromic unicoronal synostosis patients treated between 2006 and 2022 at Necker Hospital, France or Uppsala University Hospital, Sweden, were included and matched to controls. Severity of skull base, orbital and posterior skull asymmetry, degree of anterior plagiocephaly and Harlequin deformity, lateralisation, head circumference, age, timing of metopic fusion and fusion of peri-pterionic sutures were investigated.
Results: Ninety-five patients and ninety-three controls were included. Skull base asymmetry was linearly related to orbital asymmetry ($p < 0.001$), correlated with earlier CT scans ($p = 0.004$) and anterior ($p < 0.001$) and posterior ($p = 0.03$) plagiocephaly. Posterior plagiocephaly was more common in patients (31%) compared with controls (5%) ($p < 0.001$). A patent metopic suture above nine months of age was associated with severe Harlequin deformity ($p = 0.04$) and a lower head circumference when fused ($p = 0.03$). Fronto-sphenoidal suture fusion was associated with later CT scans ($p < 0.001$) and less skull base asymmetry ($p = 0.002$). Spheno-parietal fusion was correlated with decreased skull base asymmetry ($p = 0.03$). Right lateralisation was more common in females.
Conclusions: Heterogenicity of unicoronal synostosis seems to be predominantly explained by variability in skull base morphology. Peri-pterionic fusions might limit deformity.

Craniofacial deformity in non-syndromic unicoronal synostosis (UCS) varies greatly.[1] Anterior plagiocephaly, Harlequin deformity (HD) and asymmetries of the orbits and skull base are the most commonly described elements of skeletal deformity. Surgical treatment address both aesthetic and functional imperatives.[2,3] Still, there is a lack of robust standardised and objective measures to quantify severity[1] and the relevance of different aspects of severity has not been elucidated.

Different surgical treatment approaches have been described, including fronto-orbital advancement (FOA), distraction osteogenesis (DO) and endoscopic strip craniectomy combined with helmet.[1] At most craniofacial centres, UCS patients are treated with a unique surgical method at a standard age. Centres offering different methods usually base their decision on the age at presentation and parental preferences, implantation of devices and use of helmets. As no one surgical treatment has proved clear superiority,[1,4-6] it is likely that not all patients, even within a given age class, would similarly benefit from a uniform treatment approach. The inter-individual heterogeneity could thus justify patient-specific approaches, based on individual parameters yet to be defined.

The potential functional impairments in UCS are related to psychological issues and ophthalmological anomalies likely resulting from malformed orbits.[3,7-13] Previous studies have described a variable orbital shape in UCS[3,10,11,14] and reported inconstant skull base deformity.[15-20] The mechanisms underlying this variability are largely unknown. UCS can been associated with ipsilateral fusion of sutures around the pterion and the lateral orbital frame. Progressive fusion of these additional sutures has been suggested to relate to phenotypic variability.[21-25] Patients with milder deformities tend to be diagnosed later, but the anatomical specificities of less severe cases have not been precisely assessed.

The aim of the present study was to objectively quantify the degree of preoperative severity of orbital and skull base asymmetry, anterior plagiocephaly and HD to investigate the relation between UCS-specific deformities and their association with the degree of positional posterior plagiocephaly, age, head circumference, additional suture fusions and lateralisation.

Methods

Patients and controls

All patients with non-syndromic isolated UCS with available preoperative CT scans of sufficient quality performed between 2006 and 2022 at Necker – Enfants Malades Hospital (AP-HP), Paris, France or Uppsala University Hospital, Uppsala, Sweden, were considered for the study. Patients with identified genetic anomalies or craniofacial syndromes such as Muenke syndrome were excluded. Controls were age-matched to patients and had received CT scans for minor trauma without presenting any craniofacial syndromes, intracranial anomalies, dislocated fractures or comorbidities potentially influencing the investigated parameters. The study complied with the Declaration of Helsinki was ethically approved by the European Joint Programme for Rare Diseases Advisory Regulatory Ethics Board and in accordance with routines at the two centres. For Uppsala University Hospital, informed consent was obtained and the study was approved by the Ethical Review Board of Uppsala and for Necker – Enfants Malades Hospital, ethical aspects of the study were validated by the Data Protection Officer, as previously described.[26]

Shape analyses

Data preparation

Preoperative CT scans were collected from PACS (Vue Motion, Carestream). Adequate quality was determined

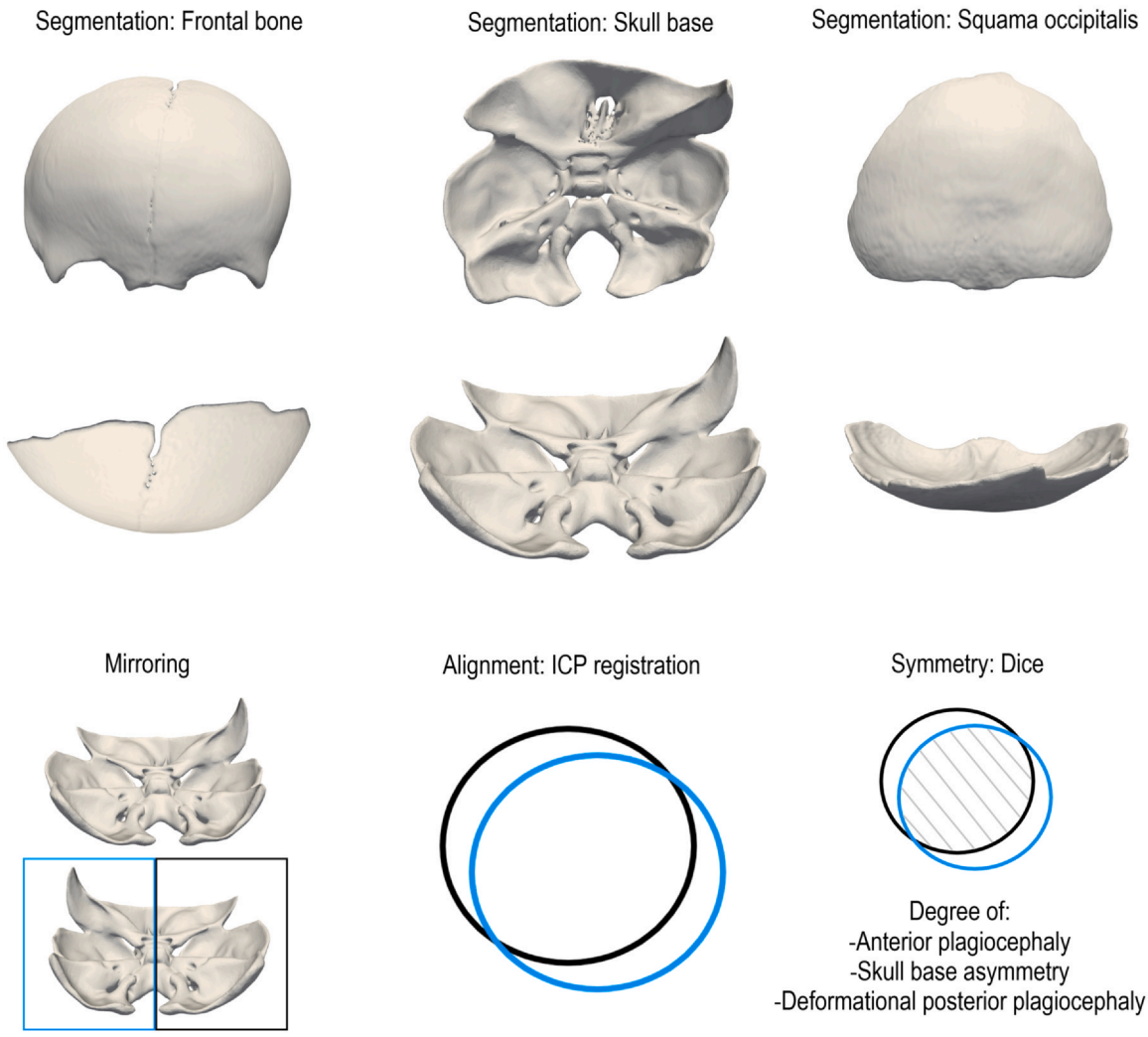

Figure 1 Segmented bone structures included in the study: frontal bones to calculate degree of anterior plagiocephaly, skull bases to calculate skull base asymmetry and squama occipitalis to calculate the degree of posterior plagiocephaly. Segmented structures were automatically mirrored and aligned followed by subsequent objective 3D morphological analyses.

by the low slice thickness, small voxel size and absence of artefacts. Skull bases were semi-automatically segmented in BoneSplit 0.9.2 and orbits in OrbSeg 0.9.3, as previously described.[14,27-29] Segmentations were voxel based and no landmarks were used. The skull base is composed of the whole sphenoid, ethmoid and temporal bones, pars basilaris and lateralis of the occipital bone and the orbital roof and supraorbital bandeau of the frontal bone (demarcated one centimetre above the ipsilateral orbit) (Figure 1). Very thin bones were not removed (vomer, palatine, lacrimal and nasal bones) due to technical difficulties on low-dose CT scans, assuming that their potential impact on the results would be negligible. The maxilla was kept to ensure adequate automatic alignment, as removing it could influence centroid matching. Squama occipitalis was segmented separately for analysing posterior plagiocephaly and the whole frontal bone for analysing the severity of anterior plagiocephaly (Figure 1). Morphological analyses were based on automatic 3D calculations on segmented shapes in Python and included mirroring and alignment by iterative closest point registration,[30] followed by subsequent analyses, as described below (Figure 1).

Severity of asymmetries

Symmetry between the ipsi- and contralateral sides was quantified using the Dice similarity coefficient (Dice). Dice measures the overlap of voxels between shapes, resulting in a symmetry value for each patient, where 100% corresponds to maximum symmetry (Figure 2).[31] It enables comparison of symmetry between patients regardless of age and quantifies severity without having to define a sagittal plane, a tangible issue in UCS.[32,33] Dice was used to objectively determine the severity of skull base and orbital symmetry as well as the degree of anterior and posterior plagiocephaly. Controls were included in all analyses except anterior plagiocephaly because none of them had visible frontal asymmetry based on radiological evaluation.

For posterior plagiocephaly, only subjects < 6 months of age were included to avoid important biases: effect of

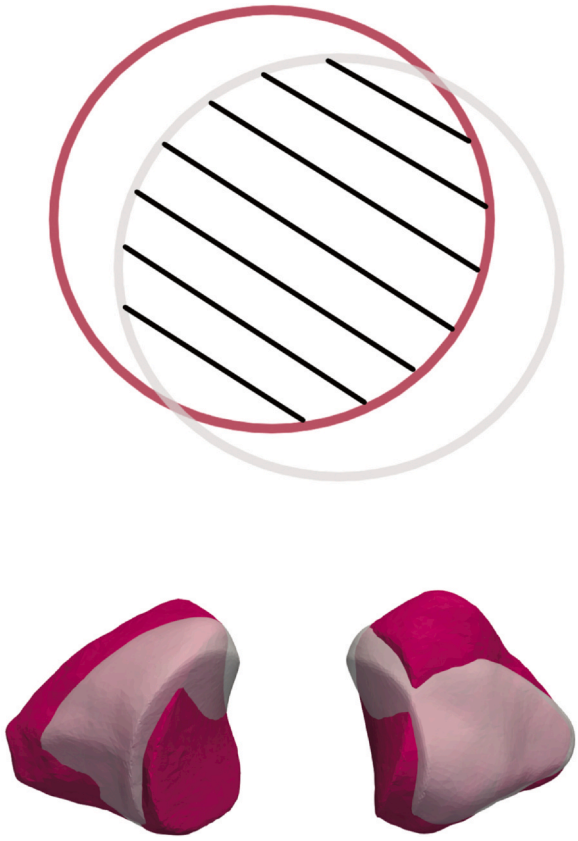

Figure 2 Calculation of symmetry as the Dice similarity coefficient. Above: 2D area with black stripes illustrating the volume overlap between two shapes (red and grey) measured in percentage. Below: example of the setup after pre-processing before calculating symmetry between ipsi- (red) and contralateral (grey) orbits.

ongoing non-surgical treatment (physiotherapy or helmet therapy) and spontaneous improvement in older children. To establish a relevant cut-off value for clinically significant posterior plagiocephaly, data from medical records were compared to calculated values.

Harlequin deformity

A novel method to objectively quantify HD was developed, based on previously described indices.[3,22,34] Both previous methods (orbital index and modified orbital index) only measured the anterior orbital rim and used non-anatomical landmarks, which could lead to less accuracy, less reproducibility and inadequacy in quantifying the elevation of the orbital roof inside the orbit, which is an important part of the HD definition. The improved orbital index (IOI) was calculated in OrbSeg 0.9.3 as the quotient of the width over the diagonal of the ipsilateral orbit (Figure 3). The diagonal was defined as the distance between the most superolateral corner inside the orbit and the most medial point of the zygo-maxillary suture. The width was defined as the distance between the fronto-zygomatic suture and dacryon. Consequently, a lower IOI was correlated with more severe HD.

Growth and suture fusion

Head circumference

The head circumference (HC) was measured on CT scans, as previously described[35] (Figure 4). Briefly, the head length and mandibular width were calculated through the placement of four landmarks and inserted into age- and gender-specific equations.[35] As the equation was based on healthy subjects and relied on the assumption that the head is shaped like a sphere, a compensatory value for the head length in UCS was calculated as the best mathematical fit between the clinically measured and calculated HC at the same age, which was available in 12% of the patient cohort.

Suture fusion

Suture fusion of patients and controls was determined radiologically on axial slices in the bone window by the first author (HL). Unclear cases were determined together with two of the more senior authors (RK and DN). Choice of sutures and grouping into age classes were based on previous studies.[21-25,36,37] Fronto-sphenoidal (FS), spheno-parietal (SP) and spheno-zygomatic (SZ) sutures were assessed. Age classes were defined as $\leq$3 months, 3–9 months and $\geq$9 months for the metopic and $<$ 3 months, 3–5 months, 5–12 months and $\geq$12 months for FS. No classes were defined for SP and SZ due to the lack of reference data. Sutures on the ipsilateral side were defined as patent, fused if $\geq$50% obliterated or inadequately visualised due to artefacts (NA). The contralateral side was used to control for suture patency.

Statistical analyses

Statistical analyses were conducted in R (R Core Team 2021). The level for rejecting the null hypothesis was set at 0.05. Linear regression elucidated linear relations between skull base and orbital symmetry and between skull base symmetry and anterior or posterior plagiocephaly. T-tests were used to compare the degree of anterior plagiocephaly by skull base symmetry and orbital symmetry by HD and to investigate differences in posterior plagiocephaly between UCS and controls, metopic fusion, skull base and orbital symmetry. Mann–Whitney U tests were used to compare skull base symmetry by posterior plagiocephaly or metopic fusion, HD by metopic fusion and standard deviation (SD) of HC by fusion of metopic or FS. Mann–Whitney U tests or t-tests were used to compare skull base symmetry, HD or anterior plagiocephaly by age or suture fusion. The Wilcoxon signed-rank test was used to compare the calculated HC to the clinically measured HC.

Results

Patients and controls

Ninety-five UCS patients and ninety-three controls were included. The mean age at CT scan for patients was

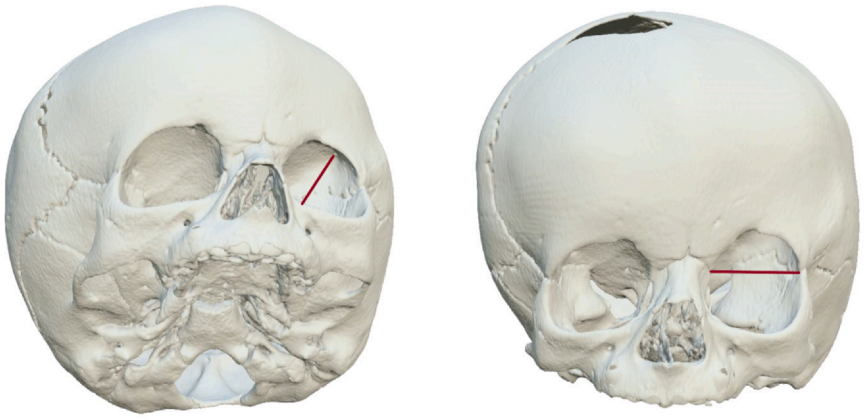

Figure 3 Improved orbital index calculated as the quotient of the width over the diagonal. Left: the diagonal defined as the line between the most superior lateral orbital corner inside the orbit and the most medial point of the zygo-maxillary suture. Right: the width defined as the distance between the fronto-zygomatic suture and dacryon.

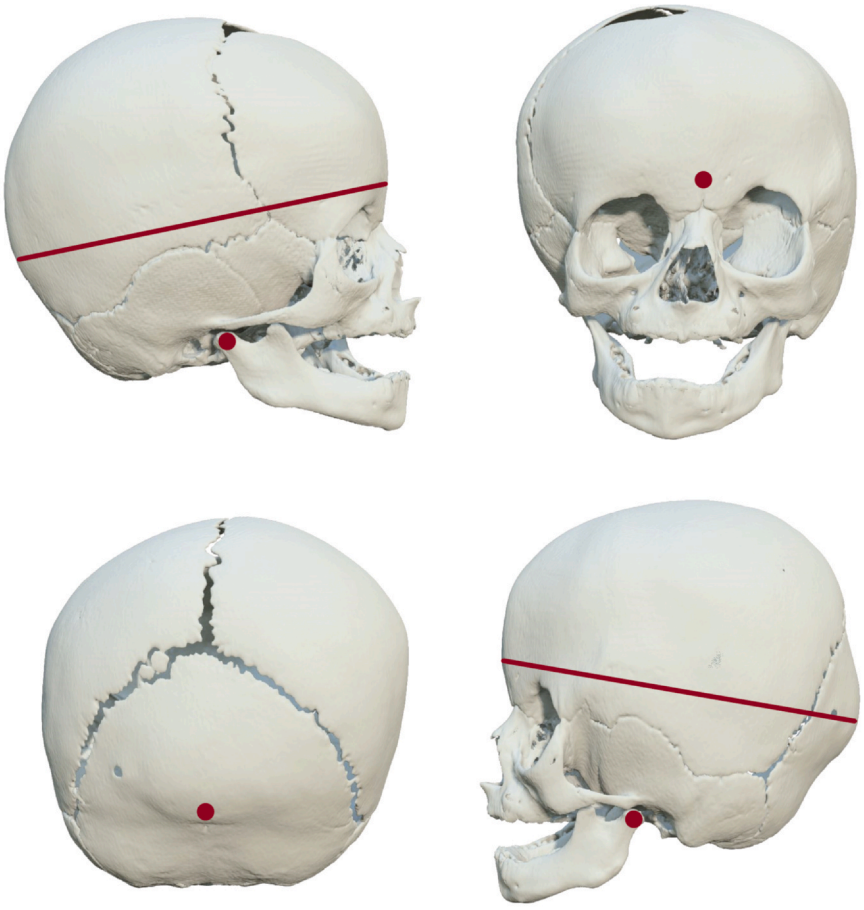

Figure 4 Calculated head circumference (red lines) based on CT scan measurements of head length (glabella to opisthocranion) and mandibular width (most lateral points of the mandible).

269 ± 201 and 205 ± 106 days for UCS and controls, respectively (Table 1). The female-to-male ratio and right-to-left lateralisation were both 2:1 when including all patients (Table 1). The lateralisation ratio was 2.4:1 for females and 1.4:1 for males (Table 1).

Shape analyses

Skull base and orbital asymmetries were significantly more pronounced in UCS compared to controls ($p < 0.001$, $p < 0.001$). The mean skull base symmetry was 46% in UCS

Table 1 Descriptive data.

	Unicoronal synostosis	Controls
Subjects (n)	95	93
Age at CT (days)	$\bar{x} = 269$	$\bar{x} = 205$
	SD = 201	SD = 106
	Range 3–1038	Range 1–417
Sex	F: 66	F: 49
	M: 29	M: 44
Lateralisation	Right: 64 (all); 47 (F) 17 (M)	-
	Left: 31 (all); 19 (F) 12 (M)	
Severity of anterior plagiocephaly (Dice)	$\bar{x} = 46\%$	-
	Range 22–64	
Severity of Harlequin deformity (IOI)	$\bar{x} = 0.77$	-
	Range 0.63–0.94	
Severity of skull base asymmetry (Dice)	$\bar{x} = 46\%$	$\bar{x} = 67\%$
	Range 32–60	Range 50–89
Severity of orbital asymmetry (Dice)	$\bar{x} = 84\%$	$\bar{x} = 96\%$
	Range 74–92	Range 93–98
Positional plagiocephaly (prevalence <6 months)	31%	5%

n = number, $\bar{x}$ = mean, F = female, M = male, Dice = Dice similarity coefficient, IOI = improved orbital index.

and 67% in controls and orbital symmetry was 84% in UCS and 96% in controls (Table 1). Skull base and orbital asymmetries were correlated in UCS ($p < 0.001$, adjusted R-squared 0.67) and there was a clear clustering between patients and controls (Figure 5). Posterior plagiocephaly was 11/36 (31%) in UCS and 2/38 (5%) in controls under six months of age ($p < 0.001$) (Table 1). Patients with severe HD had worse orbital asymmetry ($p < 0.001$) and more severe anterior plagiocephaly ($p = 0.02$). Patients with severe anterior plagiocephaly had more severe skull base asymmetry ($p < 0.001$) and more severe posterior plagiocephaly ($p = 0.04$). There was a significant relation between skull base asymmetry and posterior plagiocephaly in UCS ($p < 0.001$, adjusted R-squared 0.35). No linear relation was found between anterior and posterior plagiocephalies

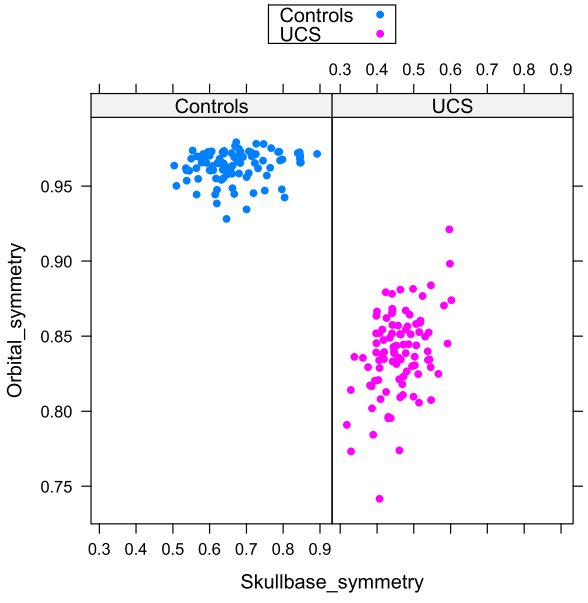

Figure 5 Relation between skull base symmetry (x-axis) and orbital symmetry (y-axis) in UCS (pink) and controls (blue).

($p = 0.04$, adjusted R-squared 0.07). Skull base asymmetry was significantly more pronounced in UCS with severe posterior plagiocephaly ($p = 0.03$). There were no significant differences in skull base ($p = 0.83$) or orbital ($p = 0.77$) asymmetries when compared by lateralisation.

Growth and suture fusion

Growth

There was no significant difference between the clinically measured and calculated HC ($p = 0.62$). These were matched with a precision of +/− 0.5 SD when the head length was compensated by 1.12. Metopic fusion occurred later in UCS ($p = 0.008$) and was significantly associated with lower SD on growth curves ($p = 0.03$), but FS fusion was not ($p = 0.33$). Patients with FS, SP or SZ fusion had HC closer to 0 SD on growth curves compared to those with patent sutures.

Suture fusion

Table 2 summarises suture fusions. The coronal, FS, SP or SZ were not fused in any control. In UCS ≥9 months of age, the metopic suture was patent in 24%, with more severe HD in patients with a patent metopic suture ($p = 0.04$). FS was patent in all patients ≤3 months, fused in 1% between 3 and 5 months, 45% between 5 and 12 months and 94% ≥1 year. Patients with FS fusion were significantly older ($p < 0.001$). The one patient over one year with patent FS had the most severe skull base asymmetry in the cohort and all older patients with patent FS except one had skull base asymmetry within the most severe quartile. Skull base asymmetry was significantly less severe in patients with fused FS ($p = 0.02$). FS fusion was associated with 2% less HD and 1.5% less anterior plagiocephaly, though not statistically significantly ($p = 0.11$, $p = 0.31$). SZ or SP was only fused when FS was fused. Patients with SP fusion had significantly lower skull base asymmetry ($p = 0.03$), less severe HD ($p = 0.03$) and less severe anterior plagiocephaly

Table 2 Suture fusion.

		Metopic		FS	SZ	SP
Group (n)		UCS (95)	Controls (93)	UCS (89)	UCS (92)	UCS (91)
Patent (n)	≤3 months	14/14	16/16	≤3 months: 14/14	90/92	85/91
	3–9 months	30/43	16/52	3–5 months: 10/11		
	≥9 months	9/38	2/25	5–12 months: 26/47		
				≥12 months: 1/17		
Fused (n)	≤3 months	0/14	0/16	≤3 months: 0/14	2/92	6/91
	3–9 months	13/43	36/52	3–5 months: 1/11		
	≥9 months	29/38	23/25	5–12 months: 21/47		
				≥12 months: 16/17		

FS = fronto-sphenoidal, n = number, SZ = spheno-zygomatic, SP = spheno-parietal, UCS = unicoronal synostosis.

($p = 0.003$). The combined FS and SP fusion compared to only FS was associated with less severe anterior plagiocephaly ($p = 0.002$).

Age

Patients with worse skull base asymmetry were significantly younger, both when analysing all subjects ($p = 0.04$) and when comparing the most and least symmetric quartiles ($p = 0.004$). Age was lower in the group with worse orbital asymmetry (median = 100 days younger), however not statistically significant ($p = 0.15$). Patients with more severe anterior plagiocephaly were younger (mean 95 days younger), though not statistically significantly ($p = 0.11$).

Discussion

The present study found that morphological heterogenicity of UCS was predominantly explained by variability in skull base asymmetry. Fusions of sutures around the pterion were related to less skeletal asymmetry and strong correlations between skull base and orbital asymmetry were identified. Underlying skull base asymmetry likely influences the functional outcome via orbital deformation and UCS-associated peri-pterionic fusions may constitute a subset of this condition, which develops less compensatory deformity. These findings may both add to our understanding of UCS and contribute to future development of more individualised surgical treatment protocols aimed at correcting the skull base morphology.

Shape analyses

A robust linear relation was found between skull base and orbital asymmetry. Because orbital asymmetry is related to ophthalmological symptoms,[3,9,10,14,22] this finding suggests an important relation between skull base deformation and functional outcome. It is well established that skull base asymmetry affects facial symmetry in craniosynostosis. Consequently, these findings stress the importance of skull base symmetry in improving both aesthetic and functional outcomes.

Dice might be a promising candidate as a standardised objective measurement of UCS severity because it objectively and automatically quantifies the central morphological issue of asymmetry, is complex enough to capture the intricate severity and obscure details of deformity and is simple enough to understand and use. Dice can be compared regardless of size changes due to growth. It is, however, sensitive to artefacts and minor details, explaining why no values among controls reached 100%. Dice can be applied to other modalities such as 3D photogrammetry. There is great potential for using 3D photography to evaluate long-term morphological outcomes, as it comes with no risk to the patient and can be repeated regularly. A novel method to quantify HD was developed and it correlated with orbital asymmetry. The IOI provides an easy and reproducible way to evaluate ipsilateral orbital severity when objective 3D measures are not available.

The identified association with positional posterior plagiocephaly in UCS supports previous findings, although this relationship is not well understood.[38,39] In the control cohort, the prevalence was very low, possibly owing to successful initial treatment, method of assessment, criteria for asymmetry or the representativity of the studied sample. It is plausible that primary skull base asymmetry would cause posterior plagiocephaly in severe cases, which stresses the importance of providing early adequate information to parents to prevent the progress of deformity.

Lateralisation was unrelated to differences in severity. However, a previously unreported male-to-female difference in lateralisation was identified. Future studies are needed to elucidate the relevance of this finding.

Growth and suture fusion

Patients with an early CT scan had a more severe phenotype, which constituted a selection bias, in that more severe cases tended to have their diagnostic CT scan earlier. Furthermore, older patients more often had ipsilateral suture fusions around the pterion, especially the FS, which were not fused contralaterally or in any control. Without performing multiple longitudinal CT scans on the same patients, it is impossible to differentiate FS fusion as an event in the natural history of untreated patients from a subset in this condition. However, considering that FS and SP fusion combined was associated with less skull base deformity and that older patients with patent FS had more severe skeletal asymmetry, we suggest that the fusion of peri-pterionic sutures may constitute a limiting factor to compensatory deformity. This could be explained by a change in the direction of inhibited growth and expansion by multiple suture fusions, resulting in an altered sum vector preventing the development of asymmetry (Figure 6). The metopic

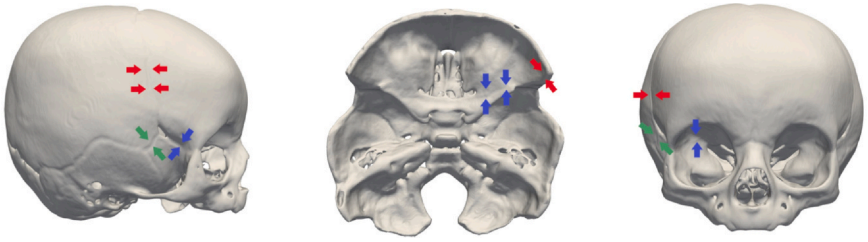

Figure 6 Theoretical direction of inhibited growth due to coronal (red arrows), spheno-frontal (blue arrows) or spheno-parietal (green arrows) fusion.

suture fused later in UCS and a patent metopic suture above nine months of age were related to more severe deformity, possibly due to unhindered compensatory growth. Interestingly, while patients with fused metopic sutures had less HC, patients with fused FS did not, implying that fusion of peri-pterionic sutures should probably be viewed as a primary phenomenon rather than related to brain growth.

Implications for surgical treatment

The goal of surgical treatment is to correct deformity and prevent functional impairment while ensuring normal growth. Given the wide phenotypic spectrum of UCS, a more tailored approach might be preferred. FOA is the most widely practiced method, considered to offer safe and predictable results, but requires extensive craniotomies and is associated with long-term ophthalmological impairment. It corrects the frontal outline and orbital rim but leaves much of the anterior skull base uncorrected. However, it is not known which surgical treatment approach best addresses the anterior skull base, although DO has been suggested.[40] DO offer a less invasive, more dynamic technique, typically performed earlier. Anterior skull base osteotomies are partial and a gradual moulding effect of the distraction forces on the anterior skull base could enhance the correction of orbital anatomy and the reduction of facial mid-line scoliosis. Drawbacks are the need for two surgeries and risks of device-related complications. Given the current data, a reasonable approach could be to advocate DO at an earlier time point for more severe cases and reserve conventional FOA for patients with milder deformity. Future comparative outcome studies with matched cohorts, including both advanced image analysis and clinical data pre- and post-operatively, are needed to establish the best surgical practice.

Limitations

The main limitation was variability in age. However, the symmetry index was size-independent, age groups were used and variability in age was necessary to investigate its influence on asymmetry. Some controls presented low skull base symmetry; the accuracy could have been influenced by positional deformity, limited voxel resolution or registration errors, particularly for thin bone regions. Partially subjective steps were included in the radiological evaluation of sutures and the placement of anatomical landmarks before calculating the IOI and HC. Functional severity associated with shape characteristics was not assessed. Although all patients with a clinical suspicion of syndromic associations underwent genetic panel testing, it was not performed on all children. No post-operative data were included.

Conclusions

Heterogenicity of UCS seems to be predominantly explained by variability in skull base morphology. Peri-pterionic fusions might limit deformity.

Guidelines

STROBE guidelines were followed.

Ethical approval statement

Ethical Review Board of Uppsala Reg. no. 2013/402. Ethical Review Board of Uppsala Reg. no. 2017/452. European Joint Programme for Rare Diseases Advisory Regulatory Ethics Board 22 – Lif.

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Conflict of interest

None.

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