Longitudinal study of the neurodevelopmental characteristics of treated and untreated nonsyndromic
craniosynostosis in infancy

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ABSTRACT

Purpose: Nonsyndromic craniosynostosis (NSC) are a group of congenital disorders sharing premature fusion of one or more of the cranial sutures that restricts and distorts growth of the skull and underlying brain. This study examined the neurodevelopmental sequelae of NSC both prior to and following reconstructive cranial surgery.

Methods: Sixty-four consecutive referrals with mixed forms of untreated NSC aged 4 to 16 months ($M=8.9$, $SD=2.9$) comprised the pre-operative cohort. Forty-four of these patients aged 6 to 32 months ($M=21.2$, $SD=4.5$) underwent post-operative developmental evaluation. Neurodevelopmental function was assessed with the mental (Mental Development Index [MDI]) and motor (Psychomotor Development Index [PDI]) scales of the Bayley Scales of Infant Development-2nd edition.

Results: Children with untreated NSC displayed significantly lower mental ($M=97.5$) and motor ($M=87.7$) scores than normative expectations, with the distribution of scores also differing significantly from the normative distribution. Post-operatively, children continued to display significantly lower mental ($M=89.5$) and motor ($M=88.0$) abilities, with mental abilities falling significantly lower than pre-operative levels. An increased prevalence of severe motor delay was found, and no child displayed accelerated development. Subgroup comparisons revealed no differences in mental or motor skills between the primary diagnostic subtypes (sagittal and metopic synostosis) both prior to and following corrective surgery.

Conclusions: NSC is associated with an increased incidence of developmental delay in both treated and untreated conditions. Timing of surgery appears unrelated to developmental outcome.

KEYWORDS: craniosynostosis, neurodevelopment, infancy, craniofacial disorders, neurosurgery

INTRODUCTION

Isolated or nonsyndromic craniosynostosis (NSC), is a congenital craniofacial disorder which occurs with an incidence of approximately 1 in 2,000 live births [1, 2]. The condition involves the premature fusion of one or more of the cranial sutures and results in abnormal restriction and distortion of the skull and underlying brain. The resultant phenotypic head shape is determined by the site of sutural fusion (see Figures 1-3), with additional factors, such as timing of onset, affecting the severity of the deformity.

INSERT FIGURES 1-3 HERE

Craniosynostosis carries a known risk of neurological, and concomitant neurodevelopmental, impairment by a range of mechanisms. These include the effects of raised intracranial pressure due to growth of the brain in a restricted cavity [3-6]. Abnormal brain growth in a distorted calvarium may result in localized areas of compression. There is also evidence of abnormalities in both cortical subcortical morphology [7] [8], which may suggest potentially altered neural circuitry. The risk of impairment is particularly critical when one considers the rapid changes in brain growth and development in the pre- and postnatal phase.

Management of craniosynostosis involves reconstructive cranial surgery, warranted to treat, ameliorate or prevent neurological impairment, as well as for improved cosmesis.

There is an increasing body of literature documenting neurodevelopmental outcomes in infants with untreated craniosynostosis during early infancy, and prior to corrective surgery. Less well understood are the longer-term outcomes in NSC during later infancy. It remains controversial as to whether surgical intervention, and its' timing thereof, is associated with altered neurodevelopmental outcome in NSC. Also poorly understood are potential contributions of other correlates (e.g. sociodemographic variables) to neurodevelopmental status in these conditions.

Pre-treatment Neurodevelopmental Studies in Nonsyndromic Craniosynostosis

Empirical investigations into the neurodevelopmental features of untreated NSC have revealed mixed findings; in part due to methodological differences associated with varying interpretations of 'normal' and 'delayed', wide variations in ages studied and inclusion of comparative control groups in only few studies. Some have shown that for untreated infants with various forms of NSC, mental developmental scores do not significantly differ from normative population averages [9-13]. However, other studies have found that these children perform significantly below normative expectations or control samples [14-16] with higher than expected risk of mild to significant delay in cognition [17].

Motor skills appear the most susceptible to impairment, with studies evaluating this skill domain in untreated patients with mixed forms of NSC reporting significantly lower performances on motor skill abilities on varying editions of the Bayley Scales of Infant Development (Bayley Scales) compared with normative population estimates or control group samples [9, 14-19]. In fact, mean motor developmental scores in several of these samples have been placed within the mildly delayed range compared with cognitive scores, which fell typically within normal limits in several studies [14, 16, 17, 20].

Pre- and Post-Surgical Neurodevelopmental Outcomes in Nonsyndromic Craniosynostosis

Mixed findings have emerged from longitudinal studies addressing pre- and post-surgical developmental characteristics of infants with NSC. Some authors have reported normal mental abilities both prior to and following surgery. For example, Speltz et al., [12] compared 19 infants with sagittal synostosis with a control group on the Bayley Scales of Infant Development. Mean MDI scores were placed within the normal range at each assessment phase prior to and twice following synostosis correction, and no significant group differences were found when compared with the normal population. Similarly in Kapp-Simon and colleagues' [11] sample of 84 infants with mixed NSC evaluated prior to treatment (mean age 8.1 months) and post-operatively (mean age 18.4 months), mean mental abilities fell within the normal range at each assessment phase, with the distribution of scores following a normal distribution.

In contrast, other studies have found mental abilities to be deficient both pre- and post-operatively in NSC. Starr and colleagues [20] reported persistent, significantly lower mental abilities than a control group sample in their post-operative cohort (n=168), as well as auditory comprehension deficits. Cohen and colleagues similarly reported mildly delayed, and unchanged mental abilities, in 22 patients with NSC following surgical repair of the synostosis.

Mixed findings have also been found with respect to motor skill outcomes. Speltz et al., [12]'s sample of 19 infants with sagittal synostosis were found to display mean PDI scores on the BSID-II within the normal range and not significantly different from a control group pre-operatively (mean age 4 months), and at each of two assessment phases post-operatively (mean ages 12 and 24 months post-operatively). Gewalli et al., [19] also found no significant differences in pre- and post-surgical global developmental quotients in their sample of 26 children with sagittal synostosis, with mean scores falling within the average range on the Griffiths Developmental Scale. Longitudinal studies have however shown improvements post-operatively in gross motor skill function compared with pre-operative levels (impaired range) in infants with isolated synostosis [14] [18].

Timing of surgical intervention, severity of synostosis and neurodevelopmental functioning

With respect to the contribution of timing of surgical intervention and developmental outcome, most studies addressing this issue have failed to find an association between age at surgery and post-operative developmental status [11, 14, 20-22]. However, Arnaud et al., [23] and Bottero et al., [24] found that post-operative mental outcome was better when surgery was performed before one year of age. Speltz et al [12] found that age at surgery was inversely correlated with Bayley growth coefficients; although this trend was not significant.

Diagnostic subtype comparisons

There has been limited attention paid to diagnostic subtype comparisons between the various NSC and neurodevelopmental function in NSC. Kapp-Simon and colleagues and Da Costa et al., [9, 11] found no significant differences between the diagnostic subtypes and MDI scores. However, in a later study, they found significant diagnostic group differences on MDI variables [16], being lowest for sagittal and unicoronal synostosis, as did that of Cohen and colleagues [14].

Sociodemographic factors and neurodevelopmental function

Evidence from clinical groups, 'at risk' due to complex or chronic medical conditions (e.g. prematurity, traumatic brain injury), have identified relationships between developmental outcomes and family environmental factors, such as parental education and socioeconomic status [25]. Of the very few studies to address this in the NSC literature, no association between such risk factors and neurodevelopmental function has been identified to date [9, 16, 20]. However, in their sample of patients, lower socioeconomic status was associated with lower mental status in children with metopic synostosis compared with children coming from a more stable background. Gender differences in neurodevelopmental outcome do not appear apparent in the studies drawing these comparisons in the literature [16]

Aims and Hypotheses

This study sought to elucidate the following:

1. Is NSC associated with deficits in cognitive and motor function prior to and/or following synostosis repair?
2. Are there differences in the risk of developmental function relative to the fused suture location?
3. Does timing of surgical intervention influence neurodevelopmental outcomes in NSC?
4. Is there an association between sociodemographic variables and neurodevelopmental status in NSC?

METHODS

Sample

All infants presenting with untreated craniosynostosis to the craniofacial service at the RCH, Melbourne, Australia were referred the treating craniofacial surgeon for pre- and post-operative neurodevelopmental evaluation as part of standard clinical management. All had a confirmed diagnosis of NSC (via CT scan) and a diagnosis was confirmed at operation in all cases. There was no reported prior history of head injuries or neurological condition unrelated to their diagnosis that may have confounded assessment findings.

Cranial reconstructive surgery

Patients with sagittal synostosis underwent total vault remodeling using The Melbourne Procedure [26]. A fronto-orbital advancement was performed in patients with metopic or unicoronal synostosis. There were no reported intra- or post-operative neurological complications in the study sample.

Measures and Procedure

All patients were assessed by the same neuropsychologist (ADC) at each of the pre- and post-operative developmental examinations. The BSID-II [27] was administered as a measure of infants' cognitive and psychomotor function. This is a standardized, norm-referenced objective test of infant developmental status from 16 days to 42 months. It yields separate indices of mental and psychomotor development in the mental development index (MDI) and psychomotor development index (PDI), respectively. The measure has demonstrated reliability and validity, and is one of the most common assessment measures of infant developmental functioning. The index scores have a mean of 100 and standard deviation of 15. Performance scores on the MDI and PDI scales are classified into four categories, ranging from accelerated at the upper, and significant delay at the lower functional spectrum (as shown in Table 4). Socioeconomic status was evaluated using the Daniel Scales of Occupational Prestige [28].

Statistical Analysis

Analysis of data was performed using SPSS for Windows, Release 19.0 (SPSS Inc., Chicago, Illinois). Univariate descriptive statistics were conducted to describe sample demographic characteristics and BSID-II indices. One-sample *t*-tests, chi-square and odds-ratio analyses were employed to determine differences between the clinical group and normative data on the BSID-II, and for intra-group comparisons. Paired sample *t*-tests were performed to compare pre- and post-operative performance of the NSC group on the BSID-II indices and other sociodemographic and medical

variables. Pearson's correlations were calculated to examine the relationship between medical and sociodemographic factors with the developmental outcome variables. A p -value of $<.05$ was considered statistically significant for all analyses unless otherwise specified.

RESULTS

1.0 Demographic Characteristics

The pre-operative sample comprised 63 children with mixed forms of NSC. Sixty-nine percent ($n=44$) of these infants completed developmental assessments following their reconstructive cranial surgery. In keeping with population incidence rates and findings from other research samples, the pre- and post-operative samples comprised primarily sagittal synostosis (41.3% and 36.4%, respectively), followed by metopic synostosis (31.7% and 34.1%, respectively). The post-operative sample was again predominantly male (71.4%). The overall sample ranged between 4 and 32 months of age, with mean age at pre-operative neurodevelopmental evaluation being 8.5 ($SD=2.7$) months, and post-operative assessment being 21.2 ($SD=4.5$) months. Mean socioeconomic status (SES) fell within population averages at both T1 ($M=3.7$, $SD=1.7$) and T2 ($M=3.9$, $SD=1.7$). There were no significant differences between the sample tested at the pre-operative phase alone (T1) and the pre- and post-operative patients (tested at both T1 and T2) on any of the sociodemographic variables assessed.

1.1 Prematurity

The pre-operative cohort included a subset of children ($n=6$) who were born preterm (classified by gestational age < 36 weeks). This sample comprised primarily metopic ($n=4$), followed by sagittal ($n=1$) and multisutural synostosis ($n=1$). Four of these children were seen for post-operative assessment. When the preterm cohort was removed from all analyses, the significant trends between the clinical sample and population averages remained for all measures. Consequently, these patients were included in all analyses. The distribution of the sample according to sutural involvement, as well as other medical and sociodemographic characteristics is presented in Table 1.

INSERT TABLE 1 HERE

2.0 Neurodevelopmental Outcomes

2.1 Pre-operative developmental function (T1)

The mean differences on pre-operative MDI and PDI scores relative to population averages has been presented in Table 2.

2.1.1 Mental (Cognition/ Language) abilities

Patients' MDI scores fell significantly below population expectations, $t(1, 61) = 2.85$, $p = .007$, and within the lower end of the normal range, 95% CI = [9.3; 98.5].

2.1.2 Motor skills

Mean PDI were also significantly lower than population norms, $t(1, 62) = 7.80$, $p < .001$, falling within the mildly delayed range, 95% CI = [84.5; 90.8]. Risk-ratio analyses revealed that patients had

a 2.5 times increased risk of performing within the delayed range compared with the normative population (see Table 6).

2.1.3 Mental and motor skill functioning of patients with prematurity (gestational age <36 weeks) compared with the normative population

When the preterm subset were removed from the analyses, the significantly lower MDI ($M=97.4$, $SD=6.8$), $t(1, 55)=2.87$, $p=.005$ and motor ($M=88.1$, $SD=12.3$), $t(1, 56)=7.30$, $p<.001$ scores of the clinical group compared with normative averages remained. Consequently, the preterm cases were included in all analyses.

2.2 Patient classifications of mental and motor function compared with the normative population

Chi-square analyses were conducted to determine whether the proportion of children in the clinical sample demonstrated similar or discrepant neurodevelopmental functioning from that which would be expected in a normal distribution.

2.2.1 Cognitive/ Language development

There were higher percentages of the NSC performing within the normal or accelerated range (90.5%) compared with population averages (87.4%). None of the NSC group displayed accelerated development. However, chi-square analyses revealed these trends were not associated with significant overall between-group differences in the distribution of MDI scores, $\chi^2(1, N=63)=0.28$, $p=.597$.

2.2.2 Gross and fine-motor skill development

Chi-square analyses also revealed significant differences in the distribution of PDI scores of the clinical group compared with population averages, $\chi^2(1, N=63)=12.07$, $p<.001$. This was associated with an over-representation of mild or severe developmental delay in the NSC group (31.7%) compared with population averages (14.8%). None of the patient sample displayed accelerated motor skill development. Tables 3 to 5 provide the distribution of scores of the patient group compared with normative averages according to the Bayley classification scale.

2.3 Post-operative developmental function (T2)

Table 2 presents the comparisons between the clinical group compared with population averages and post-operative function on mental and motor scores.

2.3.1 Cognitive/ Language Skills

Patients' post-operative MDI scores fell significantly below population expectations, $t(1, 42)=4.51$, $p<.001$, 95%CI [83.6; 94.4], although still within the normal range. Post-operative MDI scores

in this group also fell significantly lower than the pre-operative performances $M_{DIFF}=-7.5$ ($SD=16.9$), $t(1, 41)=2.84$, $p=.007$.

2.3.2 Motor skills

Mean PDI scores in the patient group were also significantly lower than population norms, $t(1, 38)=5.37$, $p<.001$, 95%CI [83.5; 92.8], although still within the normal range. Post-operative PDI scores in this group did not significantly differ from pre-operative levels, $M_{DIFF}=2.9$ ($SD=15.4$), $t(1, 39)=1.188$, $p=.242$.

2.3.3 Mental and motor skill functioning of patients with prematurity (gestational age <36 weeks) compared with the normative population

When the preterm subset ($n=4$) was removed from the analyses, the significantly lower mental ($M=89.3$, $SD=15.5$), $t(1, 39)=4.38$, $p<.001$ and motor ($M=87.7$, $SD=14.3$), $t(1, 35)=5.08$, $p<.001$) abilities of the clinical group compared with normative averages, remained. Consequently, the preterm cases were included in all analyses.

INSERT TABLE 2 HERE

2.4 Post-operative patient classifications of mental and motor functioning compared with the normative population

Chi-square analyses were performed to determine whether the proportion of children in the clinical sample demonstrated similar or discrepant neurodevelopmental functioning from that which would be expected in a normal distribution.

2.4.1 Cognitive/ Language development

Chi-square analyses revealed significant differences in the distribution of MDI scores between the NSC group and normative population, $\chi^2(1, N=44)=12.12$, $p<.001$. This was associated with lower proportions of the NSC group performing within the normal or accelerated range (68.1%) compared with population averages (87.4%). However, there was an overrepresentation of mild or severe delays in the NSC group (31.9%) compared with the normative population (12.6%). Risk-ratio analyses revealed that these patients were also 2.1 times more likely to be performing in the delayed range compared with normative population averages.

2.4.2 Gross and Fine-motor development

Chi-square analyses also revealed significant differences in the distribution of PDI scores of the clinical group compared with population averages, $\chi^2(1, N=39)=18.12$, $p<.001$. This was associated with an over-representation of mild or severe developmental delay in the clinical group

(41.0% compared with predicted population estimates of 14.8%). Again, none of the clinical group displayed accelerated motor skill development. Risk-ratio analysis indicated that the NSC group was 3 times more at risk of functioning in the delayed range compared with normative expectations post-surgery. The distribution of scores of the patient group compared with normative averages according to the Bayley classification scale is presented in Tables 3 to 5.

INSERT TABLES 3 to 5 HERE

2.5 Diagnostic subtype comparisons on mental and motor domain scores

Table 6 provides mean MDI and PDI scores for each of the four craniosynostosis subgroups. As shown, mean MDI scores were all within the average range, varying from 95.9 in multisutural synostosis, to 99.1 in metopic synostosis. PDI scores were generally lower, and ranging from 82.6 in unicoronal synostosis to 90.1 in patients with metopic synostosis.

Statistical group comparisons on MDI and PDI variables were performed for the two most prevalent diagnostic subtypes; sagittal and metopic synostosis. No significant differences were found between these subgroups on each of the MDI $t(1, 43) = 1.35, p = .186$ and PDI, $t(1, 44) = 0.61, p = .546$ indices.

INSERT TABLE 6 HERE

2.6 Pre- and Post-operative gender comparisons on mental and motor domain scores

Table 7 lists means and standard deviations for the four developmental assessments by gender. There were no significant gender differences on any of the pre- and post-operative MDI and PDI scores.

INSERT TABLE 7 HERE

2.7 Relationship between mental and motor domain scores and sociodemographic variables

Pearson's correlations revealed positive significant relationships between presurgery MDI and PDI scores, but no significant relationships between postsurgery MDI and PDI scores. Presurgery PDI scores were also significantly positively correlated with post-surgery PDI scores. Pearson's correlations revealed no significant correlations of MDI and PDI variables with respect to socioeconomic status, parental age (maternal and paternal) or maternal education level. Age at surgery was also unrelated to post-surgery MDI and PDI scores. A negative correlation was found between gestational age and MDI ($r = -0.4$), although this trend was not significant. MDI I scores were

unrelated to MDI II or PDI-II scores. However, PDI I scores were significantly correlated with both PDI I and PDI II performance scores. Results of correlation analyses are presented in Table 8.

INSERT TABLE 8 HERE

DISUSSION

This study sought to determine whether infants with NSC display neurodevelopmental impairments at two time points; during the early infancy phase prior to operative intervention, and during later infancy following surgical correction of the deformity. The contribution of age at surgical intervention and sociodemographic variables upon neurodevelopmental outcome was also explored.

Is NSC associated with neurodevelopmental impairment during early infancy prior to treatment?

The mental abilities of this sample were significantly poorer overall than the control group or normative averages; a finding consistent with prior studies (e.g. [9, 14-16]. Furthermore none of these patients displayed accelerated ability, thus suggestive of a lowering of developmental potential as a group compared with their non-afflicted counterparts.

Similarly, as demonstrated in previous studies, this sample of infants with NSC also displayed significantly poorer gross motor skills than normative averages [9, 16-18]. There was an over-representation of infants functioning in the delayed range, and, as with mental abilities, none of this sample displayed accelerated ability. Motor skills were also found to be significantly weaker overall than mental abilities, suggesting that such skills may be more susceptible to dysfunction during early infancy.

Do neurodevelopmental delays in mental and motor skills persist during later infancy and following treatment of the deformity?

There was a persistence of motor skill impairment in this sample with the risk of delay increasing from 2.5 to 3.0 times from pre- to post-treatment. These findings are commensurate with a number of other studies with respect to motor skill function in this population, and suggest that such skills appear most vulnerable to impairment in NSC prior to and/ or following treatment [9, 14, 20, 29].

The mental abilities of this sample remained significantly lower than normative averages. However, the likelihood of functioning in the delayed range post-surgery increased. On closer inspection of the mental scale items (which form a composite measure of both cognition and language), language appears to be the primary contributor to lowered test performances during this developmental phase. Such findings may be reflective of studies in both infant [30] as well as childhood NSC samples [31], in showing the presence of language impairments exist during the infant phase, and persist into the school-age years.

Are there prognostic indicators for developmental delay in NSC during later infancy?

The relationship between pre- and post-operative developmental function in NSC was examined. Pre-operative motor skill development was predictive of subsequent motor development in later infancy and following treatment. No relationship between pre- and post-operative mental function was identified. With respect to prognostic markers, the presence of motor skill delay during early infancy (particularly when significant in nature) may warrant closer developmental monitoring of subsequent motor skill development over time. Such findings have additional prognostic significance with respect to future neurocognitive outcomes, with studies in other populations linking deficits in early motor development to subsequent problems in cognition [32, 33].

Are there certain diagnostic subtypes at greater risk of neurodevelopmental impairment?

Patients with unicoronal synostosis were found to display weaker mental abilities overall (mildly delayed range), although meaningful statistical comparisons with other subtypes were precluded due to sample size. Comparison of the primary diagnostic subtypes (sagittal and metopic synostosis) yielded no significant group differences in mental or motor abilities both pre- and post-operatively. Whilst this may suggest that the overall risk for developmental impairment is broadly similar across diagnostic subtype, a larger patient cohort will be necessary to elucidate subtle differences between the subgroups of NSC.

Is surgical intervention a contributing factor in neurodevelopmental dysfunction in NSC?

In addressing the neurodevelopmental correlates of these conditions, treatment intervention, and the timing thereof, has often formed a primary line of enquiry. Whilst the cosmetic benefits are evident, it remains unclear as to whether surgical intervention mitigates or even increases the risk of neurodevelopmental impairment.

That an increased incidence of neurodevelopmental impairment post-operatively was found in the current, and other surgical NSC samples, does not necessarily imply a causal relationship between surgical intervention and developmental outcome.

The potential contribution of, predisposing, patient-specific factors upon neurodevelopmental outcome should be considered. For example, in infants undergoing cardiac surgery, the presence of a genetic syndrome, gestational age and birth weight have been found to be significant determinants of neurodevelopmental outcome. Further, operative management variables were shown to be unrelated to post-operative developmental status in these groups (e.g. [34] [35]).

It may also be that the craniosynostosis is a marker of anomalous brain development in NSC, rather than a causal effect. For example, there is evidence for altered patterns of both cortical and

subcortical neural organization in NSC, and further, that many such alterations in brain morphology do not mirror the overlying skeletal dysmorphology [8, 36].

With respect to age at surgical intervention, no significant relationship emerged with neurodevelopmental status. This does not necessarily imply that timing of treatment has no bearing upon neurodevelopmental outcomes. The majority of infants (95%) in our patient sample underwent corrective surgery before 18 months of age (median age of 9.7 months). ‘Late’ treatment cases are hence under-represented in the current sample. Anecdotal evidence from our centre of patients whose congenital deformity is not clinically detected during the ‘normal’ treatment phase has indicated a more severe pattern of, in particular, language impairment (both receptive and expressive) compared with their earlier treated counterparts. A more systematic study of these patients is an important line of further investigation in determining the merits of early vs. late treatment intervention in these conditions.

To determine whether surgical intervention does contribute to neurodevelopmental impairment in NSC, a randomized controlled trial would be required, which would include a treatment and non-treatment cohort. On the basis of the neurological risk factors associated with non-treatment alone (e.g. raised intracranial pressure), it would be ethically remiss to withdraw the option for treatment.

Timing of disruption to brain growth and development: Early Vulnerability Theory

The formation and maturation of the brain involves a series of programmed developmental processes, which commences in the third gestational week, and continues well into adulthood. There exist ‘critical’ or ‘sensitive’ periods which mark phases whereby specific neural circuitry is maximally sensitive to acquiring certain kinds of information. Brain disruption or insult during a critical period is thought to be particularly detrimental, causing a cessation of development or altering its course. This may result in an emergence of deficit over time, with children failing to make age-appropriate developmental gains.

The theoretical relation between craniosynostosis and cognitive impairment assumes a pathway by which abnormal suture fusion interferes with brain development and concomitant neurodevelopment during the gestational and early infancy phase. This corresponds with a time of increased vulnerability due to the brains’ immature form. Similar to other clinical populations (e.g. bacterial meningitis, cyanotic heart disease, following cranial irradiation) a young age at illness has been consistently associated with neurodevelopmental impairment [37-42]. Furthermore, those sustaining lesions within the prenatal period or first year of life have been found to be at highest risk of impairment [37, 43]. It is hence plausible that the etiopathogenesis of premature suture fusion itself has functional sequelae even before treatment can be considered. The unanswered question is: can any form of surgical intervention mitigate these sequelae?

Strengths and Limitations

An important strength of this study is the narrow age of the cohort. Previous studies have included samples of wide breadth of age and variant times of surgical intervention. Infants of later age at the time of surgical intervention may be deemed at higher risk of raised intracranial pressure and other associated neurological risk factors. These additional factors may mask the contribution of age-related effects upon developmental outcome.

With respect to study limitations, the issue of inclusion/exclusion criteria is an important consideration. The presence of a known gene mutation for craniosynostosis has been associated with an increased risk of neurodevelopmental dysfunction. Genetic screening was not routinely performed in this cohort. However, to minimize the relative contribution of gene mutations and other potential correlates of neurodevelopmental impairment, a conservative approach was applied. Infants who were known carriers of gene mutations and/ or whom displayed clinical features of a possible syndromal disorder, were excluded from the study.

Conclusion and Future Directions

This study suggests a mild, but clinically relevant risk for developmental impairment in patients with NSC.

In elucidating the causal and correlative features of developmental dysfunction in these conditions, future research would ideally incorporate neuroimaging studies (e.g. MRI, PET scans), so that pre- and post-operative functional integrity of cortical and subcortical structures is correlated with neurodevelopmental data. These data may help further elucidate the effects of craniosynostosis upon the developing brain and the potential implications of intervention or conservative management of these conditions upon development.

Operative treatment variables have not been systematically studied in association with developmental outcome in SSC. Recent evidence showing lower developmental scores in association with lengthier surgery and higher exposure to inhaled anaesthesia in SSC[44] provides an important line of further inquiry in this population group.

REFERENCES

- [1] Cohen MJ, MacLean R (2000) *Craniosynostosis: Diagnosis, Evaluation, and Management*. Oxford University Press, New York
- [2] Singer S, Bower C, Southall P, Goldblatt J (1999) Craniosynostosis in Western Australia, 1990-1994: a population-based study. *American Journal of Medical Genetics* 83: 382-387
- [3] Gault D, Renier D, Marchac D, Jones B (1992) Intracranial pressure and intracranial volume in children with craniosynostosis. *Plastic and Reconstructive Surgery* 90: 377-381
- [4] Siddiqi S, Posnick J, Buncic R, Humphreys R, Hoffman H, Drake J, Rutka J (1995) The detection and management of intracranial hypertension after initial suture release and decompression for craniofacial dysostosis syndromes. *Neurosurgery* 36: 703-708; discussion 708-709
- [5] Thompson D, Harkness W, Jones B, Gonzalez S, Andar U, Hayward R (1995) Subdural intracranial pressure monitoring in craniosynostosis: its role in surgical management. *Child's Nervous System* 11: 269-275
- [6] Renier D, Lajeunie E, Arnaud E, Marchac D (2000) Management of craniosynostosis. *Child's Nervous System* 16: 645-658
- [7] Aldridge K, Kane A, Marsh J, Panchal J, Boyadjiev S, Yan P, Govier D, Ahmad W, Richtsmeier J (2005) Brain morphology in nonsyndromic unicoronal craniosynostosis. *The Anatomical Record Part A Discoveries in Molecular and Cellular Evolutionary Biology* 285: 690-698
- [8] Aldridge K, Kane A, Marsh J, Yan P, Govier D, Richtsmeier J (2005) Relationship of brain and skull in pre- and postoperative sagittal synostosis. *Journal of Anatomy* 206: 373-385
- [9] Da Costa A, Anderson V, Savarirayan R, Wrennall J, Chong D, Holmes A, Greensmith A, JG M (2012) Neurodevelopmental functioning of infants with untreated single-suture craniosynostosis during early infancy. *Child's Nervous System* 28: 869-877
- [10] Arnaud E, Renier D, Marchac D (1995) Prognosis for mental function in scaphocephaly. *Neurosurgery* 38: 476-479
- [11] Kapp-Simon K, Figueroa A, Jocher C, Schafer M (1993) Longitudinal assessment of mental development in infants with nonsyndromic craniosynostosis with and without cranial release and reconstruction. *Plastic and Reconstructive Surgery* 92: 831-839; discussion 840-831
- [12] Speltz M, Endriga M, Mouradian W (1997) Presurgical and postsurgical mental and psychomotor development of infants with sagittal synostosis. *Cleft Palate-Craniofacial Journal* 34: 374-379
- [13] Warschausky S, Angobaldo J, Kewman D, Buchman S, Muraszko K, Azengart A (2005) Early development of infants with untreated metopic craniosynostosis. *Plastic & Reconstructive Surgery* 115: 1518-1523
- [14] Cohen S, Cho D, Nichols S, Simms C, Cross K, Burstein F (2004) American society of maxillofacial surgeons outcome study: preoperative and postoperative neurodevelopmental findings in single-suture craniosynostosis. *Plastic and Reconstructive Surgery* 15: 841-847; discussion 848-849
- [15] Ruiz-Correa S, Starr J, Lin H, Kapp-Simon K, Cunningham M, Speltz M (2007) Severity of skull malformation is unrelated to presurgery neurobehavioral status of infants with sagittal synostosis. *Cleft Palate Craniofacial Journal* 44: 548-554
- [16] Kapp-Simon K, Leroux B, Speltz M (2005) Multi-site study of infants with single-suture craniosynostosis: Preliminary report of pre-surgery development. *Cleft Palate-Craniofacial Journal* 42: 377-384
- [17] Panchal J, Amirshaybani H, Gurwitsch R, Cook V, Francei P, Neas B, Levine N (2001) Neurodevelopment in children with single-suture craniosynostosis and plagiocephaly without synostosis. *Plastic and Reconstructive Surgery* 108: 1492-1498
- [18] Bellew M, Chumas P, Mueller R, Liddington M, Russell J (2005) Pre- and postoperative developmental attainment in sagittal synostosis. *Archives of Diseases in Childhood* Apr; 90: 346-350
- [19] Gewalli F, Guimarães-Ferreira J, Sahlin P, Emanuelsson I, Horneman G, Stephensen H, Lauritzen C (2001) Mental development after modified pie procedure: dynamic cranioplasty for sagittal synostosis. *Annals of Plastic Surgery* 46: 415-420
- [20] Starr J, Kapp-Simon K, Cloonan Y, Collett B, Cradock M, Buono L, Cunningham M, Speltz M (2007) Presurgical and postsurgical assessment of the neurodevelopment of infants with single-suture craniosynostosis: comparison with controls. *Journal of Neurosurgery* 107(2 Suppl): 103-110
- [21] de Leon M, Speltz M, Cunningham M (2000) Does sagittal synostosis adversely affect early psychological development? Presented at the annual meeting of the UW Star-Bridges Program, Seattle
- [22] Toth K, Collett B, Kapp-Simon K, Cloonan Y, Gaither R, Cradock M, Buono L, Cunningham M, Dawson G, Starr J, Speltz M (2007) Memory and Response Inhibition in Young Children with Single-Suture Craniosynostosis. *Child Neuropsychology* 26: 1-14
- [23] Arnaud E, Meneses P, Lajeunie E, Thorne J, Marchac D, Renier D (2002) Postoperative mental and morphological outcome for nonsyndromic brachycephaly. *Plastic and Reconstructive Surgery* 110: 6-12
- [24] Bottero L, Lajeunie E, Arnaud E, Marchac D, Renier D (1998) Functional outcome after surgery for trigonocephaly. *Plastic and Reconstructive Surgery* 102: 952-958; discussion 959-960

- [25] De Moura DR, Costa JC, Santos IS, Barros AJD, Matijasevich A, Halpern R, Dumith S, Karam S, Barros FC (2010) Risk factors for suspected developmental delay at age 2 years in a Brazilian birth cohort. *Paediatric and Perinatal Epidemiology* 24: 211-221
- [26] Greensmith AL, Holmes AD, Lo P, Maixner W, Heggie AA, Meara JG (2008) Complete Correction of Severe Scaphocephaly: The Melbourne Method of Total Vault Remodeling. *Plastic and Reconstructive Surgery* 121: 1300-1310 1310.1097/1301.prs.0000304592.0000356498.d0000304596
- [27] Bayley N (1993) Bayley Scales of Infant Development (2nd edition)(Bayley-II). Psychological Corporation, San Antonio, TX
- [28] Daniel A (1983) Power, privilege and prestige: Occupations in Australia. Longman-Cheshire, Melbourne
- [29] Speltz ML, Kapp-Simon K, Collett B, Keich Y, Gaither R, Craddock MM, Buono L, Cunningham ML (2007) Neurodevelopment of Infants with Single-Suture Craniosynostosis: Presurgery Comparisons with Case-Matched Controls. *Plastic and Reconstructive Surgery* 119: 1874-1881
- [30] Korpilahti P, Saarinen P, Hukki J (2011) Deficient language acquisition in children with single suture craniosynostosis and deformational posterior plagiocephaly. *Childs Nervous System* Nov 15. [Epub ahead of print]
- [31] Shipster C, Hearst D, Somerville A, Stackhouse J, Hayward R, Wade A (2003) Speech, language and cognitive development in children with isolated sagittal synostosis. *Developmental Medicine and Child Neurology* 45: 34-43
- [32] Siegel L (1989) IQ is irrelevant to the definition of learning disabilities. *Journal of Learning Disabilities* 22: 468-478
- [33] Diamond A (2000) Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. *Child Development* 71: 44-56
- [34] Fuller S, Nord AS, Gerdes M, Wernovsky G, Jarvik GP, Bernbaum J, Zackai E, Gaynor JW (2009) Predictors of impaired neurodevelopmental outcomes at one year of age after infant cardiac surgery. *European Journal of Cardio-Thoracic Surgery* 36: 40-48
- [35] Tabbutt S, Nord AS, Jarvik GP, Bernbaum J, Wernovsky G, Gerdes M, Zackai E, Clancy RR, Nicolson SC, Spray TL, Gaynor JW (2008) Neurodevelopmental Outcomes After Staged Palliation for Hypoplastic Left Heart Syndrome. *Pediatrics* 121: 476-483
- [36] Aldridge K, Marsh J, Govier D, Richtsmeier J (2002) Central nervous system phenotypes in craniosynostosis. *Journal of Anatomy* 201: 31-39
- [37] Anderson V, Bond L, Catroppa C, Grimwood K, Keir E, Nolan T (1997) Childhood bacterial meningitis: Impact of age at illness and medical complications on long term outcome. *Journal of the International Neuropsychological Society* 3: 147-158
- [38] Franco S, Cornelius V, Andrews B (1992) Long-term outcome of neonatal meningitis. *American Journal of Diseases in Childhood* 146: 567-571
- [39] Grimwood K, Nolan T, Bond L, Anderson V, Catroppa C, Keir E (1996) Risk factors for adverse outcomes of bacterial meningitis. *Journal of Pediatric Child Health* 32: 457-462
- [40] Wright M, Nolan T (1994) Impact of cyanotic heart disease on school performance. *Archives of Diseases in Childhood* 71: 64-70
- [41] Anderson V, Smibert E, Ekert H, Godber T (1994) Intellectual, educational, and behavioural sequelae after cranial irradiation and chemotherapy. *Archives of Diseases in Childhood* 70: 476-483
- [42] Rubinstein C, Varni J, Katz E (1990) Cognitive functioning in long-term survivors of childhood leukemia: A prospective analysis. *Developmental and Behavioural Pediatrics* 11: 301-305
- [43] Duchowny M (1996) Identification of surgical candidates and timing of operation: An overview. In: Wyllie E (ed) *The treatment of epilepsy: Principles and practice*, 2nd edn. Williams & Wilkins, Baltimore, pp 967-975
- [44] Naumann H, Haberkern C, Starr J, Kapp-Simon K, Hopper R, Speltz M (2012) Duration of exposure to cranial vault surgery: associations with neurodevelopment among children with single-suture synostosis. *Paediatric Anaesthesia* 22: 1053-1061

FIGURES AND TABLES

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FIG. 2 Metopic synostosis

FIG. 3 Unicoronal synostosis

TABLE 1. Sample demographic characteristics.

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FIG. 1 Sagittal synostosis

FIG. 2Metopic synostosis

FIG. 3Unicoronal synostosis

TABLE 1. Sample demographic characteristics.

Demographic Characteristics	T1 (N=64)	T1 and T2 (n=44)	T1 only (n=20)	<i>P</i>
Age in months, <i>M (SD)</i> ; Range	8.5 (2.7) 4.3-16.5	21.2 (4.5) 6.7-32.0	9.5 (3.1) 5.5-16.5	.160
Male Gender, % (n)	71.9 (46)	72.7 (32)	70.0 (14)	.730
Female Gender, % (n)	28.1 (18)	27.3 (12)	30.0 (6)	
Socioeconomic Status*, <i>M (SD)</i>	4.6 (1.0)	4.6 (0.9)	4.8 (1.1)	.303
<i>Synostosis diagnostic subtype</i>		% (n)	% (n)	
Sagittal	40.6 (26)	36.4 (16)	50.0 (10)	.186
Metopic	32.8 (21)	34.1 (15)	30.0 (6)	
Unicoronal (right/ left-sided)	15.6 (10)	15.9 (7)	15.0 (3)	
Multisutural	10.9 (7)	13.6 (6)	5.0 (1)	
<i>Medical/ Developmental History</i>				
Prematurity, % (n)	7.8 (5)	9.5 (6)	10.0 (2)	.860
Age at surgery, <i>M (SD)</i>		10.8 (9.8)	-	
Maternal age, <i>M (SD)</i>	30.4 (5.2)	31.2 (4.8)	27.8 (5.6)	.03
Paternal age, <i>M (SD)</i>	32.7 (4.2)	32.9 (4.5)	31.9 (3.5)	.495

T1= pre-operative, T2= post-operative

*Socioeconomic status was determined according to Daniel's Scale of Occupational Prestige [28], in which the scale ranges from 1.0 to 6.9, and where a low score reflects high occupational prestige.

TABLE 2. Mean difference of the clinical group compared with population averages on pre-and post-operative developmental scores.

Neurodevelopmental measure	Test Score <i>M (SD)</i>	Mean difference from normal population	95% Confidence Interval	<i>P</i>
T1 MDI	97.5 (6.9)	-2.5	94.3-98.5	.007
T1 PDI	87.8 (12.5)	-12.2	84.5-90.8	<.001
T2 MDI	89.5 (15.2)	-10.5	83.6-94.4	<.001
T2 PDI	88.0 (14.0)	-12.0	83.6-93.1	<.001

T1= Pre-operative; T2= Post-operative

BSID-II, Bayley Scales of Infant Development; Second Edition, MDI, Mental Development Index; PDI, Psychomotor Index

TABLE 3. Distribution of the standardized distribution by classification of mental development index scores

MDI Score Groups	Standardized distribution (%)	T1†		T2§	
		%	N	%	N
Accelerated	16.5	0	0	4.5	2
Normal	68.7	90.6	57	63.6	28
Mild delay	12.5	6.3	4	11.4	5
Severe delay	2.3	3.1	2	20.5	9
Total	100.0	100.0	63	100.0	44

T1= Pre-operative; T2= Post-operative

BSID-II, Bayley Scales of Infant Development; Second Edition, MDI, Mental Development Index

† χ^2 (1, $N = 63$) = 0.279, $p = .579$

§ χ^2 (1, $N = 44$) = 18.12, $p < .001$

TABLE 4. Distribution of the standardized distribution by classification of psychomotor development index scores

PDI Score Groups	Standardized distribution (%)	T1†		T2§	
		%	N	%	N
Accelerated	14.8	0	0	0	0
Normal	72.6	69.4	43	59.0	23
Mild delay	11.1	19.4	12	17.9	7
Severe delay	1.5	11.3	8	23.1	9
Total	100.0	100.0	63	100	39

T1= Pre-operative; T2= Post-operative

BSID-II, Bayley Scales of Infant Development; Second Edition, PDI, Psychomotor Index

† χ^2 (1, $N = 63$) = 12.07, $p < .001$

§ χ^2 (1, $N = 39$) = 18.12, $p < .001$

TABLE 5: Comparison of pre- and post-surgical risk of neurodevelopmental delay in patients with NSC compared with normative averages

BSID scale	% mild/ significantly delayed		Risk Ratio	95% CI
	normal population	NSC		
T1 MDI	14.8	9.5	0.6	0.3-1.4
T2 MDI	14.8	31.9	2.1**	1.4-3.4
T1 PDI	12.6	31.7	2.5**	1.7-3.7
T2 PDI	12.6	40.1	3.0**	2.2-4.8

T1= Pre-operative T2= Post-operative

BSID-II, Bayley Scales of Infant Development; Second Edition: MDI, Mental Development Index; PDI, Psychomotor Index

* $p < .05$, ** $p < .001$

TABLE 6. Diagnostic group comparisons on mental and motor measures: Pre- and post-treatment

Variable	Diagnostic Group									
	Sagittal†		Metopic†		Unicoronal§		Multisutural§		Total Sample	
	<i>M</i> (SD)		<i>M</i> (SD)		<i>M</i> (SD)		<i>M</i> (SD)		<i>M</i> (SD)	
	<i>Range</i>		<i>Range</i>		<i>Range</i>		<i>Range</i>		<i>Range</i>	
	T1 (n=26)	T2 (n=26)	T1 (n=21)	T2 (n=15)	T1 (n=10)	T2 (n=7)	T1 (n=7)	T2 (n=6)	T1 (n=64)	T2 (n=44)
MDI	96.4 (8.0)	93.7 (18.6)	99.1 (4.9)	86.5 (14.4)	98.7 (6.3)	85.9 (11.3)	95.9 (8.6)	91.0 (12.4)	97.0**6.4)	89.5**15.2)
	80-111	69-124	86-106	54-104	87-109	69-99	79-104	69-105	80-109	54-124
PDI	87.8 (11.2)	86.7 (12.7)	90.1 (14.2)	89.5 (14.7)	82.6 (15.0)	82.2 (18.4)	87.9 (8.8)	93.0 (12.7)	85.9**13.8)	88.0**14.0)
	58-106	69-104	50-108	69-110	55-101	66-112	81-106	69-105	50-108	66-112

T1= Pre-operative; T2= Post-operative

BSID-II, Bayley Scales of Infant Development; Second Edition, MDI, Mental Development Index; PDI, Psychomotor Index

† compared with BSID normal population; § sample too small for statistical comparison with normal population

*p<.05, **p<.001

TABLE 7. Gender comparisons on mental and motor measures: Pre- and post-treatment

	Male (n=44)	Female (n=17)	Difference	Significance
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SEM)</i>	
T1 MDI	97.3 (6.7)	98.1 (7.8)	-0.79 (2.0)	.69
T1 PDI	88.4 (11.6)	86.2 (15.1)	2.2 (.55)	.55
	(n=31)	(n=12)		
T2 MDI	88.5 (16.5)	92.3 (11.5)	-3.8 (5.2)	.47
T2 PDI	88.0 (13.0)	88.0 (16.8)	0.0 (5.0)	1.0

T1= Pre-operative; T2= Post-operative

BSID-II, Bayley Scales of Infant Development; Second Edition, MDI, Mental Development Index; PDI, Psychomotor Index

† compared with BSID normal population; § sample too small for statistical comparison with normal population

*p<.05, **p<.001

TABLE 8. Correlations among sociodemographic and developmental variables

Variable	MDI I	PDI I	MDI II	PDI II
Gestational age (T1)	-.09	-.31*	-.22	-.38*
Socioeconomic status	.02	-.13	-.29	.09
Maternal education level				
Maternal age	.02	-.08	-.02	-.31
Paternal age	-.01	.04	-.07	-.37*
Age at surgery	-	-	.09	-.02
MDI-I	-	.44**	-.07	.14
PDI-I		-	.07	.41**

* Correlation is significant at the 0.05 level

** Correlation is significant at the 0.05 level