Treatment type is associated with population hand preferences in patients with unilateral coronal synostosis: implications for functional cerebral lateralization.

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Operative treatment of craniosynostosis remains the gold standard, yet there is considerable disagreement among clinicians as to the optimum age of correction and the “best” type of procedure. Notwithstanding the aesthetic concerns, most of the controversy in the care of patients with craniosynostosis centers on the primary objective of treatment: limiting or avoiding adverse neurodevelopmental effects. Cranial expansion normalizes intracranial pressure when it is elevated, but the beneficial or protective effect of these procedures on overall cognition is less defined.

Variables that may adversely impact cognitive function of patient with craniosynostosis include the presence of certain associated syndromes, the number of affected sutures, the timing of surgical intervention, and, possibly, the type of procedure.

Background: Left-handedness is a highly conserved marker of cerebral functional laterality in the human population; elevated rates of left-handedness have been documented in patients with unilateral coronal synostosis treated with fronto-orbital advancement. The purpose of this study was to determine whether the prevalence of left-handedness in patients with nonsyndromic unilateral coronal synostosis is related to treatment.

Methods: The incidence of left-handedness was compared among three groups: patients who were previously treated for unilateral coronal synostosis with endoscopic suturectomy and postoperative helmet therapy (group I); patients with unilateral coronal synostosis managed with fronto-orbital advancement (group II); and healthy, unaffected controls (group III).

Results: Group I was composed of 19 patients; the side of synostosis was equally distributed (nine right and 10 left), and female gender was more common (n = 13). Mean age at endoscopic suturectomy and helmet therapy was 85.3 days, and the determination of handedness was performed at a mean age of 89.3 months. The rate of left-handedness in group I was 5.3 percent, not significantly different from that of the controls (group III) (11.5 percent) (p = 0.69) but significantly less than that observed in the fronto-orbital advancement patients (group II) (30.2 percent) (p = 0.023).

Conclusions: Patients who underwent endoscopic suturectomy and helmet therapy for nonsyndromic unilateral coronal synostosis and healthy controls demonstrated functional cerebral lateralization with respect to handedness that differed from patients who underwent fronto-orbital advancement. The reason may be related to the type of procedure, secondary effects of general anesthesia, or age at which the procedure was performed.
performed. Even patients with single-suture synostosis, the majority of whom have normal range intelligence, demonstrate subtle developmental abnormalities that suggest some permanent alteration of brain function. These functional differences may be the result of mechanical (local or diffuse pressure on the developing cerebrum), physiologic (molecular alterations that caused the fusion and affects cerebral development), or iatrogenic (e.g., anesthesia-induced neural apoptosis) influence. Regardless of cause, these alterations to cerebral activity are permanent and manifest as subtle and problematic cognitive disabilities.

We previously reported that patients with unilateral coronal synostosis treated with conventional fronto-orbital advancement are three times more likely to be left-handed than unaffected age-matched controls (50.2 percent versus 11.4 percent). Furthermore, the prevalence of left-handedness was over twice as high when the fusion was on the left compared with the right side (44.4 percent versus 20.4 percent). Although the reason for this change was unclear, it signified an unequivocal alteration of normal functional cerebral laterality (i.e., functional specialization of the hemispheres) in this population. The present study examines the incidence of left-handedness in a cohort of patients with nonsyndromic unilateral coronal synostosis who underwent endoscopic suturectomy and helmet therapy. The result is compared to our previously reported cohort of unilateral coronal synostosis patients and an age-matched control group to determine whether this procedure, which is shorter, less invasive, and typically performed at a younger age than fronto-orbital advancement, affects this manifestation of cerebral functional laterality.

PATIENTS AND METHODS

After obtaining institutional review board approval, the authors performed a review of a prospectively gathered database for patients aged 6 months or younger undergoing endoscopic suturectomy and helmet therapy for nonsyndromic unilateral coronal synostosis at a large craniofacial center from July of 2004 to March of 2010 (group I). The procedure is a simple suturectomy performed with endoscopic assistance through two short incisions. Postoperative helmet therapy is initiated approximately 1 week after the procedure and continued until the desired phenotype is achieved or until 12 months of age. Demographic data included sex, laterality of synostosis, age at endoscopic release, and age at follow-up. Patients with mutations implicated in unilateral coronal synostosis (FGFR2, FGFR3, Pro250Arg EFNB1, and TWIST) were excluded from the study. Families were contacted at clinical follow-up or by telephone; parents were queried as to which hand their child used specifically for writing. Left-handedness was defined as the preferred use of the left hand for writing; ambidexterity was defined as equal use of either hand for writing.

Statistical Analysis

Results were compared to our previously published data from the same authors, comparing left-handedness in patients undergoing bilateral fronto-orbital advancement for nonsyndromic unilateral coronal synostosis (group II) with normal controls (group III). To maximize consistency across data sets, age at inquiry (in years) was coded as an integer, as had been done in the earlier data set. Independent unpaired t tests were used to compare continuous variables between two groups. Chi-square analyses were used to compare categorical data between groups. Three-group comparisons for continuous variables were performed with analysis of variance. Univariate paired comparisons were corrected for multiple testing using a Bonferroni adjustment. The main planned comparison was between the endoscopic suturectomy and helmet therapy group and open fronto-orbital advancement. Logistic regression was used to perform a multivariate test of the association between left-handedness and treatment while adjusting for the covariates age at inquiry, laterality, and sex (multiple testing correction was not necessary here because it is implicit in the multivariate approach). All tests were performed using SPSS Version 16 (SPSS, Inc., Chicago, Ill.) and SAS version 9.3 (SAS Institute, Inc., Cary, N.C.), with values of \( p < 0.05 \) considered significant. In paired comparisons, when two comparisons were made, a value of \( p < 0.025 \) was required for significance.

RESULTS

A total of 19 consecutive endoscopic suturectomy and helmet therapy patients were identified in group I. No patients were excluded. The male-to-female ratio was 6:13. Side of synostosis was similar to that of group II, with nine patients (47.4 percent) having right unilateral coronal synostosis (Table 1). Mean age at endoscopic suturectomy and helmet therapy was 2.8 ± 1.3 months. Mean age at follow-up was 7.6 ± 1.7 years. Group II (standard open fronto-orbital advancement) was composed of 86 patients. Fifty-eight patients...
Table 1. Patient Characteristics by Treatment Group*  

<table>
<thead>
<tr>
<th>Variable</th>
<th>I (ES + HT)</th>
<th>II (Open FOA)</th>
<th>III (Healthy Controls)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>19</td>
<td>86</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>13 (68.4%)</td>
<td>58 (67.4%)</td>
<td>54 (56.3%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Right UCS laterality</td>
<td>9 (47.4%)</td>
<td>51 (59.3%)</td>
<td>NA</td>
<td>0.39</td>
</tr>
<tr>
<td>Age at endoscopic release, mo</td>
<td>2.8 (1.3)</td>
<td>9.9 (8.1)</td>
<td>NA</td>
<td>0.0002</td>
</tr>
<tr>
<td>Age at inquiry, yr</td>
<td>7.6 (1.7)</td>
<td>8.8 (5.1)</td>
<td>9.9 (3.5)</td>
<td>0.049</td>
</tr>
<tr>
<td>Left-handedness</td>
<td>1 (5.3%)</td>
<td>26 (30.2%)</td>
<td>11 (11.5%)</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

ES + HT, endoscopic suturectomy and helmet therapy; FOA, fronto-orbital advancement; UCS, unilateral coronal synostosis.

*Mean (SD) or no. (%) is shown. For left-handedness, the difference between ES + HT and open FOA was significant (p = 0.023), but the difference between ES + HT and healthy controls was not (p = 0.69).

(67 percent) were girls and 51 (58 percent) had right unilateral coronal synostosis. Mean age at fronto-orbital advancement was 9.9 ± 8.1 months and mean age at follow-up was 8.8 ± 5.1 years. A total of 96 healthy controls were recruited; there were 54 girls (56 percent) and the mean age at inquiry was 9.9 ± 3.5 years (Table 1).

Chi-square analysis comparing the three treatment groups (3 × 2 contingency table) documented no significant differences in sex among the three groups (p = 0.25). Testing of differences in age at follow-up using one-way analysis of variance documented small but significant differences between groups (p = 0.049). Finally, left-handedness was significantly different between groups (p = 0.0015). For the main planned comparison between endoscopic suturectomy and helmet therapy and open fronto-orbital advancement, there were no significant differences in sex (p = 0.93), unilateral coronal synostosis laterality (p = 0.39), or age at inquiry (p = 0.08), but age at treatment was significantly lower in endoscopic suturectomy and helmet therapy (p < 0.0001). Left-handedness was significantly lower in endoscopic suturectomy and helmet therapy (5.3 percent) compared with fronto-orbital advancement (30.2 percent) (p = 0.023) but not significantly different from left-handedness in healthy controls (11.5 percent) (p = 0.69) (Fig. 1).

On multivariate analysis, treatment group remained significantly associated with handedness after adjusting for age at inquiry, laterality, and sex (p = 0.0011). Compared with the fronto-orbital advancement group, controls were significantly less likely to be left-handed (OR, 0.25; 95 percent CI, 0.11 to 0.57; p = 0.0009), as were those who underwent endoscopic suturectomy and helmet therapy (OR, 0.12; 95 percent CI, 0.01 to 0.96; p = 0.045).

DISCUSSION

Humans and other higher primates manifest many forms of nonrandom functional cerebral laterality such as speech and language, visual and auditory preference, and footedness and handedness. Although the significance of these forms of hemispheric specialization in humans and other animals has been debated, the highly conserved nature of these findings appears to suggest some evolutionary or adaptive advantage. Handedness is the most conspicuous and, consequently, most widely studied area of cerebral functional lateralization. The population distribution of hand preference is remarkably constant and ranges from 8 to 12 percent. Models to explain the persistent finding of left-handedness in human populations include genetic theories, environmental, and combination. A popular genetic theory maintains that humans are naturally right-handed and are homozygous for a “right-shift” allele. Heterozygotes are equally likely to be right- or left-handed. This model may explain familial left-handedness and the consistent prevalence of left-handedness across all human populations, but is not universally accepted. Environmental, or “pathologic,” left-handedness occurs in association with brain injury in children, such as infection or trauma, low birth weight, prematurity, and right congenital hemiplegia (left hemispheric insult). The increased incidence of left-handedness in these groups is well described, although the majority of left-handed people have no demonstrable history of cerebral insult. Satz suggested that left-handedness in a population is a combination of both genetic and pathologic influences.

This study demonstrates that patients with unilateral coronal synostosis treated with endoscopic suturectomy and helmet therapy have a handedness distribution that is not different from that of the normal population, but is markedly lower than the 30.2 percent left-handedness prevalence we previously reported in patients after fronto-orbital advancement for the same condition. Although we are unable to comment on the underlying reason(s) for this disparate finding, it suggests that some empirically observed aspects of
cognitive function (in this case, functional laterality) are not inherent in the condition and may be altered by the type and/or age of treatment. There are many differences between the fronto-orbital advancement procedure used to treat our historical cohort of unilateral coronal synostosis patients and the endoscopic procedure used in this report. Specifically, the fronto-orbital advancement is more invasive and longer in duration, and has a higher risk of transfusion. Moreover, the endoscopic release was performed at a much younger age. It is impossible to determine which, if any, of these variables is responsible for the dramatic shift of cerebral functional laterality that we observed in our fronto-orbital advancement patients, but each has reason for consideration.

The extensive dissection and bone repositioning required to perform the fronto-orbital advancement procedure may have adverse effects on neural development. A conventional fronto-orbital advancement obligatorily strips perios- teum and dura not only from the affected coronal suture but also from the contralateral open coronal suture and the anterior aspect of the sagittal suture. Several recent reports suggest that this type of manipulation can alter normal sutural patency and induce premature fusion of previously uninvolved sutures. This can affect subsequent cranial growth and may increase the risk of latent intracranial hypertension.

The adverse effects of general anesthetic on the developing infant brain may also alter neural development. There is a growing body of literature that suggests prolonged exposure to certain inhalational anesthetic agents can induce neural apoptosis and developmental delay in animal models and in human infants. This effect is inversely proportional to age (younger more affected) and positively correlated with duration (longer more detrimental). Endoscopic suturectomy and helmet therapy is performed at a younger age, but the duration of anesthesia is typically less than 1 hour. By comparison, fronto-orbital advancement is traditionally performed at a later age, but requires at least 3 to 4 hours of general anesthesia. In addition, the fronto-orbital advancement requires a greater overall physiologic challenge to the infant and, often, a blood transfusion; the effect of those factors is unclear.

Another possibility is that there is a benefit to early release. Patel et al. found that age at operative correction of sagittal synostosis was inversely correlated with cognitive outcomes. This effect was observed in both of their treatment groups, extensive remodeling procedure and an endoscope-assisted procedure, but the open procedure performed better overall. Although the authors classified the minimally invasive procedure as an endoscope-assisted suturectomy, the technique used was effectively a pie procedure because it included a posterior cinching suture and extensive lateral wedge barrel staves. Mathijsen et al. found no benefit to early release in 220 patients with unilateral coronal synostosis. Although it is possible to perform fronto-orbital advancement at a younger age, there are several potential disadvantages to this approach. Early fronto-orbital advancement has been associated with a higher rate of relapse than the same...
procedure performed at an older age. Moreover, there is a higher overall anesthetic-related complication rate in children younger than 6 months, and the risk of neural apoptosis would theoretically be compounded in a younger infant. For these reasons, we have avoided early open release and typically perform these procedures at approximately 9 months of age.

There are several important limitations to this study. The minimum age of children in this investigation and our prior cohort was 4 years. Some authors have suggested that hand preference can change up to 9 years of age, but most authorities posit that handedness is fixed before 4 years of age. Another potential weakness of our study was using parental opinion to assess hand preference. Some investigators rely on various modifications of the Edinburgh Handedness Inventory. However, this methodology has also been criticized because such questionnaires assess only the examinee’s recollection of hand preference. It is known that subjects who indicate certain hand preferences on a questionnaire often do not, in practice, validate their answer when observed directly. Nevertheless, although other mechanical tasks can be learned equally well with either hand, writing cannot. Studies confirm that writing but not other measurements of hand performance correlates strongly with scores on two handedness inventories. Our methodology finds vindication in the fact that the distribution of handedness in our control group was nearly identical to that of reports that used more complex methods of ascertaining. Finally, our sample size in the endoscopic suturectomy and helmet therapy group was not large, and the left-handedness event rate was low. The fact that we found a very strong correlation between treatment group and left-handedness indicates that power was not a problem for this study, but our findings cannot be taken as conclusive proof that fronto-orbital advancement increases left-handedness prevalence or that endoscopic suturectomy and helmet therapy reduces it. Further confirmation of this finding is needed from additional studies. Also, we cannot assume that the effect from treatment to left-handedness is a causal one: investigation of in utero handedness and whether it changes after treatment might shed more light on the question of causation.

CONCLUSIONS

Patients who underwent endoscopic suturectomy and helmet therapy for nonsyndromic unilateral coronal synostosis, and healthy controls, demonstrate functional cerebral lateralization with respect to handedness that differs from that of patients who underwent fronto-orbital advancement. Prevalence of left-handedness observed in patients undergoing endoscopic suturectomy and helmet therapy was significantly lower than in those who underwent open fronto-orbital advancement. It is possible that the type of procedure, secondary effects of general anesthesia, or age at which the procedure was performed might have affected left-handedness, but further work at additional centers is needed to confirm this finding, and to investigate a possible causal connection.

REFERENCES

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