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Presurgical and postsurgical assessment of the neurodevelopment of infants with single-suture craniosynostosis: comparison with controls

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Abstract

Object—Although most infants with single-suture craniosynostosis (SSC) appear to have neurodevelopmental test scores in the average range, SSC has been associated with cognitive and motor delays during infancy. Whether and when surgery improves such deficits are not yet known. The authors aimed to compare the pre- and postsurgical neurodevelopmental status of patients with SSC with those of control infants without craniosynostosis.

Methods—The authors conducted a large, multicenter, longitudinal study of 168 infants with craniosynostosis and 115 controls without synostosis who were of similar age, race, sex, and socioeconomic status. The authors assessed participants by using the Bayley Scales of Infant Development, Second Edition (BSID-II) and the Preschool Language Scale, Third Edition (PLS-3) at enrollment, before patients' intracranial surgery, and when participants were 18 months of age (after surgery for patients).

Results—After adjusting for potential confounding factors in linear regression analyses, the authors found a tendency for patients to perform similarly to or slightly worse than controls on neurodevelopmental examinations at both visits. After surgery, the patients' mean scores were 0.6 to three points lower than those of controls on the five BSID-II and PLS-3 scales ($p = 0.02–0.07$). Compared with controls, patients had 2.3 and 1.9 times the adjusted odds of scoring in the delayed range on either BSID-II scale (Mental Development Index and Psychomotor Development Index) for the first and second visits, respectively ($p = 0.001$ and $p = 0.015$, respectively). The patients' mean adjusted test scores were nearly unrelated to the timing of their surgery.

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Conclusions—These findings support recommendations for neurodevelopmental screening in infants with SSC. Longer follow-up, as is being conducted with the patients in the present study, will be critical for identifying the potential longer-term correlates of SSC and its surgical correction.

Keywords

cranioplasty; neurodevelopment; pediatric neurosurgery; single-suture craniosynostosis

Single-suture craniosynostosis is the premature fusion of one suture in an infant's skull and occurs in approximately one in 2000 live births. Infants in whom a diagnosis of SSC is made typically undergo surgery as soon as it is deemed safe, both for cosmesis and to reduce the risk of sequelae such as raised ICP. A further justification for surgery is to reduce the possibility of neurodevelopmental deficits that may be caused either directly by the brain malformations that appear to accompany the skull malformation,[1,2] or indirectly through ICP. Single-suture craniosynostosis has been associated with cognitive and motor delays during infancy as well as an elevated risk of learning and language disabilities in school-age children and adolescents.[14,22] Despite the rationale for intracranial surgery in infants, we still lack a definitive understanding of the association between SSC and neurodevelopment.

In addition to a need for larger study samples and more sensitive measures of neurodevelopment, one factor limiting the current understanding of the implications of SSC for neurodevelopment is the preponderance of cross-sectional studies.[14] Such approaches have been particularly limiting for the study of SSC in infants for at least two reasons. First, infancy is generally a period of rapid change in neurocognitive development, thus studying infants at only one time point may not be predictive of subsequent function. Second, infants with SSC typically undergo corrective surgery during the 1st year of life, which could influence neurodevelopment. For example, later surgeries are thought to cause longer exposure to increased ICP, thereby leading to a greater likelihood of compromised neurodevelopment.[3,22] However, this specific hypothesis cannot be conclusively addressed using cross-sectional data.

Although there have been some longitudinal studies of neurodevelopment among infants with SSC, researchers in only one such investigation studied a control group of infants unaffected by craniosynostosis.[20] Without control groups it is impossible to know whether any changes in neurodevelopmental test performance observed in patients with SSC over time are due to factors other than the diagnosis or timing of surgery, such as normal growth and development, lack of test–retest reliability, differing sensitivity of tests at different ages, or examiner testing bias.

To overcome these limitations, we are conducting a large, longitudinal study in which infants with and without SSC are assessed prior to surgery (for patients with SSC) and reassessed at approximately age 18 months, by which age the surgery has been completed. In comparisons conducted before surgery between a smaller group of patients and control infants recruited through May 2005, patients had lower mean standardized scores than controls on measures of cognitive ability and motor function.[21] These deficits were comparable regardless of the location of synostosis, age at assessment, sex, and maternal IQ. Measures of early language functions revealed no meaningful differences between patients and controls. In the current paper, we present group differences at age 18 months with a larger sample size, as well as change observed over time in both groups. To address the hypothesis that earlier surgery reduces the risk of neurocognitive deficit, we also examined associations between patients' age at surgery and postsurgery neurodevelopmental status.

Clinical Material and Methods

Study Population

Participants included infants with SSC ("patients") and frequency-matched (group-matched) infants without craniosynostosis ("controls"). Participants were enrolled after informed consent had been obtained from their parents. The study was approved by the institutional review boards at each of the four participating centers: Children's Hospital and Regional Medical Center in Seattle; the Cleft Lip and Palate Institute and Northwestern University in Chicago; Children's Health Care of Atlanta; and St. Louis Children's Hospital. This research is in full compliance with Health Insurance Portability and Accountability standards.

Patients—Infants with SSC were referred to the project at the time of diagnosis by the treating surgeon or pediatrician. Infants were eligible if, at that time, they met the following criteria: 1) had SSC (sagittal, metopic, unilateral coronal, or unilateral lambdoid synostosis) confirmed on computed tomography scans; 2) had not yet undergone reconstructive surgery; and 3) were 30 months of age or younger at the time of recruitment. Exclusion criteria for patients included the following: 1) premature birth (< 34 weeks' gestation); 2) a presence of major medical or neurological conditions (for example, cardiac defects, seizure disorders, cerebral palsy, significant health conditions requiring surgical correction, and so forth); 3) presence of three or more extracranial minor malformations as defined by Leppig and coauthors;[16] or 4) presence of major malformations. Twins were eligible to participate in the study if one of them had SSC. As of April 20, 2006, 257 patients were enrolled, and these patients represented 84% of all those eligible. Forty-five families (14.7%) declined to participate, primarily due to distance or time constraints (61% of those who declined).

Controls—Infants were eligible as controls if they had no known craniofacial anomaly and did not meet any of the exclusion criteria for patients (described earlier). Infants with isolated minor medical conditions such as colic, acid reflux disease, or allergies were eligible. Control group participants were recruited through pediatric practices, birthing centers, and announcements in newsletters and other publications of interest to parents of newborns. Controls were frequency-matched to the patients regarding factors related to neurocognitive performance that also may be related to the occurrence of craniosynostosis (that is, potential confounders): 1) age at enrollment (within 3 weeks older or younger); 2) sex; 3) family SES within the same Hollings-head four-factor classification category;[10] and 4) race/ethnicity. Further details regarding the control-matching and -screening procedures have been described earlier, although since that time the individual matching of controls was relaxed in favor of group matching.[21] As of April 20, 2006, 177 control group participants were enrolled and these represented 41% of all those who were eligible. However, the majority of those families who declined (76%) did so by not having responded within 3 weeks of enrollment of a patient of a similar age (see description of earlier individual-matching methods).[21] Those families eligible to participate who actively declined did so primarily due to distance or time constraints (81% of those who actively declined).

Study Group—The current analysis pertains to the 168 patients and 115 controls who had completed both sets of assessments (described later in *Test Administration Procedure*) by April 20, 2006.

Measurement Tools

The BSID-II—The BSID-II was used to measure infants' cognitive and psychomotor statuses.[4] This test is a standardized, norm-referenced objective test of an infant's developmental status from 16 days to 42 months, 15 days of age. The BSID-II provides

updated norms based on 1700 children stratified according to the 1988 updated US census report. It yields separate indices of mental (MDI) and psychomotor (PDI) development. The BSID-II manual provides information about reliability and validity. This test continues to be one of the best and most frequently used instruments to assess infant development.[7]

Language Functioning—The PLS-3 was used to assess expressive and receptive language skills.[24] The PLS is a norm-referenced, individually administered objective test of infant language. Norms are provided for infants and preschoolers from 2 weeks to 83 months of age and are based on the assessment of more than 1900 children stratified according to the 1984 updated US census report. It yields two scale scores: receptive (PLS-AC) and expressive (PLS-EC) language, and a total language score (PLS-TL). Reliability and validity data are provided in the PLS-3 manual.[24]

The PLS-3 provides age norms in 6-month categories. As a consequence of this wide range, the standard scores of similarly aged infants with identical raw scores vary widely on either side of age category "break" points. As one of these points occurs at 18 months, except where noted in *Data Analysis*, we elected to use raw scores instead of standard scores in our analyses of the PLS-3, adjusting for age of assessment.

Examiner Training and Reliability—All BSID-II and PLS-3 assessments were performed by trained psychometrists and videotaped for reliability purposes. Before being allowed to test infants in this project, examiners from all sites provided two sample tapes for review and feedback by one investigator (K.K.S.). Approximately 10% of all subsequent assessments were independently reviewed to ensure reliability and were rescored if necessary. Agreement on individual items was 96.5% for the MDI, 93% for the PDI, and 98.9% for both the PLS-AC and PLS-EC.

Test Administration Procedure

We obtained informed consent following the institutional review board–approved protocols of each participating institution. At the first and second visits, psychometrists administered the BSID-II and the PLS-3. At the first visit, mothers were then additionally individually interviewed to obtain medical history data. In a quiet room they independently completed a 12-minute IQ test, the Wonderlic Personnel Test, as described previously.[21]

Data Analysis

To estimate the differences in mean test scores between patients and controls at the time of either the first or second visit, we performed linear regression analyses adjusting for the following matching factors: sex; family SES (Hollings-head four-factor classification,[10] included as a continuous score); age at assessment (continuous); race/ethnicity (Caucasian or other); and recruitment site. To evaluate whether differences at the second visit could be accounted for by differences already present at the first visit, we refit the regression model of scores at the second visit adjusting for Visit 1 scores. We also tested whether patient–control differences were themselves different across the two time points by fitting an interaction term (participant group × visit).

To evaluate whether patients' test scores varied by diagnosis group (that is, site of the fused suture), we estimated group-specific means, adjusting for the matching factors. To test the differences in means, we fit a linear regression model including indicators of diagnostic group and compared this model to a reduced model that excluded these terms by using a likelihood ratio test with four degrees of freedom. We also evaluated whether patient–control differences in mean test scores at Visit 2 were different for male and female infants

by including in the primary regression model a multiplicative interaction term (participant group × sex).

We performed data analyses focusing on specific aspects of the test score distributions. First, we compared the proportion of patients and controls testing in the "delayed" range (that is, scores < 85 for the MDI or PDI) at the first and second visits by fitting logistic regression models.[11] The logistic regression model is used to compare the odds of developmental delay in patients with that in controls. Second, we compared the proportions of patients and controls in categories corresponding to more severe developmental delay (categories being from a four-category ordered categorical grouping of test scores: accelerated, > 115; within normal limits, 85–115; mildly delayed, 70–84; or severely delayed, < 70) by fitting ordered logistic regression models.[11] The ordered logistic regression model produces estimates of the odds of being in the next lower-score category (that is, development that is more delayed compared with less delayed, or delayed compared with development within normal limits) among patients compared with controls. With these models, we compared patient–control ORs across the two time points by fitting an interaction term (participant goup × visit). Finally, we evaluated whether a delay noted at the first visit (that is, scores < 85) predicted a delay at the second visit for the whole study population and separately for patients and controls by fitting logistic regression models. All the analyses were adjusted for the matching factors.

To evaluate whether postsurgical test scores are related to patient age at the time of intracranial surgery, we fit linear regression models in which test scores were regressed on age at surgery (in months) adjusted for the matching factors. These were the only analyses regarding PLS-3 scores in which we used standardized scores instead of raw scores with age adjustment.

To explore potential biases in the data, we performed several secondary analyses. We repeated the primary analyses after excluding various subsets in separate analyses, such as patients who were assessed within 6 (12 patients) or 9 (53 patients) months after surgery, patients in whom sequencing of exons in craniosynostosis syndrome–causing genes-detected mutations (five patients),[19] and participants who had used intervention services, such as speech or developmental therapy, between the first and second visits (five controls and 19 patients). We also repeated the primary analyses adjusted for maternal IQ.

We conducted all statistical analyses by using Stata statistical software (version 9.0, Stata Corp.).

Results

The majority of patients (64%) and controls (59%) who were assessed at both visits were male (Table 1). The majority of patients and controls were between 17 and 19 months old at the second visit (Table 1); the median age in both groups was 18.4 months (interquartile range 18.1–18.8 months). No infant was younger than 17 months at the second assessment, and the upper end of the age range was 31 months. A somewhat smaller proportion of patients than controls were Caucasian (73% compared with 81%). Patients were also less often from families of higher SES (64% in Hollingshead Levels I–II compared with 79% of controls), with a concomitantly higher proportion from families of lower SES. The distribution of specific diagnoses (that is, the affected suture) among the patients has not changed materially since our last report,[21] with sagittal synostosis occurring in approximately half of the patients. As noted in our earlier report, left unicoronal synostosis occurs more often in female patients (15 of 16 infants), with a more equal sex distribution

among patients with right unicoronal synostosis. Sagittal and metopic synostosis occurred more frequently among male infants.

Patient–Control Comparison at First and Second Assessments

On average, both the patient and control groups performed several points lower than age-standardized norms (BSID-II standardized scores are presented in Table 2; PLS-3 standardized scores not shown). After adjusting for potential confounding factors, on average patients tended to perform similarly to or slightly worse than controls on neurodevelopmental examinations at both visits (Table 2). At the second (18-month) visit, the mean differences on the five tests (MDI, PDI, PLS-AC, PLS-EC, and PLS-TL) ranged from 0.6 to three points lower than controls and were more pronounced for BSID-II scores than for PLS-3 scores ($p = 0.02–0.07$). Deficits in mean BSID-II test scores of patients after surgery compared with controls were attenuated after adjustment for scores at Visit 1 (from ~ three points lower to 1.8 points lower; $p > 0.15$ for MDI and PDI after adjustment; Table 2). The slight deficits in mean PLS scores seen in patients after surgery were similar regardless of whether they had been adjusted for scores at the first visit.

After adjusting for the matching factors, patients affected with lambdoidal synostosis performed worse, on average, on all tests, compared with the other patient groups, whereas those with sagittal synostosis tended to perform better than the other patient groups (Table 3, $p > 0.05$ for all comparisons). Average 18-month test score differences between patients and controls were similar for comparisons among female infants and among male infants (data not shown).

Patient–Control Comparisons of the Proportion Considered Delayed

For the MDI, approximately 10% of controls and 15% of patients tested in the delayed range (< 85 points) at the first visit; this percentage increased to 19 and 30%, respectively, at the second visit (Table 4). These proportions were much higher for the PDI, with approximately 30% of controls and 45% of patients being delayed at Visit 1, and 47 and 56%, respectively, at Visit 2. At the first assessment, compared with controls, patients had 1.6 and 1.9 times the adjusted odds of scoring in the delayed range for the MDI and PDI, respectively ($p = 0.21$ and $p = 0.01$, Table 4), and 2.2 times the adjusted odds of scoring in the delayed range on either or both scales ($p = 0.001$). At patient age 18 months these adjusted ORs were very slightly attenuated (if at all) with patients at 1.9 times the adjusted odds of being delayed on either scale ($p = 0.02$ for patient–control difference; $p = 0.45$ for difference between patient–control differences at the two time points). Performing the same comparisons on the four-category score produced similar OR estimates (data not shown).

Testing in the developmentally delayed range at the first visit was predictive of delay at the second visit for both patients and controls. After adjusting for the matching factors and participant group status, those delayed at Visit 1 had 2.7 and 1.6 times the odds of being delayed at the second visit on the MDI and PDI, respectively ($p = 0.01$ and 0.08, data not shown). These ORs did not differ meaningfully for patients and controls but were somewhat stronger for controls on the MDI.

The 18-Month BSID-II and PLS-3 Scores in Relation to Patients' Timing of Surgery

After adjusting for participants' study site, sex, SES, and race, patients' mean test scores were nearly unrelated to the timing of their surgery (Table 5). For the five different neurodevelopmental examinations, the mean difference in test scores associated with a 1-month increase in timing of surgery ranged from −0.48 to 0.04 ($p > 0.15$ for all comparisons). These differences were adjusted for the matching factors, including age at assessment, which is correlated with age at surgery. There was some variation in these

adjusted differences according to the fused suture site, but after adjustment there was no particular pattern across tests or by suture site ($p > 0.05$ for all comparisons, data not shown).

Subanalyses to Explore Potential Biases

Excluding patients who were assessed within 6 (or 9) months following their surgery or those harboring SSC-related genetic mutations yielded only very slightly different estimates and probability values and did not meaningfully affect the results of any analyses (data not shown). Excluding the patients and controls who had used intervention services before the second assessment slightly attenuated some of the patient–control differences noted at both visits, although mean PLS-3 scores were virtually unchanged at the second visit. Adjusting for maternal IQ scores at the second visit slightly attenuated the patient–control differences.

Discussion

In this large, longitudinal comparison study, we observed small but consistent deficits among patients with SSC compared with nonsynostotic controls on most neurodevelopmental assessments. Patients' mean scores were slightly lower than those of controls, and patients were at greater odds of testing in the delayed range on the MDI and PDI of the BSID-II. Because the observed deficits are adjusted for participants' study sites, sex, age at assessment, SES, and race, they are not due to differences in these characteristics between patients and controls. Although the small differences in mean scores may not appear to be clinically relevant, analyses of dichotomized scores (that is, delayed compared with not delayed) suggested that patients with SSC have 1.5 to two times the odds of scoring in the delayed range on either the MDI or PDI, or both.

Our findings are similar to those reported previously.[14,20] Although the literature has been somewhat inconsistent regarding neurodevelopmental deficits in infants with SSC, many of the investigations in which researchers identified such deficits lacked comparison groups of nonsynostotic children.[14] In contrast, authors of most studies in which control groups were included, such as ours, have demonstrated only modest (if any) deficits compared with age-appropriate controls.[6,20] Based on a comprehensive review of literature on this topic, it was proposed that, compared with nonsynostotic peers, infants and children with SSC may be at three to five times the risk of cognitive deficits.[14] Our results regarding the relative odds of delay suggest that indeed, patients are at higher risk, although perhaps not to the extent proposed. Nevertheless, greater risks may emerge at older ages, and particularly in school-age children.[5]

Imaging studies of the brains of apparently healthy, non-synostotic children have suggested that specific cognitive deficits may be anatomically specific. For example, problems with executive functions, such as working memory, have been associated with the dorsolateral frontal regions of the brain.[9,18,23] Such findings suggest that the neurocognitive phenotype of SSC, if such exists, may be specific to the affected suture site, given that fusion of different sutures appears to cause specific morphological changes in the brain.[14] Our data do not support this hypothesis, however, because we did not observe great variation in test scores across the patient groups, and such variation was not specific to particular neurocognitive examinations. Patients with lambdoidal synostosis did tend to perform slightly worse than patients with other types of SSC, regardless of the type of assessment. This finding could be due to the small number of patients (11), particularly considering the multiple covariate adjustment, and would not be conclusive without a larger sample. Most importantly, both the immaturity of the infant brain and the corresponding global quality of infant tests such as the BSID-II limit the extent to which functions associated with specific regions of the brain can be assessed at this age. Assessments of older children by using

comprehensive neuropsychological test batteries will allow for a more definitive test of suture-related differences.

Relative to controls, the average deficits observed at the first assessment, before patients had undergone surgery for SSC, persisted at the postsurgery assessment when the patients were 18 months of age. Moreover, either across patient groups or separately for each patient group, we observed a lack of association between mean test scores and age at surgery. Previous longitudinal studies of infants have produced inconsistent findings with regard to the hypothesis that surgery corrects or prevents SSC-associated cognitive deficits and that early surgery is better. In most studies, consistent with our results, infants with SSC scored at approximately average levels of cognitive development both before and after surgery, and age of surgery has generally not been found to be related to neurodevelopment.[3,8,12,17,20] In support of a protective effect of surgery, however, developmental status has been inversely correlated with age at surgery in at least one investigation,[20] and postsurgical improvements in neurodevelopmental test scores were reported in a sample of infants with sagittal synostosis.[6] One could speculate that such improvements would be greatest in terms of balance, movement, and other psychomotor functions, which could be negatively affected by the malformation of the skull before surgery and by asymmetry in coronal and metopic synostosis. However, we noted no such differences between the BSID-II MDI and the PDI.

Despite the consistency of our observations with most previous comparison studies, there are several factors that could have biased these results toward negative findings, that is, toward finding smaller pre- and postsurgical differences than may truly exist. First, assessments in infants may not be sensitive enough to detect postsurgical differences, if they exist. Second, there may be a refractory period after surgery during which recovery from the surgery itself causes infants to perform worse than they are able. That is, surgery may temporarily negatively influence scores. The shortest assessment time after surgery for any infant included in the analysis, however, was 6 weeks, and only two were assessed within 2 months of surgery. It is therefore unlikely that scores were biased downward due to the acute effects of surgery. Third, even if surgery improves neurodevelopmental function (and even if early surgery is better), it is unknown how long it would take to achieve such improvements following surgery. We noted little difference in the relationship between postsurgery test scores and age at surgery, regardless of the amount of time that had elapsed since surgery. Such improvements may not be apparent, however, until children are much older than 18 months. Finally, the interrelationships among age at diagnosis, timing of surgery, time elapsed since surgery, and age-related changes in neurodevelopment are complicated. It is possible that we did not appropriately account for these interrelationships in adjusted regression models or that the relationship between postsurgery scores and timing of surgery is not linear and cannot be adequately captured through linear regression analyses. As we collect more data through third assessments when the study participants are 36 months old, we will continue to explore the form of these relationships.

Despite these potential limitations, this investigation also had several notable strengths. First, it is among the largest of any longitudinal comparison study of SSC.[14,22] The finding that both patients and controls scored below test norms highlights the risks associated with relying solely on normative data sets for comparison with patients, as has been the practice in much of the existing research on this issue. Second, the inclusion of study populations from four large craniofacial centers spanning the US should make the results more easily generalized than if we had included only a single center. To optimize the multicenter design we put forth considerable effort to achieve a high level of interrater reliability across examiners. Third, we performed extensive sensitivity analyses to explore potential biases. These analyses strengthen the validity of our findings because the observed deficits were not explained by any patients' having genetic mutations that may have caused the synostosis, or

by confounding due to differences in maternal IQ. The findings also were not altered meaningfully after excluding patients and control participants who had used speech, occupational, developmental, or other services between the first and second assessments.

Conclusions

Historically, views on the neurodevelopmental implications of SSC have changed greatly, but only relatively recently have there been rigorously designed and conducted studies in which evidence is provided to support these views. It is critical that we continue to elucidate whether there is a neurodevelopmental phenotype associated with SSC and, if so, what characterizes it. The findings we report here support previous recommendations for neurodevelopmental screening in infants with SSC.[13,15,21] We are continuing to follow both patients and controls, with assessments at 3 and, eventually, 7 years of age. Such continued follow-up is necessary for identifying the potential longer-term correlates of SSC and effects of surgical correction.

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Abbreviations used in this paper

BSID-II	Bayley Scales of Infant Development, Second Edition
ICP	intracranial pressure
MDI	Mental Development Index
OR	odds ratio
PDI	Psychomotor Development Index
PLS-AC	Preschool Language Scale Auditory Comprehension
PLS-EC	PLS Expressive Communication
PLS-TL	PLS Total Language
PLS-3	PLS, Third Edition
SES	socioeconomic status
SSC	single-suture craniosynostosis

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TABLE 1

Demographic characteristics of patients with SSC and nonsynostotic controls at the 18-month neurodevelopmental assessments

	No. of Patients (%)						
	Type of SSC						
Characteristic	**Sagittal**	**Metopic**	**Rt Unicoronal**	**Lt Unicoronal**	**Lambdoid**	**Total (%)**	**No. of Controls (%)**
total	86	35	20	16	11	168 (100)	115 (100)
sex							
female	20	10	12	15	4	61 (36)	47 (41)
male	66	25	8	1	7	107 (64)	68 (59)
age (mos)							
17–19	71	24	15	9	7	126 (75)	96 (83)
>19	15	11	5	7	4	42 (25)	19 (17)
race/ethnicity							
Caucasian	68	23	16	9	9	125 (74)	93 (81)
other	18	12	4	7	2	43 (26)	22 (19)
familial SES *							
I (high)	19	8	4	5	4	40 (24)	28 (24)
II	35	14	8	5	5	67 (40)	63 (55)
III	15	6	7	3	1	32 (19)	17 (15)
IV	15	4	0	2	0	21 (12)	4 (3)
V (low)	2	3	1	1	1	8 (5)	3 (3)
study site							
Seattle	28	14	6	7	4	59 (35)	43 (37)
Chicago	15	12	8	7	4	46 (27)	37 (32)
St. Louis	20	1	5	1	2	29 (17)	13 (11)
Atlanta	23	8	1	1	1	34 (20)	22 (19)

* Categories are based on the Hollingshead index.

TABLE 2

Comparisons of mean pre- and 18-month postsurgical neurobehavioral test scores among 168 patients with SSC and 115 nonsynostotic controls *

	Mean Test Score†		Patient–Control Difference‡		
Visit & Neurobehavioral Assessments	**Patients**	**Controls**	**Mean Difference**	**95% CI**	**p Value**
presurg					
BSID-II					
MDI	92.08	94.99	−2.64	−4.81 to −0.47	0.017
PDI	84.85	88.93	−4.04	−6.78 to −1.29	0.004
PLS-3					
PLS-AC§	5.19	5.63	−0.43	−0.74 to −0.12	0.007
PLS-EC	5.36	5.30	0.03	−0.36 to 0.43	0.871
PLS-TL§	10.58	10.93	−0.37	−0.94 to 0.20	0.204
postsurg (18 mos)					
BSID-II					
MDI	90.59	94.78	−3.04	−6.16 to 0.08	0.056
PDI	83.20	85.73	−3.16	−5.84 to −0.48	0.021
PLS-3					
PLS-AC§	13.62	14.21	−0.71	−1.37 to −0.04	0.036
PLS-EC	13.11	13.59	−0.63	−1.30 to 0.05	0.070
PLS-TL§	26.80	28.14	−1.5	−2.80 to −0.20	0.024
postsurg differences adjusted for presurg differences					
BSID-II					
MDI	—	—	−1.90	−4.91 to 1.11	0.215
PDI	—	—	−1.71	−4.26 to 0.83	0.188
PLS-3	—	—			
PLS-AC§	—	—	−0.53	−1.18 to 0.13	0.116
PLS-EC	—	—	−0.62	−1.30 to 0.05	0.071
PLS-TL§	—	—	−1.43	−2.74 to −0.13	0.032

* Probability values for tests of whether the patient–control differences were themselves different between the two time points ranged from 0.07 (for the PLS auditory and total language scales) to 0.4 (for all other scales). Abbreviations: CI = confidence interval; presurg = presurgical; postsurg = postsurgical.

[†] Mean scores on the BSID-II are average age-standardized scores, whereas mean scores on the PLS-3 are average raw scores.

[≠] Adjusted for participants' study site, age at assessment (in months), SES (Hollingshead index, measured continuously), race (Caucasian vs. other), and sex.

[§] Two patients are missing.

TABLE 3

Mean adjusted postsurgical (for patients) 18-month-old neurobehavioral test scores by diagnostic group *

		Mean Score†				
		BSID-II		PLS-3		
Diagnostic Category & Suture Site	No. of Part	MDI	PDI	AC	EC	TL
control	115	94.51	86.60	14.33	13.71	28.26
sagittal	86	93.90	84.20	14.07	13.35	27.55
metopic	35	92.33	84.24	13.40	12.94	26.32
rt unicoronal	20	88.69	83.29	13.25	13.06	26.29
lt unicoronal	16	86.67	80.55	13.01	13.11	26.27
lambdoid	11	83.98	80.15	12.71	11.66	24.18
p value‡		0.09	0.81	0.45	0.46	0.42

*Part = participants.

†Scores are adjusted for participants' study site, age at testing (in months), SES (Hollingshead index measured continuously), race (Caucasian vs. other), and sex.

‡Probability values are from a two-sided likelihood ratio test of the differences among patients' diagnostic categories. Control means are listed in the table for reference purposes only.

TABLE 4

Comparisons of pre- and postsurgical (18-month) neurobehavioral delay among 168 patients with SSC and 115 nonsynostotic controls*

	% Delayed		Patient–Control OR†		
Visit & BSID-II Scale	**Patients**	**Controls**	**OR**	**95% CI**	**p Value**
presurg					
MDI	15	10	1.6	0.8–3.6	0.209
PDI	45	30	1.9	1.1–3.3	0.013
either MDI or PDI	52	32	2.3	1.4–3.9	0.001
postsurg (18 mos)					
MDI	30	19	1.7	0.9–3.1	0.080
PDI	56	47	1.6	0.9–2.6	0.079
either MDI or PDI	65	52	1.9	1.1–3.2	0.015
postsurg patient–control differences adjusted for presurg differences					
MDI			1.6	0.9–3.0	0.118
PDI			1.5	0.9–2.5	0.137
either MDI or PDI			1.7	1.0–2.8	0.062

*Probability values for tests of whether the patient–control ORs were themselves different between the two time points ranged from 0.45 to 0.86.

†Adjusted for participants' study site, sex, age at assessment, SES (Hollingshead index, measured continuously), and race/ethnicity (Caucasian vs. other).

TABLE 5

Mean difference in 18-month postsurgical test scores associated with a 1-month increase in age at surgery among 168 children with SSC

Neurobehavioral Assessment	Mean Difference*	95% CI*	p Value
BSID-II			
MDI	0.01	−0.65 to 0.67	0.970
PDI	−0.39	−0.99 to 0.22	0.208
PLS-3			
PLS-AC	0.04	−0.61 to 0.69	0.900
PLS-EC	−0.48	−1.14 to 0.18	0.154
PLS-TL	−0.24	−0.90 to 0.43	0.487

* The mean differences and corresponding CIs and probability values are from linear regression models adjusted for participants' study site, sex, age at assessment (continuous), race (Caucasian vs. other), and SES (Hollingshead index, measured continuously).