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Little Evidence of Association Between Severity of Trigenocephaly and Cognitive Development in Infants With Single-Suture Metopic Synostosis

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Abstract

OBJECTIVES—To measure severity of trigonocephaly among infants with single-suture metopic craniosynostosis by using a novel shape descriptor, the trigonocephaly severity index (TSI), and to evaluate whether degree of trigonocephaly correlates with their neurodevelopmental test scores.

METHODS—We conducted a multicenter cross-sectional and longitudinal study, identifying and recruiting 65 infants with metopic synostosis before their corrective surgery. We obtained computed tomography images for 49 infants and measured the presurgical TSI, a 3-dimensional

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Disclosure

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outline-based cranial shape descriptor. We evaluated neurodevelopment by administering the Bayley Scales of Infant Development, Second Edition, and the Preschool Language Scale, Third Edition, before surgery and at 18 and 36 months of age. We fit linear regression models to estimate associations between test scores and TSI values adjusted for age at testing and race/ethnicity. We fit logistic regression models to estimate whether the odds of developmental delay were increased among children with more severe trigonocephaly.

RESULTS—We observed little adjusted association between neurodevelopmental test scores and TSI values, and no associations that persisted at 3 years. Trigonocephaly was less severe among children referred at older ages.

CONCLUSION—We observed little evidence of an association between the severity of trigonocephaly among metopic synostosis patients and their neurodevelopmental test scores. Detecting such a relationship with precision may require larger sample sizes or alternative phenotypic quantifiers. Until studies are conducted to explore these possibilities, it appears that although associated with the presence of metopic synostosis, the risk of developmental delays in young children is unrelated to further variation in trigonocephalic shape.

Keywords

Child development; Congenital abnormalities; Cranial shape; Craniosynostosis; Metopic suture; Premature suture fusion

Premature fusion of the metopic suture occurs in approximately 1 in 15 000 live births and causes characteristic head shape and facial differences, including trigonocephaly, an increased ratio of interparietal to intercoronal distances, a frontal midline ridge, and hypotelorism (Figure 1).^{1–4} Except when these characteristic abnormalities are mild, diagnosis of metopic synostosis generally leads to craniofacial reconstructive surgery. This surgery is usually performed within the first year of life, which normalizes head shape, increases intracranial volume, and therefore minimizes the risk of sequelae such as elevated intracranial pressure.⁵

A related concern is whether children with isolated metopic synostosis may be at risk of developmental delays or deficits. Although many of the studies designed to address this long-standing question have had methodological flaws, a synthesis of current evidence suggests that the majority of children with isolated metopic synostosis perform within intellectual norms, but that the condition is associated with increased risk of cognitive, speech, language, or behavioral problems.^{6–16} Several possible mechanisms could account for this association, including chronically increased intracranial pressure and functional neurological problems caused by alterations in brain structure such as those noted in children with metopic synostosis.¹⁷ Alternatively, developmental deficits might arise from the same cause(s) as metopic synostosis, such as a genotype that independently influences the risk of both developmental delay and premature suture fusion.¹⁵

To provide evidence that may help distinguish among these possible mechanisms and to identify a possible predictor of developmental delay in children with metopic synostosis, we addressed the hypothesis that the severity of trigonocephaly in metopic synostosis patients is quantitatively associated with their pre- and postoperative mental and motor developmental test scores in the first 3 years of life. Previous evaluations of child development in relation to severity of metopic synostosis incorporated only qualitative or subjective, semiquantitative assessments^{8,10,13} or one aspect of cranial shape, the ratio of interparietal to intercoronal distances.^{7,12,16} We conducted a cross-sectional and longitudinal study as part of a larger, multicenter investigation of children with single-suture craniosynostosis. To quantify severity of trigonocephaly, we applied the recently described trigonocephaly severity index

(TSI), which incorporates data regarding the outline of a cranial shape extracted from 3-dimensional (3D) computed tomography (CT) images.¹⁸ We showed in a previous study that the TSI distinguished metopic synostosis patients from nonsynostotic control infants with 96% accuracy.¹⁸

PATIENTS AND METHODS

Participants

Participants were enrolled in a previously described, prospective, multicenter investigation of neurodevelopment among children with single-suture craniosynostosis and children without prematurely fused sutures.^{19,20} Case infants were eligible for the larger study (the Infant Learning Project) if, at the time of enrollment, they had single-suture metopic synostosis, confirmed by CT scan; had not yet had reconstructive surgery; and were 30 months of age or younger. Exclusion criteria included premature birth (ie, before 34 weeks' gestation), the presence of major medical or neurological conditions (eg, cardiac defects, seizure disorders, cerebral palsy, significant health conditions requiring surgical correction), the presence of 3 or more extracranial minor malformations²¹; and the presence of major malformations. We obtained independent institutional approval from each participating center: Seattle Children's Hospital; Northwestern University in Chicago (Children's Memorial Hospital), Children's Heath Care of Atlanta, St. Louis Children's Hospital, and Children's Hospital of Philadelphia.

Infants were referred to the study at the time of diagnosis by their treating surgeon or pediatrician. Enrolled patients in the overall study were 84% of those eligible, with lack of interest or distance or time constraints being the major stated reasons for non-participation. 3D CT scans were performed at each participating center, and deidentified imaging data were sent to Seattle for further analysis.

The 49 participants in the current study were all those with single-suture metopic synostosis for whom we obtained presurgery CT scans. Because of poor image resolution or inability to locate CT records, we were unable to process images for an additional 16 subjects with metopic synostosis who participated in the larger study of neurodevelopment.

Neurobehavioral Measures

Neuropsychological assessments were conducted at each site, with the exception of a small number of participants recruited from Children's Hospital of Philadelphia (12 case subjects and 12 control subjects) who were assessed at Northwestern University in Chicago. We assessed the infants' neurodevelopmental status during each of 3 visits: (1) before craniofacial reconstructive surgery, (2) post-surgery (except for 1 patient who did not have surgery) at an approximate age of 18 months, and (3) at approximately age 36 months.

To evaluate cognitive and psychomotor development, trained psychometrists administered the Mental Development Index and Psychomotor Development Index from the Bayley Scales of Infant Development, Second Edition (hereafter termed Bayley cognitive and motor scores, respectively).²² We also administered the Preschool Language Scale, Third Edition (PLS-3) including both the Auditory Comprehension and Expressive Communication subscales (hereafter termed receptive language or expressive language, respectively).²³ Both the Bayley and PLS-3 are standardized and norm referenced. We and others have described both instruments in detail, including more details about our test administration, reliability assessment, and quality control.^{19,20}

Processing of Images for Cranial Shape Quantitation

We obtained high-resolution CT data for participants at all sites. We reformatted and analyzed DICOM format files from all sites at Seattle Children's Hospital. We used vWorks workstations to produce 3D images. By identifying anatomic landmarks on these images, we located the cranial base, specifically from a lateral view of the 3D reformations of the cranium, by using the frontal nasal suture anteriorly and the opisthion posteriorly (Figure 2). We then shifted this plane superiorly until positioned at the level of the maximal dimension of the fourth ventricle (termed the M plane).

Quantization of Trigonocephalic Cranial Shape

We previously described the TSI and provide only a brief overview here.¹⁸ The TSI is outline based and can be measured on any of the 3 cranial image planes that we investigated. Our previous work suggested that the TSI in the M plane yielded the best accuracy in distinguishing metopic synostosis from nonsynostotic cranial shapes; thus, we incorporated only TSI in the M plane measurements in the current work.

The rationale for developing the TSI was the characteristic triangular shape of trigonocephaly. Measuring the TSI essentially involves fitting an isosceles triangle to the frontal cranial outline and estimating the area of the fitted triangle. The first step is to extract quantitative information about the cranial outline, which we performed in the polar coordinate system (Figure 3).

A circular outline mapped in polar coordinates would look like a horizontal line (because distance from the radius is constant as one varies θ , the angular distance from the polar axis); an oval outline would have relatively smooth peaks and troughs. The metopic cranial outline deviates from an oval shape in coming to a more pointed shape, observed as a sharper peak in the polar coordinate system (Figure 4). The isosceles triangle that best fits this peak will tend to have a much narrower base than triangles fit to the analogous peak of a nonsynostotic cranial outline.

The TSI is equal to the base of the triangle (or $2 \cdot \text{area}/\text{height}$), normalized by dividing by 180, which ensures that the TSI takes values between 0 and 1 (Figure 5): $\text{TSI} = \text{base of the fitted triangle}/180 = (2 \cdot \text{area}/\text{height})/180$.

TSI values close to 0 suggest more severe trigonocephaly, whereas values closer to 1 suggest mild or absent trigonocephaly (Figure 6). For ease of interpretation of regression results, we further multiplied all TSI values by 20. We subsequently refer to the TSI taken in the M plane simply as TSI or TSI₂₀.

Statistical Analysis

We estimated unadjusted statistics summarizing the distributions of neurodevelopmental test and TSI scores (mean, standard deviation, and 5th, 25th, 50th, 75th, and 95th percentiles). For all participants with metopic synostosis, we examined neurodevelopmental and TSI scores from the baseline (presurgery) visit in relation to (1) demographic characteristics, (2) the presence or absence of a usable CT scan for a participant, and (3) whether participants had neurodevelopmental testing at all 3 visits. In preliminary descriptive data analyses, we noted an association between TSI₂₀ values and age at the baseline visit, which is strongly correlated with age at diagnosis. We therefore performed a post hoc linear regression analysis to quantify this relationship.

To evaluate the association between neurodevelopmental scores and severity of trigonocephaly, we fit linear regression models adjusted for age (continuous) and race (white

vs other), including 95% confidence intervals for all estimates. In these models, the dependent variable was the Bayley cognitive, the Bayley motor, the PLS-3 receptive language, or the PLS-3 expressive language scores. We also explored whether any such associations differed by sex or age at the visit, by including in the model 1 of 2 multiplicative interaction terms ($\text{sex} \times \text{TSI}_{20}$ or $\text{age} - \text{median} \times \text{TSI}_{20}$, where the median ages were 7, 19, and 37 months at the baseline, 18-month, and 3-year visits, respectively).

In secondary analyses evaluating the same question, we categorized each neurodevelopmental standardized score according to whether it was above or below 85, a common clinical threshold for identification of elevated risk of developmental delay. We then fit age-adjusted logistic regression models in which the dependent variable was delay on each of the 4 neurodevelopmental testing scales, in separate models.

RESULTS

In the larger study, there were 65 children with metopic synostosis, of whom 49 children had preoperative CT images and were included in this substudy. Of these, 44 and 37 also had developmental testing at the second and third visits, respectively. Average unadjusted baseline developmental scores were between 90 and 96 for the Bayley cognitive and PLS-3 language scales and 83.3 for the Bayley motor scale (Table 1). Thirty-one percent were female, and the median ages at the 3 visits were 7, 19, and 37 months (Table 2).

Approximately one third of the children were of a nonwhite race, and approximately 30% were in the lowest 2 socioeconomic categories. All but 1 patient (who did not have surgery) underwent craniofacial reconstructive surgery before the second visit. Average scores were associated with sex, age, and study site, although adjustment altered average scores only slightly. Both unadjusted and adjusted averages were very similar to the metopic synostosis patient averages for the larger study that included children who did and did not have CT images available by the time of analysis. These averages were also similar for children with CT images having different numbers of study visits.

The TSI_{20} values were fairly normally distributed, with a mean of 6.0 and standard deviation of 0.9 (Table 1); the index ranged from 3.9 to 8.1. The averages and medians were very similar when restricted to children with all 3 study visits and when compared by sex, race, study site, or socioeconomic category (Table 2). For each 1-month increase in age at the baseline visit, there was an average increase of 0.11 in TSI_{20} values (95% confidence interval, 0.05–0.16)(Figure 7).

In age- and race-adjusted linear regression analyses at each visit, there was little evidence of an association between neurodevelopmental test scores and severity of trigonocephaly as measured by the TSI (Table 3). At the baseline visit, the difference in test scores associated with each 20-unit increase in TSI ranged from –0.2 to 2.0 (all $P > .3$) for all scales except the Bayley motor scale, for which a 20-unit increase in TSI was associated with nearly a 5-point increase in scores (95% confidence interval, 0.1–9.5). The latter difference did not persist at either follow-up visit. At the second visit, the difference in test scores associated with each 20-unit increase in TSI ranged from –0.8 to 0.8 (all $P > .27$) for all scales except the PLS-3 receptive language scale, for which a 20-unit increase in TSI was associated with nearly a 6-point decrease in scores (95% confidence interval, –11.4 to –0.1). This difference also did not persist at the third visit, when differences for each 20-unit increase in TSI ranged from –3.6 to 3.6 (all $P > .2$).

The results from age-adjusted logistic regression models at each visit gave largely similar results (not shown). At the baseline visit, the odds of delay on the motor scale were halved for each 20-unit increase in TSI (95% confidence interval, 0.2–1.0). Otherwise, for both

other visits for the Bayley motor scale and all 3 visits for all other scales, the odds ratios associated with a 20-unit increase in TSI ranged from 0.6 to 2.2 (all $P > .1$).

There was little evidence that the magnitude of these associations differed for boys and girls or, for most neurodevelopmental tests, for patients older or younger than the median age at each visit (not shown). The exception was for the PLS receptive language scale at age 3, when patients seen at 37 months or older had lower scores for each 20-unit increase in TSI, and patients seen at younger than 37 months of age had higher scores for each 20-unit increase in TSI. The 95% confidence interval for the interaction term was extremely wide (−31 to −6.3).

DISCUSSION

In this multicenter follow-up study of young children with single-suture metopic synostosis, we observed little, if any, linear relationship between scores on developmental examinations and severity of trigonocephaly as measured by the TSI. Although the estimated magnitude of these associations was often nonzero, the 95% confidence intervals, which help to measure the variability of the estimates, tended to be very wide. This imprecision, attributable to the relatively small sample size, as well as the multiple comparisons made, discourage firm conclusions regarding the hypothesis that severity of the metopic synostosis phenotypic correlates with neurodevelopmental test scores.

Although many studies have yielded evidence that the occurrence of metopic synostosis is associated with increased risk of developmental deficits,^{6–16} to our knowledge, there have been only 5 previous investigations addressing the same specific hypothesis as we addressed here: that beyond the qualitative diagnosis of metopic synostosis, severity of the trigonocephalic cranial shape is associated with neurodevelopment or behavior.^{7,8,10,12,16} Three of these studies had results similar to ours, in that they yielded little evidence to support this hypothesis.^{8,10,12} A positive association was noted in a fourth study, specifically relating intelligence to the ratio of interparietal to intercoronal distance⁷; however, the authors also noted that this relationship may have been attributable to the inclusion of cases with associated malformations. In a fifth study of 22 patients with nonsyndromic metopic synostosis, trigonocephaly severity as measured by the ratio of interparietal to intercoronal distance was correlated with both the Bayley cognitive ($r = 0.7$, $P > .05$) and motor ($r = 0.56$, $P < .05$) scales, although there was apparently no association between Bayley scores and subjective categorical severity ratings.¹⁶

Our null findings also agree with those of previous studies in which there was a consistent lack of observation of an association between the age at which craniofacial reconstructive surgery is performed and the risk of neurodevelopmental delay.^{8,16,20} The possibility of such an association has been of interest to investigators because it provides an indirect test of the hypothesis that surgery reduces the risk of developmental delay, either by decreasing the risk of increased intracranial pressure or by releasing the anatomic constraints on the brain, or both.^{19,24}

The current study differed in several ways from previous investigations of the same hypothesis. First, we applied a novel trigonocephaly shape descriptor, the TSI, which incorporates data from the whole cranial shape outline.¹⁸ Use of outline data should theoretically make the TSI more sensitive to features not captured by simple interlandmark distances and angles. We did not directly compare the performance of different indices on the same images; however, compared with reports regarding interlandmark distances, we observed improved accuracy for distinguishing cranial outlines of patients with metopic synostosis from those of unaffected individuals.¹⁸ Nevertheless, the phenotypic

characteristics to which the TSI is likely most sensitive are the angular severity of the forehead²⁵ and the ratio of interparietal to intercoronal distances,^{3,7,16} both of which likely influence the area of the triangle best fitting the central peak of the polar coordinate representation of the cranial outline. Thus, it is possible that there is a relationship between neurodevelopment and some aspect of phenotype severity not characterized by the TSI, such as hypotelorism or vertical growth.²

Second, we developed a rigorous case definition, attempting to recruit all eligible patients diagnosed prospectively at 4 different craniofacial centers within a 6.5-year period. Although, as in the studies of others, participation was incomplete, we also performed extensive subanalyses to evaluate the potential for various types of attrition bias, finding little evidence of bias attributable to differential participation over time by sex, race/ethnicity, age, baseline developmental scores, or TSI values. There have been few reports of factors influencing the severity of the cranial shape in metopic synostosis. We explored the possibility of confounding by various demographic characteristics and adjusted regression models accordingly. Thus, the association estimates that we present are independent of age at the baseline visit (and, because of the strong correlation between the 2, age at referral to the craniofacial center), race/ethnicity, sex, study site, and socioeconomic status.

We did observe a direct relationship between the TSI scores and age at referral. Because larger TSI values represent a milder form of trigonocephaly, this implies that patients referred at older ages had milder cranial shape phenotypes, at least in terms of the cranial shape outline. This trend is consistent with what might be expected clinically, with milder phenotypes coming to medical attention relatively later. In ongoing analyses not described here, we also observed higher average TSI values when mothers reported that few people noticed their children's atypical appearance compared with mothers who reported that "most people or everyone" noticed their children's condition (manuscript in preparation). Both observations lend further support to the use of the TSI as a descriptor of metopic cranial shape severity.

Although the TSI is an objective quantifier of cranial shape severity and is thus potentially useful for research purposes or for assessing surgical outcomes, the current data do not support the use of TSI values at the time of referral to predict subsequent neurodevelopmental delay, at least through 3 years of age. This is despite the observation over many studies that children with isolated metopic synostosis are at greater risk than their nonsynostotic peers of being diagnosed with speech, language, cognitive, or behavioral problems.^{6–16,20} Indeed, we previously reported small deficits in average neurodevelopmental test scores among the metopic synostosis patients in our study compared with controls.²⁰ The data also appear inconsistent with the notion that the cause of this association is a direct result of the synostosis via constraint-induced brain deformation. To the extent that this interpretation is supported by further studies, it may explain why observed brain malformations in children with craniosynostosis do not always correspond to regions of the cranial anomaly.^{17,26}

Although they do not provide tests of these specific mechanistic hypotheses, the current data would be more consistent with other possible explanations for the increased risk of neurodevelopmental delays among children with metopic synostosis. Such alternative hypotheses include the idea that developmental delays are specifically caused by early chronically elevated intracranial pressure or by an as yet unidentified factor, perhaps genetic, that influences both neurodevelopment and the timing of suture fusion. The current results are also consistent with those of our previous report of a lack of association between scaphocephaly severity and neurodevelopmental risk,²⁷ although the mechanisms causing delay in children with isolated craniosynostosis may differ by the affected suture.

In addition to the possibilities already mentioned that could have led us to observe artifactually null results, it is possible that the current study lacked the sensitivity to detect an association between cranial shape severity and neurodevelopmental test scores because of the sample size of only 49 cases or because the relationship is nonlinear. It is also possible that such an association will emerge when the children in this sample reach an age at which more specific neuropsychological skills can be assessed. These include executive functions such as inhibition and working memory, which are associated with frontal lobe development and typically defy reliable measurement until the early to mid-elementary school years. This possibility will be investigated when we complete neuropsychological assessments of this cohort at age 7, which is currently under way at the centers involved in this study.

In this multicenter longitudinal study of 49 infants diagnosed with metopic synostosis, we observed little evidence to demonstrate an association between severity of trigonocephaly and neurodevelopmental test scores. Detecting such a relationship with precision may require larger sample sizes or alternative phenotypic quantifiers. Until studies are conducted to explore these possibilities, it appears that, although associated with the presence of metopic synostosis, the risk of developmental delays in young children is unrelated to further variation in trigonocephalic shape.

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ABBREVIATIONS

3D	3-dimensional
PLS-3	Preschool Language Scale, Third Edition
TSI	trigonocephaly severity index

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FIGURE 1.
Volumetric reformations of the cranium of a patient diagnosed with isolated metopic craniosynostosis.

FIGURE 2.

Identification of the plane used for image analysis and measurement of the trigonocephaly severity index. We identified the nasa suture (NS) (arrow) and opisthion (O) (arrow) to locate the cranial base. We then shifted this plane superiorly until positioned at the level of the maximal dimension of the fourth cerebral ventricle (termed the M plane).

FIGURE 3.

The first step in measuring the trigonocephaly severity index is to extract quantitative information from a bone computed tomography image (A) about the cranial outline (B) in the polar coordinate system. The origin in the polar coordinate system is defined by its centroid (O). Any given point on the outline, such as p, can then be represented in polar coordinates (r, θ), where r is the distance from the origin to p and θ is the angle between the line segment Op and the polar axis (the line OR). After normalizing the axial distance from the origin by dividing by head length, α , the normalized polar representation is a scatterplot of r/α vs θ (C).

FIGURE 4.

The cranial shape outline (left) gives rise to the normalized polar representation (right), from which the trigonocephaly severity index can be calculated. The angle γ and the ordinate h_M are parameters used to compute the TSI.¹⁹ The lines labeled CS indicate the approximate location of the coronal sutures. **A,B**, represent trigonocephalic and nontrigonocephalic cranial shapes, respectively.

FIGURE 5.

Normalized polar representation of a trigonocephalic outline shape ($\rho = r/\alpha$) (A). The trigonocephaly severity index (TSI) is computed as the base of an isosceles triangle that approximates the profile of the normalized polar representation's main section (ie, the curve above the shaded area), which encodes the shape information for the frontal bones (B). The angle γ is a parameter used to compute the TSI.¹⁹ The base is computed as $2A/(180)h_M$, where A is the area of the triangle, h_M is the height of the triangle, and 180 is a normalization factor that ensures that the TSI takes values between 0 and 1. A triangle can be fitted to the outline representation (C).

FIGURE 6.

Cranial outlines with successively milder trigonocephaly, corresponding to increasing trigonocephaly severity index values. **A**, a patient with metopic synostosis and severe trigonocephaly (trigonocephaly severity index [TSI] = 0.20). **B**, a patient with metopic synostosis and moderate trigonocephaly (TSI = 0.31). **C**, a control subject unaffected by craniosynostosis (TSI = 0.52).

FIGURE 7.

Trigenocephaly severity index (TSI) values are positively associated with age at referral. Because higher TSI values represent less severe trigenocephaly, this indicates that patients with more severe trigenocephaly tended to present at younger ages.

Distribution of Baseline Neurobehavioral Test Scores in 49 Children With Isolated Metopic Synostosis^a

TABLE 1

Neurobehavioral Test	Unadjusted Summary Statistics						
	Mean	SD	Percentile				
			5	25	50	75	95
Bayley Scales of Infant Development							
<i>Mental Development Index</i>	90.8	9.3	70	86.5	93	96.5	103
<i>Motor Development Index</i>	83.3	12.5	57.5	74.5	83	92.5	107
Preschool Language Scale							
<i>Receptive Communication</i>	93.4	14.1	75	82	92	104	119
<i>Expressive Communication</i>	95.9	14.0	77	84	90	109	125
<i>Total</i>	94.1	12.8	75	85.5	96	99.5	124
Trigonocephaly severity index · 20	6.0	0.9	4.6	5.4	5.9	6.6	7.7

^aSD, standard deviation.

Average Baseline Neurobehavioral Test and Trigonocephaly Severity Index Scores in 49 Children With Isolated Metopic Synostosis by Demographic Characteristics^a

TABLE 2

Demographic Characteristic	No.	%	Bayley Scales of Infant Development		Preschool Language Scales			TSI
			Mental	Motor	Receptive	Expressive	Total	
Total	49	100.0	90.8	83.3	93.4	95.9	94.1	0.30
Sex								
Female	15	30.6	88.9	81.6	94.7	91.1	92.2	0.29
Male	34	69.4	91.6	84.1	92.8	98.0	95.0	0.30
Age group, mo								
<6	19	38.8	91.5	79.4	100.8	93.2	96.8	0.27
6-9	17	34.7	93.2	83.2	88.7	98.0	92.6	0.30
9	13	26.5	86.6	89.2	88.6	97.2	92.2	0.34
Race								
Nonwhite	18	36.7	89.8	83.1	91.3	98.1	94.2	0.29
White	31	63.3	91.4	83.5	94.6	94.6	94.1	0.30
Socioeconomic category ^b								
I	7	14.3	92.6	77.0	95.0	101.7	98.1	0.28
II	17	34.7	91.4	83.1	90.4	95.0	91.9	0.30
III	10	20.4	88.8	85.8	92.7	89.8	90.3	0.29
IV	10	20.4	92.6	85.2	102.2	98.8	100.8	0.30
V	5	10.2	86.8	84.4	85.2	97.4	90.4	0.32
Site								
Seattle	22	44.9	89.8	84.8	89.5	95.8	91.9	0.30
Chicago	21	42.9	93.0	83.7	97.0	97.5	97.0	0.30
St. Louis	2	4.1	89.0	75.5	82.5	85.5	82.5	0.27
Atlanta	4	8.2	86.0	77.0	101.3	93.5	97.3	0.28

^aTSI, trigonocephaly severity index.

^bBased on the Hollingshead index, with category I corresponding to the highest socioeconomic status.

Age- and Race-Adjusted Linear Regression Association Between Baseline (Presurgical) Neurodevelopmental Scores and Trigonocephaly Severity Index^a Values

TABLE 3

Neurobehavioral Test	Baseline Visit (n = 49)			18-Month Visit (n = 44)			3-Year Visit (n = 37)		
	β^b	95% Confidence Interval	P Value	β^b	95% Confidence Interval	P Value	β^b	95% Confidence Interval	P Value
Bayley Scales of Infant Development									
<i>Mental Development Index</i>	0.2	-3.5 – 3.8	.923	-0.4	-5.7 – 5.0	.885	-3.6	-10.3 – 3.1	.253
<i>Motor Development Index</i>	4.8	0.1 – 9.5	.037	0.8	-4.3 – 5.9	.730	0.6	-5.3 – 6.6	.813
Preschool Language Scale									
<i>Receptive Communication</i>	2.0	-3.4 – 7.4	.446	-5.7	-11.4 – -0.1	.035	-1.1	-8.3 – 6.0	.739
<i>Expressive Communication</i>	-0.2	-5.7 – 5.3	.944	-0.8	-6.1 – 4.5	.736	-3.6	-9.8 – 2.7	0.223

^alb, ub, L.R, linear regression.

^b β is the estimated coefficient from the linear regression model, ie, the average difference in neurobehavioral test scores associated with a 0.05-unit increase in trigonocephaly severity index values, adjusted for age (continuous) and race (white vs other).