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Intracranial Volume and Whole Brain Volume in Infants With Unicoronal Craniosynostosis

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Abstract

Objective—Craniosynostosis has been hypothesized to result in alterations of the brain and cerebral blood flow due to reduced intracranial volume, potentially leading to cognitive deficits. In this study we test the hypothesis that intracranial volume and whole brain volume in infants with unilateral coronal synostosis differs from those in unaffected infants.

Design—Our study sample consists of magnetic resonance images acquired from 7- to 72-week-old infants with right unilateral coronal synostosis prior to surgery ($n = 10$) and age-matched unaffected infants ($n = 10$). We used Analyze 9.0 software to collect three cranial volume measurements. We used nonparametric tests to determine whether the three measures differ between the two groups. Correlations were calculated between age and the three volume measures in each group to determine whether the growth trajectory of the measurements differ between children with right unicoronal synostosis and unaffected infants.

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Portions of this work were presented at the American Cleft Palate–Craniofacial Association meeting in Fort Worth, Texas (March 16–20, 2010).

Results—Our results show that the three volume measurements are not reduced in infants with right unicoronal synostosis relative to unaffected children. Correlation analyses between age and various volume measures show similar correlations in infants with right unicoronal synostosis compared with unaffected children.

Conclusions—Our results show that the relationship between brain size and intracranial size in infants with right unicoronal synostosis is similar to that in unaffected children, suggesting that reduced intracranial volume is not responsible for alterations of the brain in craniosynostosis.

Keywords

brain volume; coronal craniosynostosis; cranial development; intracranial volume

Single-suture craniosynostosis occurs in about 1 in 2000 live births (Cohen and MacLean, 2000) and has been associated with brain dysmorphology (e.g., Marsh et al., 1997; Aldridge et al., 2002; Aldridge et al., 2005). Of children with single-suture craniosynostosis, 24% have simple coronal craniosynostosis, where only one coronal suture fuses prematurely (Cohen and MacLean, 2000). Traditional ideas about craniosynostosis suggest that premature fusion of cranial sutures restricts growth of the brain by limiting the amount of space within the cranial vault (e.g., Aoki, 1984; Dufresne et al., 1987; Fernbach and Feinstein, 1991; Camfield et al., 2000). Suture release and/or cranial reconstruction is often recommended to allow unhindered growth of the brain, thus minimizing potential neurodevelopmental delays yet improving the cosmetic appearance of children with craniosynostosis (Renier et al., 2000; Sgouros, 2005; Kapp-Simon et al., 2007; Hukki et al., 2008).

The effects of craniosynostosis on the contents of the cranial cavity, specifically intracranial volume (ICV) are of special concern in considering the prognosis for a given patient, as well as the decision to proceed with surgical intervention. A number of studies have shown decreased ICV in children with either syndromic or nonsyndromic craniosynostosis (Sgouros et al., 1999). Some studies have indicated that children with unicoronal synostosis (UCS) often show decreased ICV (Lichtenberg, 1960; Gault et al., 1990; Camfield et al., 2000); whereas, other studies indicated similar or increased ICV measures in children with UCS compared with unaffected children (Fok et al., 1992; Polley et al., 1998; Netherway et al., 2005). Sgouros and colleagues (1999 Sgouros and colleagues (2005) found that ICV is initially decreased in infants with UCS but then increases to normal values after 6 months of age.

Decreased ICV is implicated as increasing physical constraint, limiting overall growth of the brain (Aoki, 1984), and ultimately altering intracranial morphology. In addition to the potential physical constraints resulting from the hypothesized reduced cranial capacity in children with craniosynostosis, it has been suggested that decreased ICV values correspond with increased intracranial pressure (ICP), which may cause neurodevelopmental delays (Carmel et al., 1981; Camfield et al., 2000; Renier et al., 2000; Bristol et al., 2004; Guo et al., 2007). Studies of infants and children suspected of having elevated ICP reported that approximately 4% to 25% of children with UCS actually demonstrate it, indicating that the vast majority did not display elevated ICP (Renier et al., 1982; Renier et al., 1987; Thompson et al., 1995; Cohen and Persing, 1998; Renier et al., 2000; Eide et al., 2002; Bristol et al., 2004). The link between decreased ICV and elevated ICP is tenuous; a strong relationship between ICP and ICV has yet to be identified in infants with either syndromic or nonsyndromic craniosynostosis (Fok et al., 1992; Gault et al., 1992; Tamburrini et al., 2005). Furthermore, studies of a rabbit model for UCS have shown mixed results for significantly elevated ICP compared with unaffected rabbits (Mooney et al., 1998; Fellows-Mayle et al., 2004).

The chain of logic in traditional theories of growth in craniosynostosis is that premature suture fusion leads to decreased ICV, which then constrains growth of the brain, either through increased ICP or other physical constraints. Though we cannot measure ICP or constraint, we are able to measure ICV. If it is shown that ICV does not differ in infants with craniosynostosis, then we must reconsider the possible effects of craniosynostosis on ICV, brain growth, and ICP. To determine the association of unicoronal synostosis with intracranial volume and brain size, three null hypotheses were tested during the course of this study: (1) ICV does not differ between infants with craniosynostosis and age-matched unaffected infants; (2) whole brain volume (WBV) does not differ between the two groups of infants; and (3) the volume of cerebrospinal fluid space (CSF) does not differ between the two groups. These hypotheses were tested by quantitatively comparing ICV, WBV, and volume of CSF in age-matched samples of infants with right unicoronal synostosis (RUCS) and unaffected infants using magnetic resonance (MR) images.

Materials and Methods

The study sample consists of whole brain, three-dimensional MR images from infants ranging in age from 7 to 72 weeks ($N = 20$; Table 1) and acquired at St. Louis Children's Hospital or Oklahoma University Medical Center. All image data were collected and archived following approved institutional review board protocols. This number includes 10 infants diagnosed with isolated RUCS and 10 age-matched infants unaffected by craniosynostosis (UA). Scans were acquired prior to surgery for the infants with coronal synostosis. Upon inspection of radiological images, all infants with RUCS demonstrated patency of the remaining cranial sutures. Infants unaffected by craniosynostosis were scanned due to suspected medical conditions (e.g., suspected concussions, unexplained seizures) but were subsequently determined to display no synostoses or other neurological or craniofacial anomalies. None of the infants included in the study had associated anomalies of the extremities or a family history of craniosynostosis. Four of the 10 patients with RUCS were screened for FGFR3 P250R mutations, with negative results. Though none of these infants were determined on clinical presentation to have any defined craniosynostosis-related syndromes, the presence of a mild form of Muenke syndrome could not be excluded for six of the patients in the absence of FGFR3 P250R testing.

Image Acquisition, Data Collection, and Analysis

Magnetic resonance images were obtained in the sagittal plane using a MPRAGE sequence and a 256×256 matrix (Table 1). The MR images were analyzed using Analyze 9.0 software (Mayo Clinic, Rochester, MN) to measure ICV, WBV, and volume of CSF. Analyze[®] allows the user to select a region of interest (ROI), calculating volume (mm^3) from the image resolution parameters (Fig. 1). The ROI selected to represent ICV included the entire intracranial cavity, after defining a plane through the foramen magnum. The ROI representing WBV included the cerebral hemispheres, midbrain, cerebellum, and brainstem to the level of the foramen magnum, excluding ventricles, venous sinuses, cranial nerves, and blood vessels. The last ROI, representing CSF, incorporated ventricular spaces, including the lateral ventricles, third ventricle, aqueduct, and fourth ventricle. Other CSF spaces were included in a separate ROI.

The ICV, WBV, and CSF were compared between the two groups of infants using nonparametric Mann-Whitney U tests. In addition to pairwise comparisons of these measures, correlations between age and each of the three measures were estimated using the Spearman rank tests for infants with RUCS and UA infants. Tests for equality of the correlation coefficients for each group were also completed. Statistical analyses were completed with Systat 11.0 software (Systat Software, Chicago, IL).

Results

Initial comparisons show that infants with RUCS have slightly larger WBV and ICV values (3% and 2.5% larger, respectively) as compared with UA infants (Fig. 2). However, results of Mann-Whitney *U* tests did not determine these differences between RUCS and UA for WBV and ICV to be statistically different ($p > .05$; Table 2). The CSF measures were not different for infants with RUCS and UA infants (0.0%; $p > .05$; Table 2).

Spearman rank tests to estimate correlations between age and volume measures were completed for both RUCS and UA (Table 3). These correlations are high for all measures in both groups of infants. As expected, WBV, ICV, and CSF increase with age for both groups of infants. The infants with RUCS show slightly higher correlation values as compared with UA infants for all measures, but these differences in correlations did not reach statistical significance (Table 3).

Discussion

Brain morphology in infants with craniosynostosis may reflect a response to the changes in the cranial vault associated with premature fusion of sutures (e.g., Gault et al., 1992; Mooney et al., 1998; Cooper et al., 1999). However, not all of the differences observed in the skull are reflected in shape of the brain, including differences in the brain in infants with RUCS (Aldridge et al., 2005). Many of the changes in the brain of infants with craniosynostosis noted by Aldridge and colleagues (2002, 2005) are not localized to the prematurely fused suture but demonstrate a complex developmental relationship between brain and skull during development (Richtsmeier et al., 2006).

Children with single-suture craniosynostosis have been shown to have a mild to moderate risk for neurodevelopmental delays (Speltz et al., 2004; Kapp-Simon et al., 2007; Speltz et al., 2007; Starr et al., 2007). The effects of craniosynostosis on neurodevelopment and cognition via changes in intracranial volume and intracranial pressure have received considerable attention in the craniosynostosis literature. Decreased intracranial volume and concomitant dysmorphologies of the skull are thought to increase intracranial pressure within the cranial vault (e.g., Mooney et al., 1998; Rich et al., 2003). Using MR data, this study compared ICV, WBV, and CSF in infants with RUCS and unaffected infants between 7 and 72 weeks old. Our results show that none of these values differ significantly in infants with craniosynostosis in this age range. In fact, most ICV and WBV measures were similar or slightly larger in RUCS infants at various ages (Fig. 2). These results concur with a number of studies using computed tomography scans (e.g., Fok et al., 1992; Polley et al., 1998; Netherway et al., 2005). This study further indicates the tenuous relationship between decreased ICV and UCS. These results may not be representative of the situation in infants with other types of single-suture synostoses, including bicoronal craniosynostosis, or multi-suture craniosynostosis syndromes. Fellows-Mayle and colleagues (2004) found differing results in the elevation of ICP depending on the timing (early versus late) and degree (unicoronal versus bicoronal) of craniosynostosis in rabbits. Further investigations into other types of craniosynostosis are required.

Because this study did not measure either ICP or neurodevelopment in infants with craniosynostosis, it is not appropriate to discuss whether these individuals are at risk for increased ICP or developmental delays. Increased ICP may be multifactorial in causation and may have multiple etiologies. Although ICV and WBV differences were not demonstrated in this study, localized differences demonstrated in the brains of infants with single-suture synostoses (Aldridge et al., 2005) may play a role in the neurodevelopmental delays noted in some infants and children with craniosynostosis. Indeed, tests for specific

neurocognitive functions are necessary to determine how various single-suture synostoses affect cognition. As suggested by Kapp-Simon and colleagues (2007), studies of neurodevelopmental delays may be more informative about the effects of synostoses than global tests of cognition across mixed samples.

The lack of effect on whole brain morphology in UCS further demonstrates how little we understand the interaction between brain and skull in development, especially in craniosynostosis. Indeed, it is unknown whether the primary insult is within the developing brain, the skull, or both, and it is not possible to ascertain that information with this sample. Though the relationship between skull and brain in infants with craniosynostosis is complex (Richtsmeier et al., 2006), it is clear from our study that this complex relationship is not based upon differences in overall size of the skull or brain.

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FIGURE 1. Sagittal slices and three-dimensional reconstructions from an MR image of an infant with RUCS. The left column shows the outline of the ROI (top) and reconstruction (bottom) representing ICV. The right column shows the ROI outline (top) and three-dimensional reconstruction (bottom) for WBV.

FIGURE 2. Whole brain volume (top), ICV (middle), and volume of CSF (bottom) for unaffected infants and infants with RUCS.

TABLE 1
Study and Image Parameters (Resolution) for the Magnetic Resonance Images of Each Infant*

RUCS (N = 10)				UA (N = 10)			
Age (wk)	Resolution (mm)			Age (wk)	Resolution (mm)		
	Pixel	Slice Thickness			Pixel	Slice Thickness	
7	0.78	1.3		8	0.78	1.0	
9	0.94	1.0		11	1.09	2.5	
19	0.98	1.2		15	0.78	1.2	
22	0.93	1.0		16	0.97	1.2	
26	0.9	1.3		32	0.93	1.3	
35	1.0	1.0		33	0.78	1.3	
39	0.93	1.2		38	1.0	1.0	
44	0.93	0.9		49	0.85	1.2	
54	0.98	1.3		53	0.78	1.2	
70	1.0	1.0		72	0.78	1.2	

* RUCS = right unicoronal synostosis; UA = unaffected.

TABLE 2

Mean Whole Brain Volumes (WBV), Intracranial Volumes (ICV), and Volume of Cerebrospinal Fluid Spaces (CSF) for Infants With Right Unicoronal Synostosis (RUCS) and Unaffected Infants (UA) *

	Whole Brain Volume (mm ³)	Intracranial Volume (mm ³)	CSF (mm ³)
RUCS	789,506	997,065	207,558
UA	766,365	972,118	205,753
% difference	3.0	2.5	0.0
<i>p</i> value	1.00	.821	.762

* WBV, ICV, and CSF volumes for the two groups of infants are compared as percentage of difference. The results of Mann Whitney *U* tests for differences in the two groups are shown as *p* values.

TABLE 3

Spearman Correlation Coefficients for Whole Brain Volume (WBV), Intracranial Volume (ICV), and Volume of Cerebrospinal Fluid Spaces (CSF) With Age for Infants With Right Unicoronal Synostosis and Unaffected Infants^{*}

	WBV	ICV	CSF
RUCS	.927	.952	.915
UA	.903	.927	.879
<i>p</i> value	.920	.964	.676

^{*} Results (*p* values) of hypothesis testing for differences in correlation coefficients for the two groups are shown in the last row.