The longterm neuropsychological effects of single-suture craniosynostosis on child development

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ON CHILD DEVELOPMENT

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1998
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Sheri H. Magge
Signature of Author

3-26-98
Date
The Longterm Neuropsychological Effects of Single-Suture Craniosynostosis on Child Development

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

Sheela Natesh Magge

1998
Abstract:

LONGTERM NEUROPSYCHOLOGICAL EFFECTS OF SINGLE-SUTURE CRANIOSYNOSTOSIS ON CHILD DEVELOPMENT

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The purpose of this study was to examine the longterm neuropsychological effects of single-suture craniosynostosis on the neurologic development of children, by going beyond gross measures of mental function (IQ), in an attempt to assess the incidence of more subtle neuropsychological sequelae. Retrospective analysis of Yale Department of Neurosurgery records between 1980 and 1990 was used to identify potential study subjects born with craniosynostosis, and currently between six and sixteen years of age. The children's parents were then contacted to obtain consent and arrange for the administration of a battery of neuropsychological tests. Of the 31 study subjects (n=31), there were 16 born with sagittal synostosis (n=16), 5 born with metopic synostosis (n=5), 5 born with unilateral coronal synostosis (n=5), and 5 born with multi-suture or more complicated cases of craniosynostosis (n=5). The last group was separated out to avoid confounding the study results. Of the 26 remaining study subjects with isolated, single-suture craniosynostosis (namely, sagittal, metopic, or unilateral coronal craniosynostosis), 58% were identified as having a learning disability. Furthermore, even among the sagittal group (n=16), thought to be the most benign of the single-suture craniosynostoses, 50% had a learning disability. This study indicates that although subjects fall within the normal range for intelligence, there is a significantly higher incidence of learning disabilities in this group as compared with the general population.
Acknowledgments:

This research project was funded through the James G. Hirsch, MD Endowed Medical Student Research Fellowship through the Yale Medical School Office of Student Research. I would also like to thank Dr. Charles Duncan for access to his patient population, and Ms. Eileen Ogle for her assistance with patient records. Many thanks go to Dr. Michael Westerveld for his training in neuropsychological testing and his assistance with data analysis, as well as to Dr. Tom Pruzinsky for his advice and support. Finally, I would especially like to thank my thesis advisor and mentor, Dr. John A. Persing, whose genuine concern for patients, and dedication to teaching and students, are inspirational.
Introduction:

Craniosynostosis is a craniofacial malformation in children characterized by the premature fusion of the cranial bones. This condition results in skull deformities and, in some cases, may restrict the growth of a child's brain. Descriptions of the cranial sutures closing prematurely date back to Hippocrates in the 5th century BC. (Freeman and Borkowf, 1962) In 1851, Virchow first used the term “craniostenosis” to describe the changes that occurred when the skull sutures fused prematurely. (Hemple, 1961) He noted that when a suture fused, skull growth perpendicular to the fused suture was inhibited, whereas growth parallel to the suture occurred in compensation. (Hemple, 1961) In 1890, the first surgery for craniosynostosis, a linear craniectomy of the fused suture, was performed. (Freeman and Barkowf, 1962) Thus, craniosynostosis, its affect on skull shape, and its potential for affecting brain growth, have been recognized by physicians for years.

In general, craniosynostosis is a relatively uncommon condition, with estimates of the incidence of the simple form ranging from 0.4/1000 to 1.6/1000 births. (Dufresne and Carson, 1992) Craniosynostosis can occur as part of a congenital syndrome, such as Crouzon’s or Apert’s Syndromes, or it can occur as an isolated anomaly in a particular cranial suture.

There are several different types of craniosynostosis, named for the individual sutures involved. There are normally five patent cranial vault sutures at birth: metopic, coronal, sagittal, squamosal, and lambdoidal (see Figure 1). The presence of these sutures
allows the skull to expand as the brain grows. Craniosynostosis is termed “simple” when it involves the premature fusion of only one cranial suture, and “compound” when it involves the fusion of two or more sutures. (Dufresne and Carson, 1992). Isolated, nonsyndromic, sagittal suture synostosis is the most common type of craniosynostosis. This type usually occurs sporadically, occurring with a genetic predisposition in only 2% of cases. (Ocampo and Persing, 1994)

As premature fusion of a suture prohibits growth in the direction perpendicular to that suture, skull deformities occur as a result of this restriction, followed by compensatory growth deformity elsewhere in the skull, where sutures remain patent (see Figures 2 and 3). Sagittal synostosis results in a calvarium narrow in the mediolateral axis, and elongated in the anterior-posterior direction. This skull shape is termed “scaphocephaly”. (see Figure 4) Another skull deformity, termed “trigonocephaly”, results from synostosis of the metopic suture, and deforms the skull into a triangular shape. (see Figures 5 and 6) Unilateral coronal synostosis results in an asymmetric skull, particularly in the fronto-orbital region. The skull is flattened on the side of the fused suture, and excessively prominent (or “bossed”) on the contralateral side. This skull shape is referred to as anterior “plagiocephaly” (or oblique-shaped skull). (see Figure 7) Bilateral coronal synostosis can result in a tower skull deformity, referred to as “turricephaly” (see Figure 8), and synostosis of the lambdoid suture results in posterior skull asymmetry or posterior “plagiocephaly”. (Dufresne and Carson, 1992)

The treatment of craniosynostosis, historically, has been cranial surgery to release the restriction on the growing skull, and in turn, enhance normal brain and skull growth.
(McLaurin and Matson, 1952) (see Figures 9 through 11 for pre- and post-surgical pictures) When several sutures are involved, the need for surgery is straightforward. Mental impairment and blindness are frequent consequences of non-treatment. However, because the link between cranial deformity and “functional” disability is less obvious in single-suture craniosynostosis, cranial reconstruction surgery in these cases is being defined by some as "cosmetic". This is problematic for many physicians who believe that not performing the surgery can result in craniofacial disfigurement with psychosocial sequelae, which may yield disabling effects as significant as the neurologic problems resulting from growth restriction of the calvarium on the brain. It has been anecdotally reported by physicians that children with simple craniosynostosis often seemed to have a higher proportion of learning disabilities and cognitive problems than their nonafflicted peers. However, these reports, which would be of great interest to patients’ parents, have not been systematically studied.

Past studies have attempted to assess gross mental function in children with craniosynostosis. In 1961, a study was published suggesting that isolated sagittal synostosis (scaphocephaly) rarely caused mental retardation. The authors questioned the use of craniectomy for purely cosmetic reasons, given the morbidity and mortality associated with craniectomy at the time. (Hemple et al., 1961) However, the measures of mental function used in this study were unclear. Freeman and Borkowf (1962) used developmental measures and intelligence quotients (IQ’s) to support Hemple et al.’s skepticism about the need for surgery. These opinions were naturally colored by the surgical techniques and perioperative supports available at the time. However, a more
recent study (1981) found that scaphocephaly could result in disfigurement causing lasting psychosocial problems for children. Therefore, they proposed that surgical treatment for scaphocephaly was acceptable for “cosmetic” purposes alone. (Barritt, 1981) (Shillito and Matson, 1968) The question of whether cranial reconstructive surgery for single-suture craniosynostosis is medically indicated, however, has not been fully resolved. More indepth studies of mental and social function are needed.

Several assessments of mental function in craniosynostosis patients have involved measures of intracranial pressure (ICP). Some believe that fusion of a cranial suture creates an environment in which the brain is forced to grow in a restricted space, causing an increase in ICP with related neurologic effects. These neurologic effects may be more apparent as complex functions, associated with frontal lobe development, begin to appear. This possibility, however, is as yet unclear.

However, some see ICP as a measure of the impact of growth restriction on the brain. In 1982, Renier et al. reported that ICP was elevated in one third of children with craniosynostosis in their study, when measured preoperatively. This elevation was more common when more than one suture was involved, but still was increased in a substantial number of children with single-suture craniosynostosis. Furthermore, the increased ICP decreased after corrective surgery. Although mental level, as measured by IQ or DQ (development quotient (DQ) is measured when a child is too young for IQ testing), was tested only prior to surgery, a statistically significant relationship between ICP and mental level was found; mental level decreased when ICP increased. (Renier et al., 1982)
In a later study (Renier, 1989), he found that among cases involving the coronal suture ( plagiocephaly and brachycephaly), intelligence levels were lower in the group with increased ICP as compared to those with normal ICP. Mental function was also found to be lower the longer the craniosynostosis was left untreated in all types of synostosis. In the majority of cases, ICP came down to normal, gradually, after surgery, which appeared to stop the worsening of, but did not significantly improve, mental function.

Gault et al. (1992) found that measurements of intracranial volume did not always correlate with ICP, and that some children with low intracranial volume (implying the assumption that craniosynostosis resulted in low intracranial volume) did not have an increased ICP. However, of the thirteen study subjects with intracranial hypertension and craniosynostosis, twelve had low intracranial volume. The authors stated that low intracranial volume alone could not be used to deduce which children had intracranial hypertension, although a reduced intracranial volume did identify a population with a higher likelihood of intracranial hypertension. From all these studies, one may gather that the relationship between intracranial pressure, intracranial volume, and cognitive function has not been definitively elucidated.

In contrast to Renier et al.'s studies, Kapp-Simon et al. (1993) studied mental development in infants with nonsyndromic craniosynostosis who had had corrective surgery, and compared them with those who had not. They found that there was no evidence that cranial reconstructive surgery decreased the incidence of mental retardation (as measured by mental development index scores). Furthermore, the authors reported no relation between the severity of the craniosynostosis and the child's mental functioning,
and concluded that surgery in nonsyndromic craniosynostosis was primarily a cosmetic procedure. The authors acknowledged, however, that a child's psychosocial adjustment may be improved with surgery, as the child's head shape is improved. Furthermore, Kapp-Simon et al. used the Bayley Scales of Infant Development to obtain mental development index scores for the children in their study, as they were too young for IQ testing (subjects ranged from 2 to 33 months at initial visit). The authors therefore added that the possibility of a child developing learning disabilities as s/he matures, when more subtle tests of reasoning could be employed, still existed.

Renier and Marchac (1993) contended that the conclusion of the Kapp-Simon et al. article, that mental development is not affected by nonsyndromic craniosynostosis, was erroneous due to the small sample size tested and the youth of the study population. They found that while very young children with craniosynostosis usually had normal mental development, this proportion decreased with age, especially when more than one suture was involved. The authors reiterated that surgery stopped this regression, and that better results occurred the younger the child was at the time of surgery.

None of the aforementioned studies looked at these children at a later stage of development, during their school-age years. Furthermore, none of these studies involved indepth neuropsychological testing, evaluating not only whether the child was mentally retarded, but also whether the child had a learning disability or cognitive impairment as a result of craniosynostosis. Past studies have also not involved measures of psychosocial skills which could allude to any psychosocial impairment as a result of disfigurement.
Sidoti et al. (1996) attempted to address some of these issues in a retrospective study of children born with metopic synostosis, after having observed what they thought to be a higher incidence of behavioral and learning anomalies in this population. They concluded that children with isolated metopic craniosynostosis had an increased incidence of mild neurologic disabilities. However, the methodology used in this study to assess frequency of mental retardation, learning disabilities, and behavioral problems involved chart review and a parental questionnaire. The results of parental questionnaires about learning disabilities are of questionable reliability as the parents may make incorrect assumptions about, or be unaware of, their child’s status. This study also lacks neuropsychologic testing of the children in the study.

A large prospective study of patients with sagittal suture craniosynostosis did involve neuropsychological testing, however. Arnaud et al. (1995) studied relationships between intracranial pressures and development quotients (DQ’s) before surgery, and final intelligence quotients (IQ’s) in both surgically and nonsurgically treated patients at a later follow-up date. This study showed the main predictor of final IQ to be the initial DQ. Although this study did involve neuropsychological testing, it did not examine the presence of learning disabilities in the population. In addition, the mean age at follow-up review was 6.4 years, at the latest, and thus did not extend into later school years.

Our study attempted to look at the long-term neuropsychological and psychosocial effects on children and adolescents born with single-suture craniosynostosis, in order to learn the incidence of learning disabilities in this group of patients.
Statement of Purpose:

The purpose of this study was to examine the longterm neuropsychological effects of single-suture craniosynostosis on child development, by going beyond gross measures of mental function such as IQ, and examining the incidence of more subtle neuropsychological problems, such as learning disabilities.
Methods:

Background:

This study took place at the Yale University School of Medicine, and involved the Section of Plastic Surgery, the Department of Neurosurgery, and the Division of Pediatric Neuropsychology. The data was gathered and analyzed from June, 1996 to February, 1998. The original six-month time period of fulltime research was funded by the James G. Hirsch, MD Endowed Medical Student Research Fellowship through the Yale Medical School Office of Student Research. A proposal for the study was approved by the Yale Human Investigations Committee.

Study Subjects:

Although optimally one would want to compare those children who did not have corrective surgery with those that did, the vast majority of children born with craniosynostosis in the U.S. are treated surgically within the first six months of life. This fact necessitated the comparison between children born with craniosynostosis and who have had surgical correction, with norms established for the general population. Thus, the assumption is made that residual effects of skull growth restriction prior to surgery could remain, which may or may not be dependent upon the age at surgery.

This study of the neuropsychological and psychosocial development of children born with craniosynostosis was limited to children who were 6-16 years of age at the time of the study, qualifying them for the battery of neuropsychological tests chosen. These
children had been surgically treated between 1980 and 1990. During this time frame, these children were treated by neurosurgeons in the Department of Neurosurgery at Yale. All neurosurgery operative summaries during the ten-year time period were systematically examined, and a list of patients who had had surgery for single-suture craniosynostosis was compiled. One hundred and six potential patients for the study were identified through this review of the operative summaries. All of these patients’ files were examined. Exclusion criteria were syndromic craniosynostosis such as Crouzon’s or Apert’s Syndrome, or the presence of additional neurologic complications such as seizures or mental retardation related to hydrocephalus or traumatic brain injury. A few patients had expired, and a few were too old to participate in the study.

The department’s computer database and the patients’ charts were used to compile a list of the patients’ last known addresses and phone numbers. At this point letters were sent to the parents of the eighty-one potential participants’ parents, explaining the study, the potential benefits to the child, and the lack of risk. The letter included a request for the parents and the patients (if they were from ten to sixteen years of age) to respond if they did not wish to be contacted by phone to learn more about the study. A postage-paid return envelope was provided. Of these letters, twenty-three came back “Return to Sender”, and four responded by declining to participate.

In the remaining fifty-four cases, attempts were made to contact the parents by phone. Many families had moved or changed phone numbers in the interim time since the child’s surgery. However, when attempts were successful, the study was described to the parent, and the parents’ questions were addressed. The study subjects did not receive
monetary payment for their participation in this study. However, it was explained that the child could potentially benefit scholastically from receiving free neuropsychological testing, which normally costs approximately one thousand dollars. Parents who requested feedback could receive a written summary of their child's performance on the tests. If the child was currently having problems in school, this testing could be of benefit to the child. If the child was presently doing well, this testing could be useful in case of any future problems. It was explained that neuropsychological tests provide information about how a child learns, and about a child's cognitive abilities. The adaptive behavior test provides information about the child's psychosocial adjustment. In cases in which a potential problem was identified, the investigators would arrange for appropriate referrals (in a location convenient for the patient's family) for follow-up. It was also explained that this study could potentially benefit future children born with single-suture craniosynostosis, providing valuable information regarding the necessity of surgery. There were no risks of physical or other injury to the children participating in this study. If the parents agreed to participate in the study with their child, a time for testing, which required approximately three and a half hours, was arranged. Appointments for neuropsychological testing were arranged and kept in thirty-one cases, which became the size of the final study sample.

Among the thirty-one study participants, there were sixteen cases of sagittal synostosis, five cases of metopic synostosis, five cases of unilateral coronal synostosis, and five "other" cases. Although an attempt was made to limit the study subjects to children born with isolated, single-suture craniosynostosis, five participants did not fit this criteria. Three children had bilateral coronal synostosis, one had probable lambdoidal synostosis,
and one child had hydrocephalus in addition to sagittal craniosynostosis. This information became available after a time for testing had already been arranged. Therefore, these five children were included in the study, but were placed in a separate group, so as not to confound the study results.

There are a few qualifications regarding testing procedure. One patient had taken the WISC-III in the recent past, so the test was not readministered and the previous test scores were used. As the WISC-III is a standardized test, different examiners do not interfere with data comparison. One child did not have the Vineland Adaptive Behavior Scales administered, and one child did not have the socialization domain of the Vineland administered, both due to time constraints.

*Measures:*

On the day of testing, written consent was obtained from the parents when they arrived. Also, children from ten to sixteen years of age were asked to sign an assent form. The neuropsychological tests were administered by the principal investigator after receiving administration and scoring training from Dr. Michael Westerveld, director of Pediatric Neuropsychology. A battery of six neuropsychological tests had been chosen after consultation of the principal investigator with Dr. Westerveld, Dr. Tom Pruzinsky, a psychologist experienced with reconstructive surgery patients, and Dr. John Persing, chief of the Section of Plastic Surgery. These tests are standardized and widely recognized for their validity and reliability. The tests administered were the Wechsler Intelligence Scale for Children - Third Edition (WISC III, 1991), the Wide Range Achievement Test -
Revised (WRAT-R, 1984), the Conner’s Continuous Performance Test (CPT, 1994), the Wisconsin Card Sorting Test (WCST, 1993), the Developmental Test of Visual-Motor Integration (VMI, 1989), and the Vineland Adaptive Behavior Scales (Vineland, 1984) (the latter is the only one of the aforementioned tests which is administered to a parent). Throughout this process, no one other than the investigators had access to any identifying information about the study subjects.

The particular neuropsychological tests used were chosen in order to evaluate the children on various levels, including intelligence, achievement, socialization and adaptive behavior, attention, and visual-motor skills. The WISC-III is a widely used intelligence quotient (IQ) test for children from six to sixteen years of age, which involves the administration of ten required subtests (picture completion, information, coding, similarities, picture arrangement, arithmetic, block design, vocabulary, object assembly, and comprehension) and three optional subtests (symbol search, digit span, and mazes). All subtests except for the optional mazes subtest were administered in our study. Verbal, performance, and fullscale IQ scores were obtained, along with verbal comprehension, perceptual organization, freedom from distraction, and processing speed scores. The IQ indices are standardized to have a mean of 100 points, with a standard deviation of 15 points, regardless of a child’s age.

The WRAT is an achievement test which allows one to obtain scores in reading, spelling, and arithmetic, and again has a national mean score of 100. While the WISC-III is considered to be a measure of intelligence, the WRAT is a measure of achievement or performance.
The Continuous Performance Test (CPT) is a computer test which presents letters on the screen at varying speeds and asks the child to press the spacebar everytime a letter other than “X” appears on the screen. The child is to wait until the next letter appears without pressing any keys if an “X” appears. The test is scored by the computer for different measures, with a mean score of 50, and a standard deviation of 10. The CPT is a test of executive function, focusing on measures of sustained attention and impulsivity.

The Wisconsin Card Sorting Test uses a set of cards with different shapes pictured on them, in different numbers, and in different colors. The child is asked to match the cards without be told the criteria by which to match. During the course of testing, the criteria change (of which the child is also not told), and the child is only informed as to whether the match is correct or not. This test is also scored by computer, with the standard scores having a mean of 100, with a standard deviation of 15 points. This test is also one of executive function, but focusses on the child’s problem-solving abilities and adaptation.

The Developmental Test of Visual-Motor Integration asks the child to copy a set of figures, by drawing the form below the original. The child is given a pencil without an eraser to do so. This test also has a mean of 100, with a standard deviation of 15 points, and is a measure of visual-motor function.

The Vineland Adaptive Behavior Scales was the only test administered to the child’s parent. The interview edition was used, in which the parent is asked open-ended questions about the child’s behavior in three domains: communication, daily living skills, and socialization. The answers are scored by the administrator, and the standard scores
have a mean of 100, with a standard deviation of 15. This test was administered as a measure of the adaptive behavior of the child in his or her daily life.

After all of the scores were calculated, parents who requested feedback received a written summary of their child's performance on the tests. In addition, appropriate referrals (in a location convenient for the patient's family) were made for patient follow-up when necessary and requested. All test scoring was done by the principal investigator.

Analysis:

The acquired data for the study subjects was entered into a computer spreadsheet, Microsoft Excel, with the assistance of a volunteer working with Dr. Michael Westerveld. The statistics program SYSTAT for Windows, 5.0 (1992) was used to run statistical analyses of the data, with the help of Dr. Westerveld. In evaluating the data, the investigators looked for any increased incidence of learning disabilities or cognitive problems in this patient population when compared to normative standards. Learning disabilities were evaluated by looking for discrepancies between intelligence and achievement. The WRAT reading subtest standard scores were subtracted from the verbal IQ scores, and the WRAT spelling subtest standard scores were subtracted from the verbal IQ scores. Comparisons were made between incidences within the study population and incidences within the U.S. general population. Adaptive behavior scales including socialization scores were also studied, looking for any patterns or variations in children born with craniosynostosis. Thus, both the psychosocial effects and the
neurologic effects of craniosynostosis were examined. Possible variations between types of craniosynostosis and age at surgery were also examined.
**Results:**

Of the thirty-one patients tested, 61% (n=19) were male and 39% (n=12) were female. The age ranged from 6.4 to 15.9 years with a mean of 10.6 years. The study patients were divided into groups by type of craniosynostosis for purposes of analysis (see Table 1). Group 1 consisted of patients born with sagittal synostosis and contained 16 children (52%). Group 2 consisted of patients born with metopic synostosis, Group 3 of children born with unilateral coronal synostosis, and Group 4 of cases not included in the three aforementioned groups. Each of these last three groups contained 5 children (16%).

**TABLE 1:**

<table>
<thead>
<tr>
<th>Group 1: Sagittal</th>
<th>Group 2: Metopic</th>
<th>Group 3: Unilateral Coronal</th>
<th>Group 4: Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=16</td>
<td>n=5</td>
<td>n=5</td>
<td>n=5</td>
</tr>
<tr>
<td>52%</td>
<td>16%</td>
<td>16%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Analysis of the data obtained from the neuropsychological testing of the thirty-one study subjects demonstrated several interesting patterns. When IQ scores were examined as a whole, scores fell within the normal range for the general population, with an average fullscale IQ of 104.9. Although a trend was observed with lower IQ scores for the metopic, unilateral coronal, and “other” groups, an analysis of variance (ANOVA) of the fullscale IQ scores between the four groups found no significant difference between the
groups (p=0.09). However, there was a significant difference between the verbal IQ (VIQ) and the performance IQ (PIQ) (as demonstrated by the results of the WISC-III) in the children involved in the study (see Table 2). The children had significantly higher verbal IQ’s than performance IQ’s, with a mean verbal IQ of 109.5 and a mean performance IQ of 99.2. Both scores individually fall within the normal range, but a paired T-test demonstrated that the mean difference in VIQ and PIQ was 10.32, and was statistically significant with p<0.001.

Furthermore, this pattern was also seen when the study participants were divided by type of craniosynostosis into Groups 1 - 4 as described above (see Table 2). When one moved from the sagittal group (mean VIQ=113.8, mean PIQ=105.4), to the metopic group (mean VIQ=108.6, mean PIQ=101.4), to the unilateral coronal group (mean VIQ=104.0, mean PIQ=91.0), to the “other” category (mean VIQ=102.2, PIQ=85.0), the mean VIQ and PIQ scores gradually decreased from group to group. Within each category, the pattern of greater VIQ’s than PIQ’s continued. Paired T-tests were performed on each group, showing that the mean difference between VIQ and PIQ was statistically significant in the sagittal group and the “other” group, but did not reach statistical significance in the metopic or unilateral coronal group. Lack of statistical significance in the latter two groups was thought to be due to the small sample size in each of these groups (n=5). It was also found that the VIQ-PIQ difference itself did not vary significantly between the groups (p=0.49). Thus, there was a consistent difference between the VIQ and the PIQ among all the craniosynostosis types, with statistical significance found in the overall group (n=31) and within the sagittal group (n=16).
TABLE 2:

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Verbal IQ</th>
<th>Mean Performance IQ</th>
<th>Mean Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: Sagittal</td>
<td>113.8</td>
<td>105.4</td>
<td>8.3</td>
<td>0.021</td>
</tr>
<tr>
<td>Group 2: Metopic</td>
<td>108.6</td>
<td>101.4</td>
<td>7.2</td>
<td>0.292</td>
</tr>
<tr>
<td>Group 3: Unilateral Coronal</td>
<td>104.0</td>
<td>91.0</td>
<td>13.0</td>
<td>0.052</td>
</tr>
<tr>
<td>Group 4: Other</td>
<td>102.2</td>
<td>85.0</td>
<td>17.2</td>
<td>0.029</td>
</tr>
<tr>
<td>Overall (n=31)</td>
<td>109.5</td>
<td>99.2</td>
<td>10.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The decreased performance IQ’s raised the question of visual-motor deficiencies. Problems in this area were evident not only through IQ testing, but also as represented by the results of the Developmental Test of Visual-Motor Integration. The mean standard score for the study population was 94.7, with 100 as the mean for the normal population. A Pearson correlation showed a 0.59 correlation between the standard score on the Developmental Test of Visual-Motor Integration and the performance IQ in the study population. Thus, there was consistent evidence of increased incidence of visual-motor problems in this population.

The performance and verbal IQ difference can represent a population at higher risk of developing a learning disability. (Rourke, 1985) The presence of learning disabilities in this population was examined by looking for disparities between IQ, as measured by the WISC-III, and achievement, as measured by the WRAT. Measures used were based on DSM-IV and other criteria for learning disabilities. (Ardila, 1997) (Lyon, 1996) (DSM-IV, 1994) The presence of a reading learning disability was determined by subtracting the WRAT reading subtest standard score from the verbal IQ (VIQ-WRATread). The child
was found to have a reading learning disability if the difference was greater than or equal to fifteen (accepted standard). The presence of a spelling learning disability was examined by subtracting the WRAT spelling subtest standard score from the verbal IQ (VIQ-WRATspell), and was also defined by a difference greater than or equal to fifteen.

According to these criteria, 45% of the children in the study (n=14) had a reading learning disability, and 42% of the children (n=13) had a spelling learning disability (see Table 3). Nine of the participants had a reading or spelling learning disability alone, while another nine had both a reading and a spelling learning disability. Fifty-eight percent of the study subjects had one or both types of learning disabilities (n=18). Among the children in Groups 1 - 3 (n=26), with single suture craniosynostosis of the sagittal metopic, or unilateral coronal suture, one finds that 58% have one or both learning disabilities.

The presence of one or both types of learning disabilities was also examined by type of craniosynostosis. Among the sixteen patients in the sagittal synostosis group (Group 1), 50% had a learning disability. The metopic group (Group 2) and the unilateral coronal group (Group 3) both had five patients per group, with learning disabilities identified in 80% and 60%, respectively (see Table 3). The difference in the percentage of patients in the three groups with learning disabilities was not found to be statistically different from one another (prob = 0.492).
Among the eighteen children who were found to have one or both learning disabilities, 72% were male and 28% were female, compared to 61% male and 39% female in the total study population. Among the males in the study, 68% were found to have one or both learning disabilities, whereas 42% of females were found to have a learning disability.

Another variable examined was the age at surgery. The age at surgery ranged from 35 days to 540 days in our study with a mean of 146 days (n=31). If more than one surgery was performed, the first surgery date was used. A correlative test between the age in days at surgery, the difference in performance and verbal IQ’s, the presence of a reading learning disability, and the presence of a spelling learning disability, showed no significant correlation between age at surgery and any of these measures of outcome.

Various age cutoffs were then used to divide the study population into two groups, and chi-square analysis was used to compare the number of children with one or both learning disabilities in the two groups. Three hundred and sixty-five days was used as a
cutoff age for analysis, as a child’s skull becomes rigid at one year of age. However, no statistically significant difference could be found between the two groups, probably because of the very small number of patients who had had cranial reconstruction surgery after one year of age (n=2). When 180 days (within 180 days n=23, >180 days n=8), 90 days (within 90 days n=11, >90 days n=20), and the median age at surgery of 105 days (within 105 days n=16, > 105 days n=15) were used as the age cutoffs to divide the study sample, the chi-square analysis in each case showed no statistically significant differences between the two groups in how many had one or both learning disabilities.

Types of learning disabilities in the study group were then investigated. The “ACID” profile is a particular type of learning disability identified with a pattern of decreased subtest scores in the arithmetic, coding, information, and digit span portions of the WISC-III. (Rourke, 1985) In this study, the mean score of these four subtests was compared to the mean score of the seven remaining subtests. An unpaired T-test showed that within the sample as a whole (n=31), there was no significant difference in the mean score of the ACID four subtests between the subjects with one or both types of learning disabilities (n=18) and those without a learning disorder (n=13). Another unpaired T-test showed no significant difference in the mean score of the remaining seven subtests between the same two groups. However, when one looked alone at the group of study subjects who had one or both learning disabilities (n=18), or at the group without learning disabilities (n=13), the mean score of the four ACID subtests is significantly lower than the mean score of the seven remaining subtests with p<0.001. This difference is greater in the group with learning disabilities. Thus, among children with learning disabilities, the mean
sum of the four ACID subtests scores were lower than the mean sum of the remaining seven subtests. This is suggestive of this subtype of learning disorder, although complete analysis of the ACID profile was not done.

This study also examined the adaptive behavior of the study subjects through the Vineland Adaptive Behavior Scales. This test consists of a communication domain, a daily living skills domain, and a socialization domain. For the group as a whole (n=31), the mean communication domain score was 94.3, the mean daily living skills score was 94.9, and the mean socialization score was 100.6. Paired T-tests among the three domains showed no significant differences between communication and daily living skills domain scores (p=0.86) or between socialization and communication domain scores (p=0.06), but did show a significant difference between socialization and daily living skills domain scores (p=0.036), the relevance of which is unclear.

The subpopulation of children found to have one or more learning disabilities (n=18) was then analyzed separately. In this population, the mean communication domain score was 93.5, the mean daily living skills domain score was 94.6, and the mean socialization domain score was 99.6. When the same three paired T-tests (n=17) among the three domains was performed on this population, none of the three differences reached statistical significance.

The sagittal and metopic groups were also analyzed separately. In the sagittal group, the mean communication domain score was 95.3 (n=16), the mean daily living skills score was 93.6 (n=16), and the mean socialization score was 99.3 (n=15). Again, paired T-tests showed no statistically significant differences among the domain scores in
this group. For the metopic group, the mean communication domain score was 94.2 (n=5), the mean daily living skills domain score was 106.2 (n=5), and the mean socialization domain score was 103.4 (n=5). Again, no significant differences among the domain scores was found by paried T-test.
Discussion:

This research study examined the longterm neuropsychological effects of birth with single-suture craniosynostosis. As anecdotal reports suggested that children born with craniosynostosis seemed to have more problems in school, the authors of this study believed it was necessary to go beyond studies of IQ alone, to determine whether or not more subtle, neuropsychological effects such as learning disabilities and/or psychosocial sequelae were present in these children. The findings of this study suggest that children born with single-suture craniosynostosis have significantly higher rates of learning disabilities than the general population.

Learning disabilities are representative of a discrepancy between a child’s apparent ability to learn, and his or her academic achievement. There are different types of learning disabilities, which tend to involve reading, language, and mathematics. To be classified as a learning disability the identified condition cannot be primarily due to mental retardation, emotional problems, disadvantage, or cultural differences. Approximately 5% of the total public school population in the U.S. are identified as having a learning disability. (Lyon, 1996) Estimates of the prevalence of learning disabilities range from 2% to 10%, depending on the definitions and methods used. (DSM-IV, 1994)

The results of intelligence testing in our study, as assessed by the Wechsler Intelligence Scale for Children - Third Edition, show that the mean verbal, performance, and full scale IQ's were within normal range for the study population, a finding consistent with Kapp-Simon et al.'s (1993) findings. However, one cannot conclude that
nonsyndromic craniosynostosis does not affect mental development based solely on IQ scores. More subtle discrepancies, such as learning disorders, attention disorders, and socialization difficulties, can also affect longterm outcome and could explain observations of children with craniosynostosis not being successful at later ages.

An older study population, currently between the ages of six and sixteen years, was chosen in the present study so that these more subtle effects on mental development could be examined. Our results show a statistically significant difference in the mean verbal and performance IQ's in both the sagittal synostosis group (n=16, p=0.02), and the group as a whole (n=31, p<0.001). These children had higher verbal than performance mean IQ's, with a mean difference of 8.3 points in the sagittal group, and 10.3 in the whole group.

Significant differences between verbal and performance IQ's are suggestive of a population at higher risk for learning disabilities. (Rourke, 1985) This possibility was explored by looking at differences between verbal IQ and WRAT reading achievement scores, and between verbal IQ and WRAT spelling scores, in order to identify children not functioning at the level of their measured innate intelligence. Using accepted criteria for learning disabilities (IQ-WRAT > 14) (DSM-IV, 1994), reading and/or spelling learning disabilities were identified in 58% of the children with clear single-suture craniosynostosis in the study (n=26). Among the specific subgroups of the study, 50% of the sagittal group, 80% of the metopic group, 60% of the unilateral coronal group, 60% of the “other” category, and 58% of the group as a whole were found to have one and/or both learning disabilities. If one dismisses the findings in the three middle groups due to small
sample sizes, the sagittal group (n=16) has an incidence of 50%, and the combined group of sagittal, metopic, and unilateral coronal synostosis (n=26) has an incidence of 58%, both of which are still much higher than the accepted prevalence of learning disabilities in the general population of 2% to 10% (DSM-IV, 1994). Furthermore, our incidence of learning disabilities may have been underestimated, as only spelling and reading learning disabilities were examined. The figures for the general population include all different types of learning disorders, including such conditions as mathematical disorders and disorders of written expression.

Delineation of the type of learning disabilities more prominent in this population of children might assist parents and teachers in identifying the disorders early, and intervening before the child incurs severe setbacks in school performance and self-esteem. As many children with learning disabilities are of normal intelligence, relatively simple procedural interventions can often make large differences in performance. The “ACID” profile has been identified in many children with learning disabilities, and is characterized by decreased scores in the arithmetic, coding, information, and digit span subtests on the WISC-III. (Rourke, 1985) Although the presence of this profile in our study sample was not studied in detail, when the groups of children with learning disorders (n=18) and those without (n=13) were examined separately, the mean score of the four ACID subtests was significantly lower than the mean score of the remaining seven subtests within both groups. Thus, among children identified as having one or both learning disabilities, a pattern of lower scores on the ACID subtests may be present, suggesting this specific
subtype of learning disability. Further analyses would be required in order to formally assess for the presence of the “ACID” profile.

The presence of higher mean verbal IQ scores than performance scores combined with the increased incidence of reading and/or spelling learning disorders in the study population might suggest the presence of a nonverbal learning disorder. Nonverbal learning disorder is a “nonclassical” learning disability, and is characterized by visuospatial disturbances, interpersonal and emotional problems, poorly arithmetic performance, and problems with social perception. (Ardila, 1997) Children with nonverbal learning disorder may have problems picking up subtle cues in social situations. (Rourke, 1995) One might expect these deficiencies to manifest themselves on tests of adaptive behavior. Pope et al. (1996) discuss the fact that adolescents with craniofacial anomalies in general, are exposed to various risk factors making them vulnerable to problems with social adjustment. However, when the Vineland Adaptive Behavior Scale scores were analyzed for the group (n=31), the mean socialization domain score (100.6) was actually higher than the mean communication domain score (94.3) and the mean daily living skills score (94.9). The absence of socialization problems does not exclude the diagnosis of nonverbal learning disorder. Socialization deficits may have been decreased by the improved cosmetic results of surgery. Additional work correlating socialization scores with appearance ratings could provide more information. (This is being studied currently.) The lower performance IQ scores and Developmental Test of Visual-Motor Integration scores in the study population is evidence of increased visual-motor problems in this population, which could be consistent with nonverbal learning disorder. However, the emphasis of
this study was to investigate whether a longterm effect of craniosynostosis on mental development existed. Further delineation of that effect will require future study.

A possible relationship between age at surgery and the presence of learning disabilities or VIQ/PIQ differences was explored to see if our data would support Renier and Marchac’s (1993) contention that children operated on at a younger age had better outcomes. However, correlative tests showed no relationship between age, the difference in verbal and performance IQ’s, the presence of a reading learning disability, and the presence of a spelling learning disability. Furthermore, no significant differences in the incidences of learning disabilities was found when the study population was divided using cutoff ages of 90 days, 180 days, 105 days (median age at surgery of study sample), or 365 days (age at which the child’s skull becomes rigid). However, the lack of statistical significance when 365 days (the cutoff used by Renier and Marchac) was used as the cutoff, is likely due to the small number of children in the group that had had cranial reconstruction after one year of age (n=2). Such a small number would make obtaining statistical significance very difficult. Thus, the importance of age at surgery warrants future investigation.

The significance of this study consists in its examination of longterm outcome of children born with simple craniosynostosis as measured not only by IQ, but also by other neuropsychological tests used to assess the incidence of learning disabilities. Kapp-Simon et al. (1993) themselves noted that their study focus was of overall cognitive development in infancy, and that their findings did not exclude the possibility of learning disabilities later in life. Moreover, their post-operative age at evaluation was approximately 47 months (at
the maximum). These authors recommended school age follow-up, which is the population studied in this report.

Optimally, one would like to compare children who had surgery for single-suture craniosynostosis to those who did not, rather than having a study population of only children who received surgical treatment. However, at Yale, as in the rest of the U.S., the vast majority of patients with craniosynostosis received surgery, disallowing an adequate number of patients in the non-surgery group to make significant comparisons. Furthermore, a randomized study for a clinically accepted procedure would be unethical.

Additionally, one would like to test patients pre- and post- surgery, to control for any effect that the procedure itself might have on development. However, most children have surgery within six months of age. Not only is it difficult to perform accurate testing at such a young age (IQ tests are not possible), but it is nearly impossible to assess the presence of learning disabilities. Learning disabilities cannot be adequately assessed until a child reaches school-age. It is unlikely that the results of this study were influenced by the study subjects’ surgical treatment. The most common type of craniosynostosis among the study sample was sagittal synostosis with $n=16$. Of the surgical techniques used in corrective surgery for single-suture craniosynostosis, the procedure for sagittal synostosis, a strip (linear) craniectomy, is the least invasive. This procedure consists of the removal (extradurally) of a small segment of bone, approximately two to three centimeters wide, along the course of the fused sagittal suture. Thus, the assumption is made that the postoperative results of this study represent the residual effects of craniosynostosis, and
not the surgery itself, as the possibility of injuring brain tissue by the surgery is extremely small.

Endriga and Speltz (1996) compared 19 infants born with sagittal synostosis to 20 infants without birth defects and matched the study group in age, gender, and other background factors. They used the Bayley Scales of Infant Development to assess the children at various points over time (including pre- and post-surgery), and found no significant difference in mental development among the two groups. However, the Bayley Scales of Infant Development measure the acquisition of developmental milestones with respect to motor and sensory function. This test is weighted towards sensory-motor function, and is not a measure of general intelligence. Furthermore, these authors again reported the need to look for any more subtle problems, such as with learning.

Sidoti et al.’s (1996) longterm study of children with metopic craniosynostosis attempted to assess the presence of mental retardation, learning disabilities, and behavioral problems, but relied on secondhand reports of this information (chart review and parental questionnaires). They did not perform neuropsychological testing for the purposes of the study. The authors found a “significant” incidence of mild neurologic disability in children with simple metopic synostosis, with more than a third of the patients having behavioral or cognitive problems. However, parental questionnaires are of highly questionable reliability as parents may be unaware of their child’s learning problems, or may not completely understand them. The authors believed that their methodology underestimated the true incidence of problems in this population, and suggested future investigations involving
psychometric testing. Sidoti et al. also found a slightly higher incidence of problems among the group that had surgery, but reported it to be statistically nonsignificant. Another possible reason for the discrepancy could be acquisition bias, as it is possible that those that did not have surgery had less severe deformity.

Trisdorfer et al. (1989) looked at learning disabilities by looking at medical history, school records, and parental information which could be verified. Their experience at the Craniofacial Clinic at the Children's Hospital of Philadelphia found that of the sixty eligible patients seen between January, 1988 and May, 1989, 43% had evidence of learning disabilities (the authors use a previous estimate of 10-15% in the general U.S. population for comparison). This study, however, did not limit itself to children with craniosynostosis, but looked at children with craniofacial malformations in general. Furthermore, the authors again did not perform neuropsychological testing.

In their study of pre- and post-parameters in seventeen cases of craniosynostosis, Turtas et al. (1993) did perform some neuropsychological investigation. They found that malformation of the facial skeleton pre-operatively was correlated to decreased intellectual function, and that larger cranial circumference and volume correlated with better intellectual function. However, the study consisted of only seventeen cases of varying types of synostosis, and the authors did not assess for the presence of learning disabilities.

Other criteria not included in our study but which could be incorporated into a study of longterm effects of craniosynostosis are intracranial volume and intracranial pressure. As previously discussed, studies of intracranial pressure in children with simple synostosis have not revealed a straightforward relationship between intracranial pressure,
intracranial volume, and neurodevelopmental outcome (Renier et al., 1982) (Noetzel et al., 1985) (Renier, 1989) (Gault et al., 1992). Cohen and Persing (In press) discuss the implications of intracranial pressure, noting that improvements in development and IQ have been found after cranial vault expansion in cases of documented elevated intracranial pressure. Arnaud et al. (1995) found that although the large majority of patients with scaphocephaly (sagittal synostosis) had normal intracranial pressure and normal mental function, the children found to have delays in mental function tended to be older and had elevated intracranial pressure more often than those with normal mentation. However, in their study of their twenty-year experience with isolated craniosynostosis, McCarthy et al. (1995) report that they saw no clinical or radiographic evidence of pre-operative elevated intracranial pressure in any of their cases of metopic and sagittal synostosis. However, they also state that they do not routinely monitor intracranial pressure. When available, intracranial pressure and volume are two variables which could be incorporated into future studies.

Thus, our study found that 58% of our sample of children born with single-suture craniosynostosis had a learning disability. Furthermore, of patients with a history of sagittal synostosis, previously thought to be a relatively benign condition, 50% had a reading and/or spelling learning disability. Future work in this area will help to solidify and elaborate upon the results of this study.
Conclusion:

This study went beyond measures of mental retardation, in an attempt to assess the incidence of more subtle neuropsychological sequelae in children born with single-suture craniosynostosis. The results of this study indicate that although, as found in previous studies (Kapp-Simon et al., 1993), subjects fall within the normal range for intelligence, there is a significantly higher incidence of learning disabilities in this group as compared with the general population. Of the 26 study subjects with sagittal, metopic, or unilateral coronal craniosynostosis, 58% were identified as having a learning disability. Furthermore, even among the sagittal group alone (n=16), 50% had a learning disability.

Although the psychosocial effects of disfigurement alone are enough to validate the need for surgery, the results of this study provide important information regarding “functional” outcome for parents considering treatment of a child with single-suture craniosynostosis.
Figure 1: Normal Cranial Sutures in Infancy

(reproduced from Shillito and Matson, 1968)
Figure 2:

(A) Premature synostosis: lateral view. Effect of craniosynostosis on skull shape. (B) Premature synostosis: superior view. Directional contribution of sutural growth to skull shape is illustrated by arrows. (From: Pruzansky, 1973.)

(reproduced from Kreiborg, 1981)
Figure 3: Morphologic expression of craniosynostosis. A, turbrachcephaly. B, plagiocephaly. C, trigonocephaly. D, scaphocephaly. (reproduced from Bartlett and Yu, 1994)
Figure 13.0. Left. Schematic diagram of sagittal synostosis. Arrows indicate direction of compensatory bone overgrowth in the frontal and occipital regions. Open arrows at squamosal sutures indicate sites of minimal asymmetric expansion. Right. Resulting skull shape in sagittal synostosis following asymmetric bony expansion occurring at the perimeter, coronal, and lambdoid sutures and symmetrical expansion occurring at the metopic suture. The squamosal suture does not participate significantly in this overgrowth, as it is distant to the fused sagittal suture. Bottom. Preoperative photograph of patient (from above) with sagittal synostosis.

(reproduced from Persing et al., 1989) Sagittal craniosynostosis
Figure 5: Characterization of bone growth and skull shape abnormalities seen with metopic synostosis. (- - -) indicates regions of reduced bone deposition. (+ + +) indicates regions of compensatory increased bone deposition.

(reproduced from Shaffrey et al., 1991)
Figure 6:

Left, Schematic diagram predicting the directions of abnormalities (arrows) in bone growth in the skull affected by metopic synostosis. Right, Fusion of the metopic suture results in reduced growth in the frontal bone medially, resulting in bifrontal narrowing; asymmetric compensatory expansion at the coronal suture associated with symmetrical expansion at the sagittal suture results in the characteristic trigon-shaped skull. Bottom, Preoperative photograph of a patient with metopic synostosis.

(reproduced from Persing et al., 1989) Metopic craniosynostosis
Figure 7: Left. Schematic diagram of predicted skull deformities associated with unilateral coronal synostosis. Right. Fusion of the left coronal suture results in flattening of the left frontoparietal region and bulging of the ipsilateral squamous portion of the temporal bone related to asymmetric bone deposition along the squamous suture. Similar asymmetric expansion at the perimeter metopic and sagittal sutures results in parietal bulging contralateral to the fused suture. The lambdoid suture does not participate significantly in this compensatory growth, as it is distant from the fused coronal sutures (open arrow). The right coronal suture in line with the fused suture demonstrates significant, symmetrical bony expansion. Bottom. Preoperative photograph of patient with unilateral coronal synostosis.
Figure 13.9. Left. Schematic diagram of bilateral coronal synostosis. Arrows indicate predicted direction of compensatory growth. Right. Offsetting asymmetric growth influences at the metopic and sagittal sutures results in symmetrical expansion in these areas. A perimeter suture, the squamous suture, without such offsetting asymmetric influences, develops asymmetric bone growth at the squamous suture margin, resulting in temporal bulging. Open arrows at lambdoid suture, located distant to the coronal suture, compensate only to a slight degree. Bottom, Preoperative photograph of patient with bilateral synostosis.

(reproduced from Persing et al., 1989) Bilateral coronal craniosynostosis
Figure 9:

Figure 5. Serial photographs of a child who underwent subtotal calvarectomy with cranial remodeling (Group II) for sagittal synostosis at 6 months of age. 
A. Lateral, preoperative at 5 months of age. B. Lateral, 3 months postoperative at 9 months of age. C. Lateral, 2 years postoperative at 2 years, 8 months of age.

(reproduced from Marsh et al., 1991)

A = preoperative sagittal craniosynostosis  
B = 3 months postoperative  
C = 2 years postoperative

figure continued on next page
Figure 9 (continued):

D, Top: preoperative at 5 months of age. Cranial index = 62. E, Top: 3.5 months postoperative at 9 months of age. Cranial index = 68. Note that while this postoperative cranial index is the lowest for Group II (see Figure 7), the large magnitude of change in index was characteristic for the group.

(reproduced from Marsh et al., 1991)

D = preoperative sagittal craniosynostosis
E = 3.5 months postoperative
Figure 10:


(reproduced from Eppley and Sadove, 1994)

A - D = preoperative metopic craniosynostosis
Figure 10 (continued):

(reproduced from Eppley and Sadove, 1994)

A - D = postoperative metopic craniosynostosis
Figure 11:

Figure 11. A, Pre- and B, postoperative photographs of a child with right synostotic frontal plagiocephaly and contralateral "head tilt." She had correction of the deformity at 7 months of age using the bilateral technique illustrated in Figure 9. Her preoperative radiograph is shown in Figure 5.

(reproduced from Hansen and Mulliken, 1994)

A = preoperative right unilateral coronal craniosynostosis
B = postoperative
References


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