What’s in a Name? Accurately Diagnosing Metopic Craniosynostosis Using a Computational Approach

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Background: The metopic suture is unlike other cranial sutures in that it normally closes in infancy. Consequently, the diagnosis of metopic synostosis depends primarily on a subjective assessment of cranial shape. The purpose of this study was to create a simple, reproducible radiographic method to quantify forehead shape and distinguish trigonocephaly from normal cranial shape variation.

Methods: Computed tomography scans were acquired for 92 control patients (mean age, 4.2 ± 3.3 months) and 18 patients (mean age, 6.2 ± 3.3 months) with a diagnosis of metopic synostosis. A statistical model of the normal cranial shape was constructed, and deformation fields were calculated for patients with metopic synostosis. Optimal and divergence (simplified) interfrontal angles (IFA) were defined based on the three points of maximum average deformation on the frontal bones and metopic suture, respectively. Statistical analysis was performed to assess the accuracy and reliability of the diagnostic procedure.

Results: The optimal interfrontal angle was found to be significantly different between the synostosis (116.5 ± 5.8 degrees; minimum, 106.8 degrees; maximum, 126.6 degrees) and control (136.7 ± 6.2 degrees; minimum, 123.8 degrees; maximum, 169.3 degrees) groups (p < 0.001). Divergence interfrontal angles were also significantly different between groups. Accuracy, in terms of available clinical diagnosis, for the optimal and divergent angles, was 0.981 and 0.954, respectively.

Conclusions: Cranial shape analysis provides an objective and extremely accurate measure by which to diagnose abnormal interfrontal narrowing, the hallmark of metopic synostosis. The simple planar angle measurement proposed is reproducible and accurate, and can eliminate diagnostic subjectivity in this disorder. (Plast. Reconstr. Surg. 137: 205, 2016.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Diagnostic, IV.

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What’s in a name? That which we call a rose
By any other name would smell as sweet.

Romeo and Juliet (II, ii, 1–2),
William Shakespeare

In Shakespeare’s Romeo and Juliet, Juliet makes a convincing argument that the name applied to a person or thing is meaningless and does not define or capture the essence of the entity. Yet, names do matter in the field of medicine. Once a diagnostic label is attached to a patient, it can become the premise for further or ongoing evaluation and treatment, and can have lasting physical and psychosocial effects. Thus, it is imperative to ensure that medical diagnoses are, to the extent possible, founded on precise, objective, and clinically relevant criteria.

Craniosynostosis is defined as premature closure of the cranial sutures.1 Strictly speaking,

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closure of the suture is defined by the histologic presence of bony bridging between the cranial plates. Because it is impractical to obtain a histologic sample on every patient suspected of having craniosynostosis, clinicians rely on proxies, such as radiographic evidence of closure and/or a characteristic cranial shape, to secure the diagnosis. In most instances, it is the cranial shape that raises suspicion of suture fusion and prompts radiographic (typically computed tomography) confirmation, although the necessity of this latter step is controversial. Since histologic closure of most cranial sutures occurs after skeletal maturity, radiographic evidence of fused cranial plates in infancy or early childhood is considered per se pathologic. Yet, there is one exception to this rule: the metopic suture. Unlike other cranial sutures, the metopic suture normally fuses in early infancy often well before 1 year of age. Vu and colleagues characterized the timing of metopic closure based on computed tomographic images of 159 patients evaluated for deformational plagiocephaly or trauma. On the basis of those images, the authors concluded that the age of radiographic closure was between 3 and 9 months, and that computed tomography evidence of metopic closure in an infant should not be the decisive factor in operative intervention. In a similar investigation, Weinzweig and coworkers analyzed computed tomographic images of 76 trauma patients and compared them to patients clinically diagnosed with metopic synostosis. The authors observed that the metopic suture commenced closure as early as 3 months of age and concluded in all patients by 8 months. The implication of these studies is that a radiographically fused metopic suture in an infant is not de facto pathologic. Instead, the determination of what constitutes pathologic metopic fusion rests on the shape of the forehead. Thus, the determination of what constitutes an abnormal, or “trigonocephalic,” cranial form is left to the treating clinician based on subjective impression.

In an effort to provide more objective guidance, various radiographic measures have been proposed. The most commonly used measurement is the interfrontal angle, formed by the line segments connecting the midline forehead (area of the fused metopic suture) to each coronal suture on an axial computed tomography image. This measure has been shown to be a useful tool for distinguishing normal from abnormal frontal shape, but several investigations show a significant overlap between the normal and abnormal groups. This implies that the interfrontal angle is least useful in borderline cases (Fig. 1), for whom an objective definition or diagnostic standard would be most desirable. The lack of a firm cutoff between normal and abnormal cranial shapes leaves an unsettling diagnostic ambiguity that can result in overtreatment or undertreatment.

This investigation used computerized shape analysis to identify which anatomic landmarks reflect the maximal divergence of forehead shape among patients with and without trigonocephaly; developed a population-based definition of what is normal and abnormal forehead angulation, and created a simple computed tomography measurement that can accurately distinguish pathologic frontal shape from normal variation.

**PATIENTS AND METHODS**

**Cases and Controls**

After approval of the institutional review board, we obtained scans from the image repository system in our institution for subjects diagnosed with metopic craniosynostosis with ages 0 to 12 months between the years 2005 and 2012. We retrieved all available computed tomography scans containing the words “trigonocephaly” and “metopic (crani)oosynthesis” in the radiological reports. Controls of the same age range (0 to 12 months) were selected from subjects who reported to the emergency room for trauma, and were screened to exclude hydrocephalus, intracranial tumor, intracranial hemorrhage, hardware (e.g., shunts), craniofacial trauma, and prior craniofacial surgery. Improper protocol studies or poor-quality images were criteria for exclusion from subsequent analysis, particularly for patients with an axial spacing above 5 mm. Images were acquired with the following scanners: General Electric LightSpeed Ultra and General Electric LightSpeed Discovery 690 (General Electric, Fairfield, Conn.), and Philips Brilliance 40 and Philips Brilliance 64 (Philips, Amsterdam, The Netherlands). The axial in-plane pixel size ranged between 0.26 and 0.49 mm, and the axial spacing ranged between 0.33 and 5 mm.

The data collecting procedure provided 18 subjects with metopic craniosynostosis (mean age, 4.2 ± 3.3 months; range, 0 to 11 months; 66 percent were male) and 92 controls (mean age, 6.2 ± 3.3 months; range, 1 to 12 months; 64 percent were male).

**Optimal Landmarks from Shape Analysis**

A validated image processing methodology was used on the available cases to determine the
The best anatomical landmarks located on the frontal bones and metopic suture for discriminating metopic craniosynostosis morphology from controls'. The software was implemented using open source software, including the NA-MIC kit (National Alliance for Medical Image Computing, http://www.na-mic.org), and the reconstruction shown was obtained using 3DSlicer (National Institute of Health, Bethesda, Md.).

All subjects were aligned to a normal cranial template to correct for scale and pose, using the cranial base as a reference. The left and right frontal bones and the metopic suture were automatically delineated using a novel technique. From the set of aligned normal subjects, a statistical shape model (quantifiable representation of the normal variations of the cranium) was constructed, and for each metopic subject, the deformation fields (distance to the closest normal shape derived from the shape model) were obtained over the cranial surface.

The methodology also allowed for the identification of correspondences between each subject and the template and for us to obtain the average deformation field for metopic subjects. For all metopic cases, two lateral landmarks on the left and right frontal bones and one central landmark on the metopic suture were obtained. These landmarks correspond to the point of maximum average malformation in metopic craniosynostosis at each of the three anatomical regions of interest. Figure 2 depicts the average malformation in metopic craniosynostosis represented on a normal template, and optimal landmarks are shown as red spheres. As a result, we can measure an optimal interfrontal angle centered at the landmark on the metopic suture that best describes the recession of the frontal bones and the protrusion of the fused suture area in trigonocephaly.

**Optimal Interfrontal Angle and Interfrontal Divergence Angle**

For simplicity, we defined a proxy interfrontal angle that replaces the central landmark (on the metopic suture) by one nearby placed on the same reconstructed plane that contains the two lateral landmarks (on the frontal bones). As a result of this simplification, the three landmarks can be obtained on the same multiplanar reconstruction, giving rise to a new, easy-to-obtain...
interfrontal angle that derives from the nearby optimal landmarks.

The proposed proxy measurement, called the interfrontal divergence angle, can be obtained using a general procedure, illustrated in Figure 3. First, a multiplanar reconstruction which contains both the opisthion and the most superior tips of the clinoid processes of the dorsum sellae, and which is normal to the midsagittal plane, needs to be found. The central landmark L1 (on the metopic suture) can be found as the most anterior point of the cranium in the reconstructed plane. The lateral landmarks L2 and L3 can be found as the most external crossing of the frontal bones with a ray thrown perpendicularly at the midpoint of the line connecting the exterior of the coronal sutures with the central landmark. All of the angular measurements were obtained using the Voxar 3D viewer (Toshiba, Edinburgh, United Kingdom).

**Fig. 2.** Areas of maximum deformation (blue) and new points (red spheres) for measurement of optimum interfrontal angle (OIFA) and interfrontal divergence angle (IFDA). Lateral points are placed on the frontal bones, and the central point is situated on the metopic suture.

**Fig. 3.** Using the computed tomography cut containing the opisthion and the tips of the clinoid processes, normal to the midsagittal plane, the standard interfrontal angle is constructed and the perpendicular bisector of each limb is passed outward until it contacts the frontal bones.

**Statistical Analysis**

Descriptive statistics are summarized using frequencies and percentages for categorical variables and medians/means, standard deviations, and ranges for continuous variables (Matlab V. R2011b; The Mathworks, Inc., Natick, Mass.). We performed a retrospective statistical power analysis to determine the minimum number of samples necessary for proper characterization of optimum interfrontal angles, a study that was lacking in previous work reporting a similar type of diagnostic feature.5 We used the angular values reported therein for our power analysis.

To assess the reliability of our diagnostic procedure, two operators were instructed in the methods for multiplanar reconstruction, landmark identification, and angular measurement according to the methods described above. They
then measured the interfrontal divergence angle on a subset of 18 subjects and 18 controls. Furthermore, optimum interfrontal angles and interfrontal divergence angles were obtained on the entire cohort of 18 subjects and 92 controls automatically from landmarks on the template via registration to the spatial reference for each of the subjects.

Nonparametric Spearman’s correlation was used to assess the relationship between automatic optimum interfrontal angle and automatic interfrontal divergence angle, between automatic interfrontal divergence angle and manual interfrontal divergence angle, and between manual interfrontal divergence angles from both operators. Bland-Altman plots were computed to further characterize the relationship between automatic and manual interfrontal divergence angles. Then all subsequent analysis was performed using automatic interfrontal divergence angle. To analyze the differences between the optimum interfrontal angle and interfrontal divergence angle in normal controls and metopic cases, a nonparametric Wilcoxon test was used; \( p = 0.001 \) was chosen for statistical significance. Finally, a threshold for discriminating pathologic from normal interfrontal divergence angle was obtained from the distribution of interfrontal divergence angle values, in the control population, at the mean minus two standard deviations. The accuracy of the test was validated in terms of the clinical diagnoses. Spearman’s analysis was used to assess the significance of the correlation between age and sex of the patient and their angular measurements.

**RESULTS**

**Cases and Controls**

Retrospective analysis determined that our study had a statistical power of 99 percent and a confidence interval of 1 percent. There was no significant correlation between the angular measurements and the age and sex of patients: \( \rho = -0.17 \) and \( p = 0.072 \) for age, and \( \rho = -0.03 \) and \( p = 0.74 \) for sex. Therefore, the data in the study were not stratified by age or sex.

**Interfrontal Angles**

The optimum interfrontal angles were obtained automatically for all trigonocephaly cases (116.5 ± 5.8 degrees; minimum, 106.8 degrees; maximum, 126.6 degrees) and controls (136.7 ± 6.2 degrees; minimum, 123.8 degrees; maximum, 169.3 degrees). The Wilcoxon test indicated significant differences (\( p < 0.001 \)) between the two groups. Automatic optimum interfrontal angles and automatic interfrontal divergence angles were found to have a significant Spearman’s correlation (\( p < 0.001 \)). Manual and automatic interfrontal divergence angles were also found to be significantly correlated (\( p < 0.001 \) for both operators). The average error between manual and automatic interfrontal divergence angles was found to be of 4.4 degrees, which is smaller than the standard deviation of automatic interfrontal divergence angles for each of both diagnostic groups, and equals 3.1 percent of the average value for automatic interfrontal divergence angles. Interobserver reliability \( \kappa \) score for manual interfrontal divergence angles was found to be 0.88, which is indicative of good precision.

Bland-Altman plots are provided in Figure 4 as an indication of the high correlation between manual and automatic interfrontal divergence angles. Automatic angles were found to be significantly different (\( p < 0.001 \)) for trigonocephaly cases (120.7 ± 5.9 degrees; minimum, 110.1 degrees; max, 135.7 degrees) and controls (145.8 ± 5.8 degrees; minimum, 128.2 degrees; maximum, 164.0 degrees).

**Interfrontal Divergence Angle Distribution and Accuracy of Test**

For automatic optimum interfrontal angle and interfrontal divergence angle, computed on a total of 110 cases (18 metopic cases and 92 controls), we defined a diagnostic threshold, in terms of the distribution of angular values in controls, at the mean minus two standard deviations. We then computed the accuracy of the diagnostic test for optimum interfrontal angles and interfrontal divergence angles in terms of the available clinical diagnoses. Analysis for optimum interfrontal angle resulted in an accuracy of 0.981 at 124.3 degrees. The sensitivity was 0.989 and the specificity was 0.944. Evaluation of the interfrontal divergence angle resulted in an accuracy of 0.954 at 134.2 degrees. The sensitivity was 0.956 and the specificity was 0.944. One metopic case presented optimum interfrontal angle and interfrontal divergence angle within two standard deviations of the mean in the controls, which may indicate that the clinical diagnosis was arguable. We demonstrate this case in Figure 5, together with a normal case with similar interfrontal angle.

**DISCUSSION**

The automated computational shape analysis used in this investigation yields the most accurate
diagnostic parameter reported to date for objectively quantifying forehead shape. The accuracy of the automated analysis (optimum interfrontal angle) produced an accuracy of 0.981, higher than that of prior reports.\footnote{7} The interfrontal divergence angle, which can be easily and reliably calculated using an axial computed tomographic scan, had an accuracy of 0.954 at a cut-off angle of 134.2 degrees (2 SD below the mean interfrontal divergence angle in controls), sensitivity of 0.956, and specificity of 0.944. Unlike standard measures, such as interfrontal angle, the interfrontal divergence angle captures more precisely the convexity of the frontal bones. The difference is best illustrated by considering a simple geometric model: a triangle and a pentagon of the same base width and peak height. If conventional interfrontal angle measures were applied to our geometric model, the angular measures (apex to base) would be identical for each shape. The shapes, however, are clearly not identical. The interfrontal divergence angle for each structure, by contrast, would be dramatically different. It is our opinion, based on the aforementioned data, that the interfrontal divergence angle provides the best depiction of forehead contour and allows for the most objective and precise distinction between abnormal shape and normal shape.

Our method of diagnosis relies on computed tomography scan analysis and, therefore, exposes patients to low doses of ionizing radiation. Recent concerns about the mutagenic effects of computed tomography scanning in infants and children\cite{13-15} have prompted some authors to call for relying on clinical examination exclusively to diagnose most forms of craniosynostosis.\footnote{2} Although

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Fig4.png}
\caption{Bland-Altman plots depicting interobserver reliability between (above) automated and (below) manual measurements.}
\end{figure}
the craniofacial phenotype is usually sufficient to diagnose most forms of craniosynostosis, reliance on clinical evaluation alone to diagnose and advocate operative intervention for metopic synostosis presents some challenges. There is no clear consensus regarding the threshold of forehead narrowing that constitutes a “pathologic” shape and, thus, can be considered true trigonocephaly. It is likely that most surgeons would agree on the extremes of cranial shape (either normal or grossly trigonocephalic), but intermediate shape differences present a much more nebulous picture. In the absence of a clear quantitative definition of abnormal (i.e., falling outside the second standard deviation from the mean), diagnosis relies on the surgeon’s subjective impression. This subjective method is fraught with error and the potential for overdiagnosis or underdiagnosis. Furthermore, the externally visible phenotype can be worsened by a robust metopic ridge and overlying soft tissue or bony thickening, and may not be representative of the endocortical shape of the forehead (Fig. 6). Weinzweig and coworkers observed an endocortical notch (“omega sign”) to be a good indicator of pathologic fusion; this finding was present in 93 percent of patients who carried a clinical label of metopic synostosis and in none of their controls. Other clinical signs associated with trigonocephaly, such as hypotelorism and biparietal widening, are notoriously unreliable. In fact, one center reported that only 14 percent of patients with metopic craniosynostosis had the classic triad of forehead narrowing, hypotelorism, and biparietal widening. Those authors found that a combination of computed tomographic measurements provided a 96 percent diagnostic accuracy for metopic synostosis; however, the comparison gold standard was their own subjective clinical label of normal and abnormal. Lastly, several studies have even questioned the correlation between the severity of trigonocephaly and the development of intracranial hypertension or neurocognitive delays. The small potential harm from a single head computed tomography scan seems justified against the cost and potential morbidity of an unnecessary intracranial operation.

The need for standardized and widely accepted diagnostic criteria for metopic synostosis is, perhaps, best highlighted by the inexplicable rise in the incidence of metopic craniosynostosis reported...
by some craniofacial centers throughout the world over the last two decades. Although various explanations for this changing epidemiology have been proposed, this phenomenon deserves closer scrutiny since it has only been reported by certain centers, and the upward trend for metopic synostosis has occurred while the incidence for other forms of craniosynostosis is generally unchanged. For example, our center has seen no quantifiable rise in the incidence of metopic craniosynostosis over the last 20 years. Moreover, the rise in fusions appears only to affect the metopic suture. One would be hard-pressed to present a cogent argument as to why environmental factors would affect only the metopic suture and have virtually no effect on the remaining cranial sutures. It is possible that there are specific and isolated environmental influences active only in these geographic regions, but this seems highly improbable.

Another plausible explanation is that the rise of posterior deformational flattening over the last 20 years could make some children, especially those with borderline cases of interfrontal narrowing, appear phenotypically more “trigonocephalic.” Biparietal widening is a feature of both deformational brachycephaly and severe trigonocephaly. Thus, it is conceptually possible that an accentuation of posterior cranial width in a child with mild interfrontal narrowing or a prominent metopic ridge could create the impression of true “trigonocephaly.”

This proposal derives support from two lines of inconclusive, but suggestive, evidence. First, the timing of the epidemiologic rise in metopic synostosis reported from some centers directly mirrors the dramatic rise in deformational flattening that followed supine sleeping recommendations to reduce the incidence of sudden infant death syndrome. Lee and coworkers reported a 7.1 percent per year rise in the incidence of metopic craniosynostosis in Australia over the last 25 years. DiRocco and coworkers reported a 420 percent increase in the number of patients managed for metopic synostosis between 1988 and 2007, versus a 170 percent increase for all other types of craniosynostosis. Second, the risk factors associated with metopic synostosis reported from affected centers, such as multiple births, increase maternal age, low birth weight, prematurity, and male sex, have also been implicated in the development of deformational flattening.

A final explanation is that diagnostic inconsistency or ambiguities have led to a lower threshold in some centers for considering a given forehead shape “abnormal.” Many clinicians rely on simple pattern recognition, a la Virchow, to diagnose trigonocephaly; consequently, their clinical label (normal versus abnormal) and treatment decisions are completely subjective. Clearly, there are severe examples of trigonocephaly that all clinicians (and nonclinicians) would consider abnormal. Given the wide phenotypic variability seen in this diagnostic spectrum, however, and the potential morbidity and magnitude of the treatment options, is it reasonable to rest such a decision on nothing more than the surgeon’s impressions? Such unbridled clinical latitude is rarely seen in other areas of medicine. We propose a more scientific approach: that the terms “trigonocephaly” and “metopic craniosynostosis” should only be applied to patients who demonstrate a statistically abnormal frontocranial shape, defined as an interfrontal divergence angle of less than 134 degrees. Ipso facto, the decision to operate on patients for premature metopic closure should, with rare exception, rest on accurate computed tomography-based measurements and not on clinical impression alone.

There are some limitations to this study that should be discussed. First, the number of patients in both the control and case groups was limited. The number of patents in our case group was limited by our strict inclusion criteria: the age cut-off for our study (0 to 12 months); the availability of high-quality computed tomographic scans derived only from our institution; and no associated syndrome. Although our control database included 93 patients, a greater number of patients in the control group would likely provide a more robust normative distribution. To help create greater statistical power to our analysis, we limited our analysis to patients 0 to 12 month of age. Thus, the accuracy of our measurements in older patients is unknown. We are currently expanding our normative database to include a larger number of patients over a larger range of ages; these data will be published once available. Second, our objective angular analysis does not completely escape some selection bias since the landmarks for our angular measurements were derived from an analysis of patients with a clinically diagnosed metopic craniosynostosis. The computer algorithm produces an infinite and complex set of measurements that would have been of little practical use for clinicians, especially those who do not possess the software. The comparison between clinically diagnosed craniosynostosis patients and the normative templates allowed us to identify the area of maximum shape disparity, establish reproducible landmarks, and create a useful/reproducible two-dimensional measurement. The measurement was then applied to the control group to derive the cut-off threshold. The actual cut-off measurement, therefore, stands on
normative data alone and provides a statistical definition for abnormal forehead acuity.

CONCLUSIONS

The automated analysis described in this report provides the most accurate means of measuring forehead contour reported to date. Our computational approach provides a measurement threshold below which the forehead shape falls outside the normal distribution and can be correctly described as abnormal or pathologic. The simplified interfrontal divergence angle is a two-dimensional computed tomography measurement that is extremely accurate in assessing frontal shape; if properly used, this measurement would eliminate the diagnostic subjectivity of metopic craniosynostosis.

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