Published in final edited form as:
Childs Nerv Syst. 2012 July ; 28(7): 1083–1090. doi:10.1007/s00381-012-1731-y.

Brain volume and shape in infants with deformational plagiocephaly

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Abstract

Purpose—Infants with deformational plagiocephaly (DP) have been shown to exhibit developmental delays relative to unaffected infants. Although the mechanisms accounting for these delays are unknown, one hypothesis focuses on underlying differences in brain development. In this study, we used MRI to examine brain volume and shape in infants with and without DP.

Methods—Participants included 20 infants with DP (mean age= 7.9 months, SD=1.2; *n*=12 male) and 21 controls (mean age= 7.9 months, SD=1.3; *n*=11 male). Measures included volumes of the total brain and cerebellum; midsagittal areas of the corpus callosum and cerebellar vermis; and linear distance measures used to quantify the shape of selected brain structures. We also evaluated the association between shape measures and developmental scores on the Bayley Scales of Infant and Toddler Development-III (BSID-III).

Results—Brain volume did not distinguish cases and controls (*p*=.214–.976). However, cases exhibited greater asymmetry and flattening of the posterior brain (*p*<.001–.002) and cerebellar

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vermis (p=.035), shortening of the corpus callosum (p=.012), and differences in the orientation of the corpus callosum (p=.005). Asymmetry and flattening of brain structures were associated with worse developmental outcomes on the BSID-III.

Conclusions—Infants with DP show differences in brain shape, consistent with the skull deformity characteristic of this condition, and shape measures were associated with infant development. Longitudinal studies, beginning in the neonatal period, are needed to clarify whether developmental effects precede or follow brain deformation.

Keywords

Plagiocephaly; Infant; MRI; Development

Introduction

Deformational plagiocephaly (DP) refers to asymmetry or flattening of the infant skull secondary to external force. Typical manifestations include a parallelogram shaped skull, with flattening of the left or right occiput, ipsilateral frontal bossing, and contralateral occipital bulging [8, 15]. Other forms of deformation include brachycephaly (flattening of the central occiput) and dolichocephaly (flattening of both sides of the skull). Severity varies widely, ranging from mild flattening of the skull to notable asymmetry with secondary ipsilateral anterior ear displacement and mandibular and maxillary deformation [8, 15, 26, 31]. The incidence of DP has steadily increased over the past 15 years, from an estimated 5% in the mid-1990s [17] to 20–30% currently [16, 23]. This increase is largely attributed to the “Back to Sleep” campaign and similar efforts in other countries that urge parents to position their babies in supine for sleep [17].

Although usually considered a benign and minor cosmetic condition, accumulating evidence suggests that children with DP have increased risk for developmental delays [12, 13, 18, 25, 29], though the mechanisms for this association are unclear. Such delays might reflect pre-existing differences in central nervous system (CNS) development, which make infants vulnerable to skull deformation due to limitations in their mobility. DP may then be the consequence, rather than the cause, of early developmental delays. This is currently the prevailing viewpoint [19] and the most parsimonious explanation to date for observed developmental delays in this population. However, it is possible that delays in this population also result from the deformation of underlying brain structures [11]. There is tentative evidence from the study of premature infants that cortical structures ‘shift’ to conform to positional skull deformities. Mewes et al. [24] found that premature infants, who tend to develop a dolichocephalic head shape, show a commensurate shift in brain parenchyma. Although a similar process would be expected to occur in infants with DP, we are unaware of prior neuroimaging studies that have detailed the extent and nature of such effects. Further, it is not known whether such deformation has any functional consequences for early development.

The development of specific casual hypotheses for DP is limited by the nearly complete absence of descriptive data regarding the brain development of children with this condition. We therefore collected and analyzed MRI data for 20 infants with DP (cases) and 21 infants without previously diagnosed skull deformation or other craniofacial anomalies (controls); these infants represented a subset of participants from a larger, longitudinal investigation of neurodevelopment [29]. We first compared cases and controls in relation to volumetric measures of the whole brain, cerebellum, and midsagittal areas of the cerebellar vermis and corpus callosum. We then performed linear measures between brain landmarks to characterize the shape, asymmetry, and orientation of selected brain regions for both groups,

in order to examine the presence and extent of displacement of brain structures among cases in relation to controls. Finally, we examined the association between these brain measures and standardized measures of infant development.

Method

Participants

Participants were enrolled after obtaining informed consent, using procedures approved by the Institutional Review Board of Seattle Children's Hospital. This research was conducted in full compliance with HIPAA standards.

Infants with DP—Infants with DP were recruited at the time of diagnosis in the Craniofacial Center at Seattle Children's Hospital (see Speltz et al. [29]). Inclusion criteria were a diagnosis of DP between ages 4 and 11 months. Exclusions included (1) prematurity (<35 weeks gestation); (2) a known neurodevelopmental condition (e.g., Down syndrome), brain injury, or significant vision or hearing impairment; (3) major malformations or three or more minor malformations [21]; (4) craniofacial microsomia; (5) a non-English speaking mother; (6) adoption or out-of-home placement; and (7) family plans to relocate before study completion.

Seventy-eight families were approached for participation, and 50 consented to attempt an MRI. We attempted scans with 30 children and completed 20 successful scans.

Infants without DP—Infants with no prior history of DP or other craniofacial anomalies were recruited as part of the same study. In addition to the aforementioned exclusions, these infants were ineligible if they had been diagnosed with DP or any other craniofacial anomaly. The families of 161 infants without prior diagnosis of DP were approached for participation in this part of the study. Eighty families consented to participate, and 39 attempted an MRI, and we completed 21 successful scans.

Measures

MRI acquisition—MRIs were scheduled within 28 days of participants' developmental assessment. Scans were scheduled during periods of natural sleep and completed without use of sedation. All scans were acquired on a 3-T Siemens Trio MRI scanner, using the following protocol: 0.5×0.5 mm sagittal slices, 1.0 mm contiguous slice thickness, matrix 256×215 (interpolated 224×256), TR=1950 ms, TE=2.3 ms. All of the scans completed for the study were reviewed by a radiologist for any clinical anomalies requiring further assessment.

MR image analysis: volume and midsagittal area measurements—Measurements included total brain volume, cerebellar volume, and midsagittal areas of the corpus callosum and cerebellar vermis. Hand-tracing was used to ensure accuracy, as automated measures were found to be inadequate due to inconsistent brain shape and insufficient gray–white contrast. All measurements were made using MEASURE [10]. Measures were obtained independently by two raters on ten scans, with inter-rater reliabilities ranging from intraclass correlation=0.93–0.99.

Total brain volume was measured using semi-automated thresholding procedures for segmenting brain tissue from cerebral spinal fluid (CSF) [5]. Raters examined each MRI slice to ensure inclusion of all brain tissue and exclusion of non-brain regions.

Cerebellum volume was measured according to rules outlined by Aylward et al. [6]. Cerebellum was separated from the cerebellar peduncles by drawing a straight line from the most anterolateral recess of the fourth ventricle to the notch on the lateral surface of the pons marking the transition to the smooth convex surface of the cerebellar hemispheres.

Corpus callosum and cerebellar vermis area measures were obtained by drawing these regions in the midsagittal slice. The 3D brain image was rotated to position the inter-hemispheric fissure in the vertical plane. Because the inter-hemispheric fissure was not contained in a single sagittal plane in many cases, the brain was rotated and the plane that most clearly dissected the region of interest was chosen for these measures. Midsagittal area measures were performed for cerebellar vermis and separately for two subsections (lobules I–V and lobules VI–X) and corpus callosum.

MR image analysis: linear and angle measurements—Using methods similar to those of Mewes et al. [24] and others [3, 20], we selected brain landmarks that (1) could be identified reliably and (2) were relevant to the assessment of abnormalities in brain shape, asymmetry, and orientation. Distances between these landmarks were measured, and, for some brain regions, ratios were calculated (e.g., cerebellar vermis height–width). For all ratios, the greater of the two lengths was used as the numerator, and the small of the two lengths was used as the denominator (i.e., all values were ≥1). Additionally, angle measurements were performed to quantify the degree of tilt of the corpus callosum in relation to a standard orientation. Inter-rater reliabilities for linear measures were intraclass correlation ≥0.98.

Corpus callosum: Five linear measurements were taken along the midline region of the corpus callosum (Fig. 1). These included the anterior to posterior length of the corpus callosum (CC length), the orientation of the corpus callosum relative to a line connecting the anterior and posterior commissures (CC angle), the thickness of the corpus callosum at mid-line (CC thickness), the distance from the top of the corpus callosum to a line connecting the most anterior and posterior points of the corpus callosum (CC height), and the ratio of corpus callosum height to length (CC height–CC length).

Cerebellar vermis: With the midsagittal slice oriented perpendicular to the AC–PC line, the most superior, inferior, and posterior points were marked on the outline of the cerebellar vermis, as well as the deepest (most posterior) point of the fourth ventricle (Fig. 2). Measures included vermis height, vermis width, and vermis height–vermis width.

Distances between brain and skull landmarks: Skull landmarks included the frontal border of the intracranial cavity (ICC), assessed in the midsagittal slice; the occipital border of the ICC, assessed in the midsagittal slice; and the cranial vertex (Fig. 3). Brain landmarks included the anterior and posterior commissures (AC and PC), dorsum sella, and opisthion. Using these landmarks, we generated measures including anterior to posterior skull, AC to anterior skull, PC to posterior skull, AC–PC to dorsum sella, AC–PC to opisthion, and AC–PC to cranial vertex.

Distances between landmarks within the brain: To assess brain shape and asymmetry, irrespective of skull deformation, we identified and calculated the distances between brain landmarks (Fig. 4). The brains were oriented along the AC–PC line in the midsagittal plane. Landmarks included the anterior and posterior commissures (AC and PC); points through the PC on the right and left edges of the brain, generally reflecting the widest distance across the brain in this axial slice; and the most anterior and posterior points of the brain, identified 1 cm to the right and left of the midsagittal plane. Distance measures were calculated for AC–PC distance; brain width at PC; the average anterior–posterior distances on the right and

left (brain length); brain width–length; average distance from PC to the posterior brain on the right and left (posterior brain length); average distance from PC to the anterior brain on the right and left (frontal brain length); ratio of the anterior to posterior brain distance on the right versus left (right to left asymmetry); ratio of the distance from PC to anterior brain on the right versus left (frontal asymmetry); ratio of the distance from PC to posterior brain on the right versus left (posterior asymmetry [medial]); and the ratio of the distance from the right side of the brain to right posterior brain versus the distance from the left side of the brain to left posterior brain (posterior asymmetry [lateral]).

Clinician ratings of cranial deformation—Three dimensional surface images were obtained for all participants using the 12-camera 3dMDcranial active stereo photogrammetry system [4, 29]. These photographs were deidentified, randomized, and rated for severity of cranial asymmetry by two craniofacial dysmorphologists who were blind to participants' DP status. DP severity was rated as 0=none, 1=mild, 2=moderate, and 3=severe.

Bayley Scales of Infant Development, Third Edition (BSID-III)—The BSID-III [7] was administered by trained infant psychometrists. The BSID-III yields composite scores reflecting infants' cognitive, language, and motor development. Standard scores (mean=100, standard deviation=15) were derived for each of the composite scales.

Demographic data—Demographic and medical history data were obtained using a semi-structured interview with participating mothers. The Hollingshead classification system [14] was used to measure socioeconomic status (SES). Mothers provided information on prematurity, based on reported due date and birth date. Age was corrected for prematurity for infants delivered at 35–37 weeks gestation, and for those delivered at 38 weeks gestation weighing less than 6 lb.

Analyses

Descriptive statistics (frequencies, means, and standard deviations) were calculated separately for infants with and without DP for demographic and clinical characteristics, and the two groups were compared using *t*-tests and chi-squared analyses. Descriptive statistics were also calculated separately by group for all brain measures.

We used linear regression analyses with robust standard errors to estimate group differences. These analyses controlled for gender, SES, ethnicity (white, non-Hispanic versus nonwhite or Hispanic), and age in months (corrected for prematurity). For these analyses, we used dysmorphologists' ratings to identify infants in the case group with no discernible DP on 3D imaging (i.e., severity scores of 0 from both raters) and infants without diagnosed DP that had any discernible posterior skull flattening or asymmetry (i.e., severity score >0 from either rater). Cases without discernible DP and controls with DP were then excluded from group comparisons. Measures of cerebellum volume and midsagittal areas of the cerebellar vermis and corpus callosum were adjusted for these covariates, as well as total brain volume. The magnitude of group differences was calculated using standardized mean difference effect size, calculated by dividing the adjusted group difference by the root mean square error for the regression model. Finally, with data from all participants (i.e., cases, unaffected controls, and controls with evidence of DP), we used linear regression (controlling for demographics) to examine associations between BSID scores and brain shape measures. For these analyses, we selected brain measures that had shown robust and statistically significant group differences ($p<.05$) in case–control comparisons.

Because of the exploratory nature of this research, we minimized type II errors by using unadjusted *p*-values for multiple comparisons and prioritizing effect sizes in the

interpretation of group differences. All analyses were completed using STATA SE Version 10 [30].

Results

Infants with and without DP were similar in age, gender distribution, SES, and ethnicity (Table 1). Infants with DP received lower scores on the cognitive and motor scales of the BSID-III than infants without DP. Although not statistically significant, infants with DP were also more likely than controls to have been born <38 weeks gestation. Seven controls were found to have some degree of DP based on clinicians' review of their 3D head photographs (i.e., a score of ≥1 by either rater). These infants were not included in group comparisons, but their data were used to examine associations between brain shape and infant development. All infants in the DP group were confirmed to have at least 'mild' DP. Based on radiologist review, one infant with DP and one infant in the control group had previously undiagnosed Chiari malformations and were eliminated from further analyses (note: the latter infant had already been eliminated on the basis of being a control group participant with DP).

Small group differences were observed for total brain volume and cerebellum volume, and for midsagittal areas of the corpus callosum and cerebellar vermis (Table 2). Larger differences were observed in the shape and orientation of selected brain structures and landmarks (Table 3). Relative to infants without DP, the corpus callosum of infants with DP was shorter from anterior to posterior (ES=−0.99, p=.012), thicker at the mid-point (ES=0.77, p=.053), and oriented at a greater angle relative to the AC–PC line (ES=1.13, p=.005). The cerebellar vermis height and height–width ratios were greater for infants with DP than for those without (vermis height ES=0.75, p=.059; vermis height–width ES=0.83, p=.035). Infants with DP had flattening of the posterior skull and brain, evidenced by a shorter frontal to occipital distance relative to controls (ES=−1.31, p=.001) and shortened distance from the PC to posterior border of the skull (ES=−2.15, p<.001). Perpendicular distances were greater among infants with DP for the AC–PC to dorsum sella (ES=0.72, p=.062) and AC–PC to cranial vertex (ES=1.09, p=.001). On within-brain landmark measures, infants with DP had shorter AC–PC distance (ES=−0.68, p=.092), shorter brain length (ES=−1.37, p=.001), and shorter distance from PC to the posterior brain (ES=−2.05, p<.001). Brain width (at PC) and brain width–length ratios were both greater among infants with versus without DP (brain width ES=1.54, p<.001; brain width–length ES=1.78, p<.001). Finally, posterior asymmetry was greater among infants with DP in terms of both medial asymmetry (ES=.33, p<.001) and lateral asymmetry (ES=.08, p=.002).

BSID-III motor scores were inversely associated with several brain shape measures. This included the angle of the corpus callosum (Beta=−0.61; p<.001), vermis height–width ratio (Beta=−0.34; p=.01), brain width and width–length ratio (Betas=−0.55 and −0.42, respectively; p=.002 and .014, respectively), distance from the AC–PC line to the cranial vertex (Beta=−0.50, p=.006), and medial and lateral posterior brain asymmetry (Betas=−0.29 and −0.39, respectively; p=.005 and .029, respectively). Motor development was also positively correlated with posterior brain length (Beta=.44, p=.015). Cognitive development was inversely associated with the vermis height–width ratio (Beta=−0.34, p=.01). All other associations had small effect sizes and p-values exceeding .05.

Discussion

We found little difference between infants with and without DP in total brain volume, volume of the cerebellum, or midsagittal areas of the cerebellar vermis and corpus callosum. As expected given the cranial deformation associated with DP, there were group differences

in the shape of the brain and selected structures. Compared to unaffected controls, infants with DP had greater posterior deformation and flattening of the brain; the corpus callosum was shortened and positioned at a greater angle relative to a standard orientation; and the height and height–width ratio were greater for the cerebellar vermis.

These data suggest that the brains of infants with DP show the anticipated “biomechanical” effects of development within an asymmetric and compressed skull. A critical issue is whether these effects have functional consequences. Among all infants, we found associations between several brain shape measures and neurodevelopmental outcomes. This finding is consistent with previous studies showing that corpus callosum size and shape differentiate typical from other groups of atypical children (e.g., those with prenatal alcohol exposure [9] and dyslexia [32]). However, an important difference between our study and this previous work is that the observed shape differences in our study were presumably secondary to skull deformation versus a primary CNS malformation. It is possible that deformation of the corpus callosum and other brain structures has an adverse effect on function, even in the absence of a malformation (e.g., compression of the corpus callosum and cerebellum may have resulted in worse motor or cognitive skills). Alternatively, it is also possible that early developmental delays predisposed infants to greater cranial and brain asymmetry.

Prospective studies, tracking the development of skull and brain shape over time in relation to infant development, have the potential to clarify the direction of these relationships. Future studies with longer-term follow-up may also help to determine the degree to which the shape of the brain ‘normalizes’ in relation to shape changes in the skull that are secondary to maturation or treatment (e.g., orthotic helmet treatment). A recent study by Aldridge and colleagues [2], with pre-surgery and post-surgery assessments of brain shape in children with isolated craniosynostosis suggests that normalization of brain shape does not always follow interventions to normalize skull shape. However, this remains to be studied in children with DP.

We are also unaware of studies tracking the development of corpus callosum shape over time, or of studies establishing the relevance of differences in corpus callosum shape in infancy for later development. Similarly, although the cerebellum has been implicated in a variety of neurodevelopmental conditions [22, 27, 28], there are no studies to our knowledge that have examined the implications of anomalous shape in the cerebellum or cerebellar vermis.

Two of the 41 infants in our sample (4.9%) had previously undiagnosed Chiari malformations. Aitken et al. [1] found that Chiari malformations were detected in approximately 1% of the patients who had undergone MRI (either for symptoms that were potentially related to their Chiari malformation or for other reasons). As with our brain shape findings, it is difficult to know whether these malformations predated the infant’s skull deformation or were perhaps the result of deformation compressing the posterior brain.

Limitations of our study include the relatively small sample size and limited statistical power to detect case–control differences. The range in DP severity was also restricted, with all but one of our cases having mild or ‘moderate’ DP. Replication is needed with larger samples representing the full range of DP severity to more definitively establish group differences and associations between brain shape and development.

Our findings suggest that the malleable brains of infants with DP assume the characteristic shape of the skulls within which they are contained. Further, we found that these features were associated with neurodevelopmental outcomes. Future research is needed to clarify the

directionality of these associations—that is, whether differences in brain shape precede or follow early developmental delays.

Acknowledgments

This publication was made possible in part by grant number 1 R01 HD046565 from the National Institute of Child Health and Human Development (NICHD) to Dr. Speltz, and grant number 1 UL1 RR025014 from the National Center for Research Resources (NCRR), components of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NICHHD, NCRR, or NIH.

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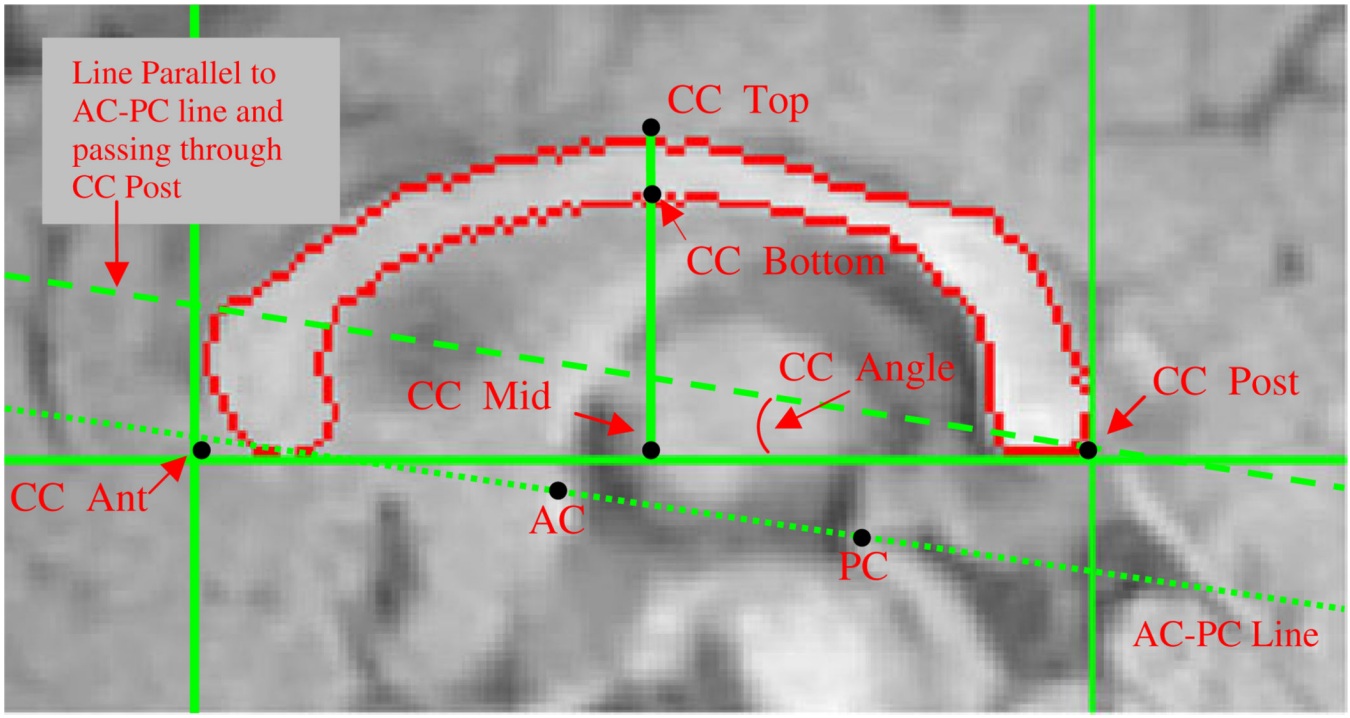

Fig. 1.

Corpus callosum measures. Landmarks for corpus callosum (CC) measures included: (1) the anterior and posterior commissures ("AC" and "PC"); (2) the point representing the intersection of the most inferior and posterior slices of the CC ("CC Post"); (3) the point representing the intersection of the most inferior and anterior slices of the genu of the CC ("CC Ant"); (4) the most superior point of the CC ("CC Top"); (5) the point directly below CC Top, at the lower border of the CC ("CC Bottom"); and (6) the point on the AC-PC line that is directly below CC Top ("CC Mid"). Using these landmarks, we generated **CC Length** (distance from CC Post to CC Ant), **CC Angle** (angle of the intersection of a line parallel to the AC-PC line and passing through CC Post with the line connecting CC Post and CC Ant), CC Height (distance from CC Top to CC Mid), **CC Thickness** (distance from CC Top to CC Bottom), and the ratio of **CC Height:CC Length**

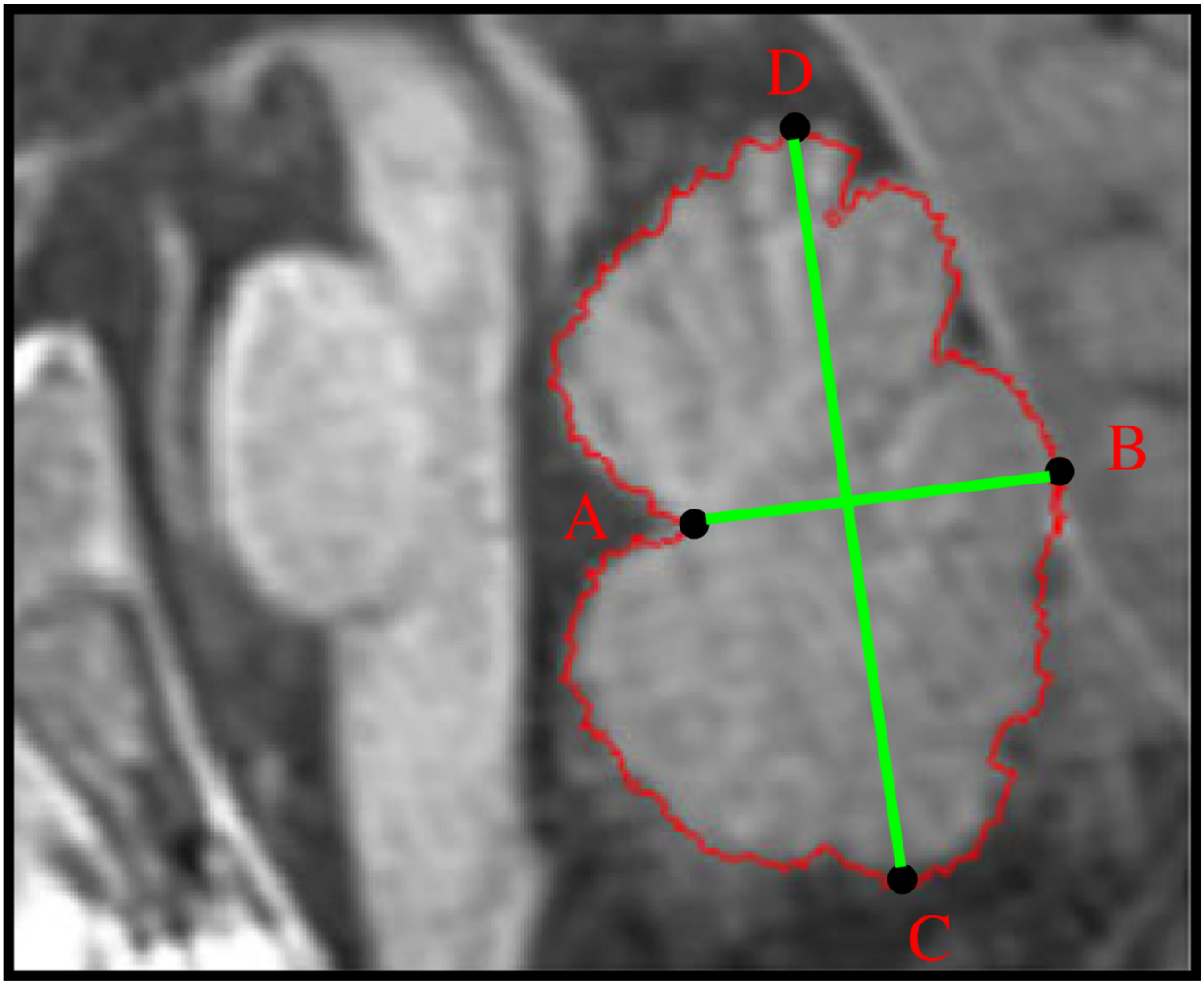

Fig. 2.

Cerebellar vermis measures. Landmarks for cerebellar vermis measures included: the most superior (D), inferior (C), and posterior (B) points on the cerebellar vermis, and the most posterior point on the fourth ventricle (A). Points were defined in AC-PC orientation. Using these landmarks, we generated **Vermis Height** (distance from D to C), **Vermis Width** (distance from A to B), and the ratio of **Vermis Height: Vermis Width**

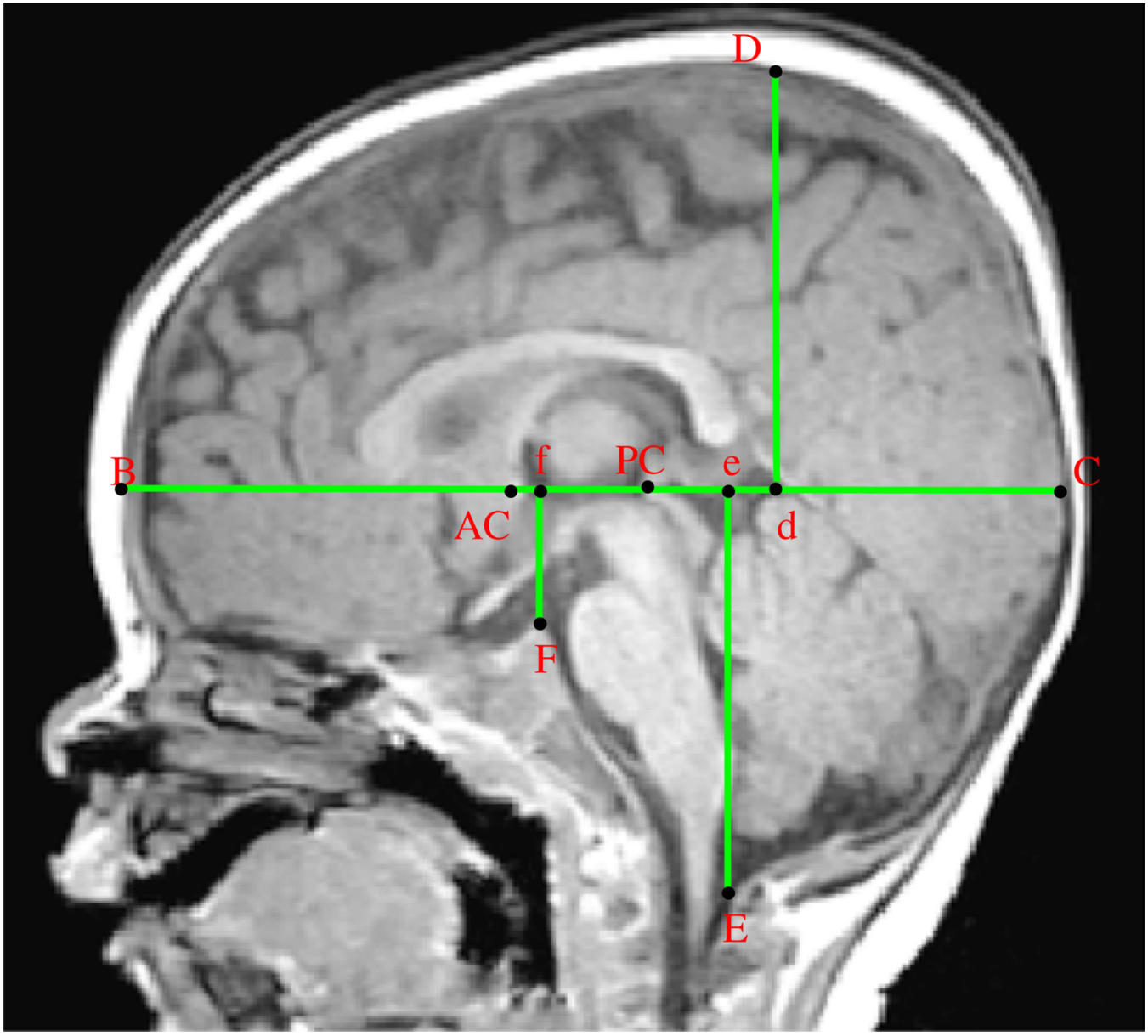

Fig. 3.

Brain Landmark to Skull Landmark Measures. Skull landmarks included: in the mid-sagittal slice, the most anterior and posterior borders of the intracranial cavity (ICC) (B and C); and the cranial vertex (D). Brain landmarks included: the opisthion (E); the dorsum sella (F); and the anterior and posterior commissures (AC and PC). We generated linear measures reflecting the distance from the **Anterior to Posterior ICC** along the AC-PC line (Line B–C), the **AC to Anterior ICC** (line AC-B), the PC to Posterior ICC(line PC-C); the perpendicular distance from the **AC-PC line to the dorsum sella** (line f-F), perpendicular distance from the **AC-PC line to the opisthion** (line e-E), and the perpendicular distance from the **AC-PC line to the cranial vertex** (line d-D)

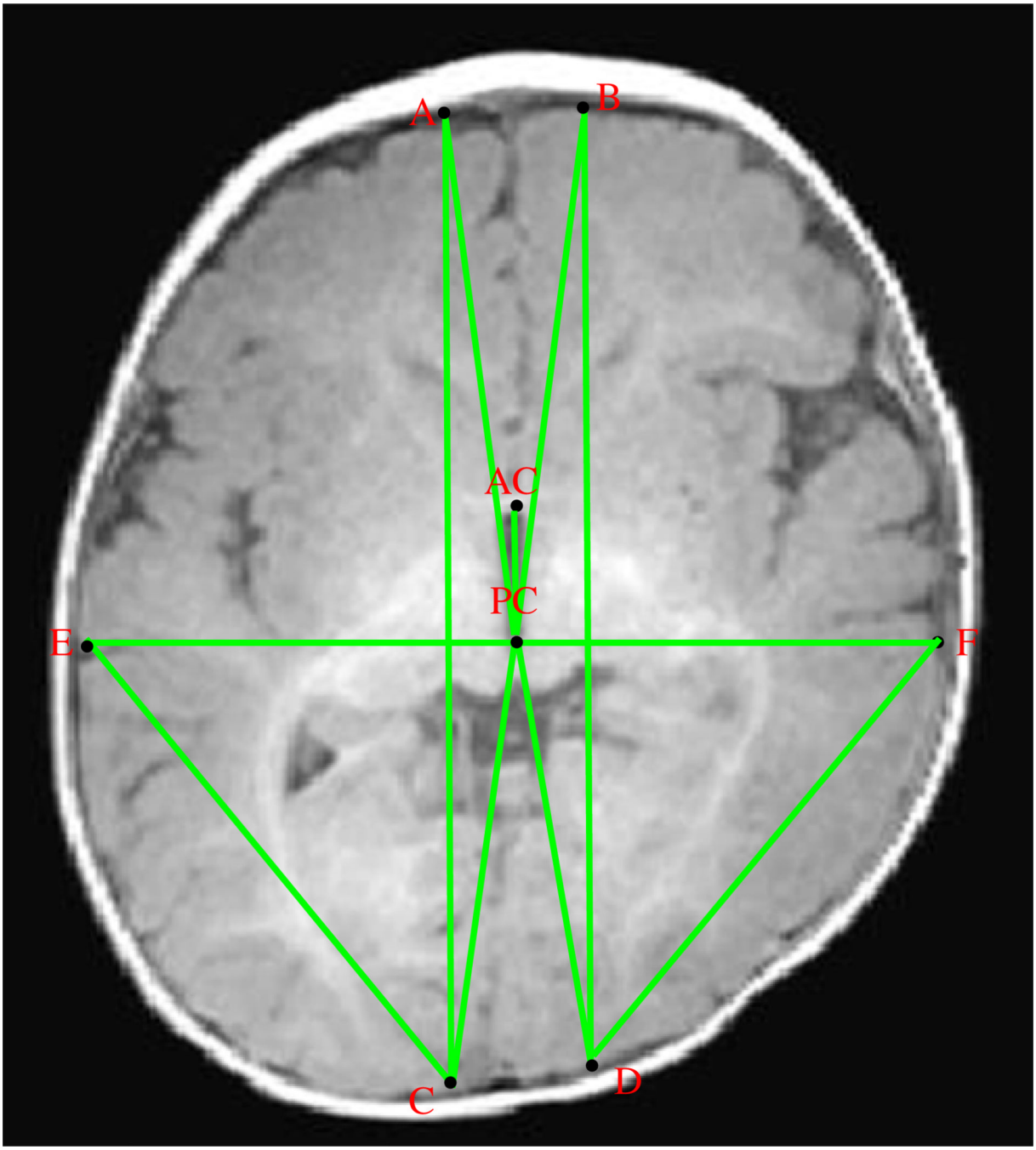

Fig. 4.

Brain Landmark Measures. Brain landmarks included: the anterior and posterior commissures (AC and PC); the most lateral points at the left and right edges of the brain (E and F) on the line going through the PC and perpendicular to the line connecting the AC and PC; and the most anterior and posterior points on the brain, identified 1 cm to the left and right of the interhemispheric fissure plane (anterior: A,B; posterior: C,D). [note: The interhemispheric fissure plane was defined as the plane passing through the midline AC and PC points. In some cases the interhemispheric fissure was displaced from this plane, especially in the posterior brain.] We used these landmarks to generate: **AC-PC distance,**

BrainWidth at PC (line E–F), **Brain Length** (average of lines A–C and B–D), ratio of **Brain Width:Brain Length, Posterior Brain Length** (average of lines PC-C and PC-D), Frontal Brain Length (average of lines PC-A and PC-B), **Right:Left Asymmetry** (ratio of line A–C:line B–D), **Frontal Asymmetry** (ratio of line PC-A:line PC-B), **Posterior Asymmetry (Medial)** (ratio of line PC-C:line PC-D), and **Posterior Asymmetry (Lateral)** (ratio of line F-C:line E-D)

Table 1

Demographic and clinical characteristics for children with deformational plagiocephaly (DP; cases) and without DP (controls)

Characteristic	Case (*n* = 20)	Control (*n* = 21)
Age in months (mean, SD)[a]	7.9 (1.2)	7.9 (1.3)
4–6	5 (25.0%)	5 (23.8%)
7–9	14 (70.0%)	14 (66.7%)
10+	1 (5.0%)	2 (9.5%)
Sex		
Male	12 (60.0%)	11 (52.4%)
Female	8 (40.0%)	10 (47.6%)
Hollingshead score (mean, SD)	41.8 (14.8)	39.6 (15.4)
I–II (high)	11 (55.0%)	12 (57.1%)
III–IV (low)	9 (45.0%)	9 (43.0%)
Ethnicity		
White/non-Hispanic	13 (65.0%)	12 (57.1%)
Hispanic	3 (15.0%)	2 (9.5%)
Asian	1 (5.0%)	1 (7.1%)
Other/more than one	3 (15.0%)	6 (28.6%)
Premature		
Yes	3 (15.0%)	2 (9.5%)
No	17 (85.0%)	19 (90.5%)
BSID scores (mean, SD)		
Cognitive*	102.5 (10.6)	107.6 (7.7)
Language	91.2 (9.8)	97.2 (13.6)
Motor***	93.1 (14.7)	108.9 (11.8)
Clinician DP severity rating (mean, SD)	1.90 (0.55)	0.0 (−)
None (0)	0 (−)	14 (66.7%)
Mild (1.0–1.5)	9 (45.0%)	7 (33.3%)
Moderate (2.0–2.5)	10 (50.0%)	0 (−)
Severe (3.0–4.0)	1 (5.0%)	0 (−)

[a] Corrected for prematurity

* $p<.05$;

*** $p<.001$

Table 2

Adjusted group differences in brain volume for children with confirmed deformational plagiocephaly (DP; cases) versus children with confirmed absence of DP (unaffected controls)

	Cases[a] (*n* = 19)	Unaffected controls[a] (*n* = 14)	Adj. diff.[b]	95% CI		*p*-Value	ES
Total brain volume (cc)	852.91 (66.65)	825.31 (81.65)	15.50	−25.41	56.42	.443	0.29
Corpus callosum (cm^2)[c,d]	0.31 (0.04)	0.31 (0.06)	< 0.01	−0.04	0.04	.895	0.05
Total cerebellum (cc)[c,e]	90.54 (12.08)	83.40 (8.65)	4.64	−2.85	12.13	.214	0.52
Cerebellar vermis (cm^2)[c,d,e]	0.89 (0.17)	0.87 (0.10)	0.02	−0.11	0.14	.789	0.11
Vermis 1–5 (cm^2)[c,d,e]	0.37 (0.05)	0.36 (0.04)	< 0.01	−0.04	0.04	.976	−0.01
Vermis 6–10 (cm^2)[c,d,e]	0.52 (0.14)	0.50 (0.07)	0.02	−0.08	0.11	.722	0.13

[a] Controls with any evidence of DP (*n* = 7) were excluded from analyses. In addition, one case and one control with previously undiagnosed Chiari malformations detected on their study MRI were excluded [note: the affected control had already been excluded due to DP]

[b] Analyses adjusted for demographic factors, including gender and chronological age (in days, adjusting for prematurity)

[c] Analyses adjusted for demographic factors and total brain volume

[d] Measures represent midsaggital area of the corpus callosum and cerebellar vermis

[e] Cerebellum measures could not be obtained for one control due to movement artifact

Table 3

Adjusted group differences in brain shape for children with confirmed deformational plagiocephaly (DP; cases) versus children with confirmed absence of DP (unaffected controls)

	Cases[a] (*n* = 19)	Unaffected controls[a] (*n* = 14)	Adj. diff.[b]	95% CI		*p*-Value	ES
Corpus callosum							
Angle	7.37 (3.68)	3.70 (3.09)	4.08	1.32	6.83	.005	1.13
Length	5.05 (0.35)	5.45 (0.42)	−0.38	−0.66	−0.09	.012	−0.99
Height	1.91 (0.31)	1.98 (0.23)	−0.08	−0.29	0.13	.435	−0.27
Width	0.35 (0.05)	0.32 (0.048)	0.04	< −0.01	0.08	.053	0.77
Height–width	2.70 (0.45)	2.78 (0.27)	−0.04	−0.31	0.24	.780	−0.10
Cerebellar vermis[c]							
Height	4.01 (0.29)	3.79 (0.28)	0.20	−0.01	0.42	.059	0.75
Width	2.35 (0.22)	2.46 (0.26)	−0.11	−0.32	0.10	.306	−0.44
Height–width	1.72 (0.17)	1.56 (0.20)	0.15	0.01	0.29	.035	0.83
Brain/skull measures							
Anterior to posterior skull	13.78 (0.54)	14.39 (0.51)	−0.66	−1.05	−0.28	.001	−1.31
AC to anterior skull	5.83 (0.26)	5.75 (0.30)	0.08	−0.13	0.29	.460	0.31
PC to posterior skull	5.97 (0.32)	6.62 (0.29)	−0.68	−0.89	−0.46	< .001	−2.15
AC–PC to dorsum sella	2.12 (0.24)	1.99 (0.23)	0.16	−0.01	0.33	.062	0.72
AC–PC to opisthion	5.48 (0.28)	5.40 (0.30)	0.06	−0.18	0.30	.614	0.21
AC–PC to cranial vertex	6.63 (0.37)	6.24 (0.39)	0.37	0.16	0.58	.001	1.09
Brain landmark distances							
AC–PC length	1.97 (0.11)	2.02 (0.09)	−0.07	−0.14	0.01	.092	−0.68
Brain width at PC	12.14 (0.65)	11.27 (0.69)	0.76	0.43	1.09	< .001	1.54
Brain length	12.94 (0.51)	13.57 (0.49)	−0.66	−1.00	−0.32	.001	−1.37
Brain width–length	0.94 (0.07)	0.83 (0.05)	0.10	0.06	0.14	< .001	1.78
Posterior brain length	5.89 (0.29)	6.51 (0.32)	−0.63	−0.85	−0.42	< .001	−2.05
Frontal brain length	7.20 (0.31)	7.19 (0.28)	−0.02	−0.21	0.16	.811	−0.08
Right–left asymmetry	1.02 (0.01)	1.02 (0.01)	< −0.01	−0.01	0.01	.512	−0.27
Frontal asymmetry	1.02 (0.01)	1.03 (0.02)	−0.01	−0.02	0.01	.397	−0.35
Posterior asymmetry (medial)	1.04 (0.03)	1.01 (0.01)	0.03	0.01	0.04	< .001	1.33

	Cases[a] (*n* = 19)	Unaffected controls[a] (*n* = 14)	Adj. diff.[b]	95% CI		*p*-Value	ES
Posterior asymmetry (lateral)	1.03 (0.02)	1.01 (< 0.01)	0.02	0.01	0.03	.002	1.08

[a]Controls with any evidence of DP (*n* = 7) were excluded from analyses. In addition, one case and one control with previously undiagnosed Chiari malformations detected on their study MRI were excluded [note: the affected control had already been excluded due to DP]

[b]Analyses adjusted for demographic factors, including gender and chronological age (in days, adjusting for prematurity)

[c]Cerebellum measures could not be obtained for one control due to movement artifact