ARTICLE

Effects of Unilateral Clefts on Brain Structure

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Objective: To evaluate potential abnormalities in brain structure of children and adolescents with unilateral clefts.

Design: Case-control study.

Setting: Tertiary care center.

Participants: Boys aged 7 to 17 years with right (n=14) and left (n=19) clefts were compared with healthy age-matched boys (n=57).

Main Exposures: Structural brain measures were obtained using magnetic resonance imaging.

Outcome Measure: It was explored whether laterality of clefts had a significant effect on brain structure. To this end, volumes of tissue types and various brain regions were evaluated.

Results: Total white matter was significantly lower in boys with right clefts compared with boys with left clefts and healthy boys. Gross regional analyses demonstrated that reductions in white matter were evident in both the cerebellum and the cerebrum in boys with right clefts. Furthermore, within the cerebrum, white matter volumes were particularly low in the frontal lobes and the occipital lobes.

Conclusions: These preliminary results suggest that right clefts may be associated with more abnormalities in brain structure. More generally, laterality of a birth defect may have a significant effect on a developing organism.

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Nonsyndromic or isolated cleft lip and/or palate (ICLP) is one of the most common congenital disorders today and it affects 10 to 11 infants per 10 000 births.[1] Isolated cleft lip and/or palate is, at least in part, caused by abnormal migration of neural crest cells to the facial prominences.[2-5] Prenatal development of the brain and the face are intimately related.[6-9] That is, the brain and face both develop from the prechordal region, where surface ectoderm will become the face and neuroectoderm will become the brain.[7,8] Abnormal facial development is therefore often accompanied by abnormalities in brain development.[6] Likewise, facial abnormalities observed in ICLP could be considered a marker for abnormal brain development. In several studies, our research group has demonstrated evidence for abnormal brain structure in both adults and children with ICLP.[10-12] In the most recent study of brain structure in children with ICLP compared with healthy comparisons, children with ICLP were found to have an overall reduction in the size of intracranial volume (ICV); and within the smaller brain cavity, the frontal lobes and the cerebellum were most significantly reduced. Furthermore, white matter was most robustly affected, with boys in particular having greater gray matter to white matter ratios.[12]

Additionally, the incidence of cognitive deficits[13,14] as well as behavioral problems[15] is higher in the cleft population compared with the normal population. These problems are evident early in development.[16] Examples include lower IQ[17] and higher incidences of learning disabilities,[13] speech and language abnormalities,[18,19] and psychosocial problems.[10,15,18-24] Specifically, children with ICLP show deficits in rapid verbal labeling and expression[25] as well as social inhibition.[15]

Findings from our research group suggest that cognitive and behavioral abnormalities in ICLP are directly related to structural abnormalities in the brain. That is, IQ

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Table 1. Characteristics of Isolated Cleft Lip and/or the Palate and Comparison Group

Characteristic	Mean (95% Confidence Interval)			*P* Value
	Right Cleft (n = 14)	Left Cleft (n = 19)	Comparison Subjects (n = 57)	
Age, y	13.0 (11.5-14.6)	11.7 (10.4-13.1)	12.2 (11.4-13.0)	.47[a]
Socioeconomic status	2.4 (2.0-2.7)	2.4 (2.1-2.7)	2.5 (2.3-2.6)	.79[a]
Right handedness, %	14	18	54	.68[b]

[a] Multivariate analysis of variance test.
[b] χ^2 Test.

was found to be associated with the size of frontal and parietal lobes[11]; speech problems were associated with cerebellar structure[26]; and being socially withdrawn was associated with regions in the ventral frontal cortex.[20,27] These findings suggest that abnormal brain development is related to abnormalities in cognition and behavior in ICLP, though other factors may be involved as well, potentially in mediating or moderating roles.

Despite the growing literature on the neurobiology of ICLP, the question of whether the side of clefting differentially affects brain structure (or function) is unexplored. An important clue that the side of clefts may indeed be important comes from the observation that the ratio of left-sided to right-sided clefts is 2:1,[3,5,28] which appears to be the case for both men and women.[29,30] Importantly, human development and biology is characterized by asymmetry of structure and function.[31] This suggests that the side of a defect has biological significance[30] that may be manifested in brain structure.

In the current study, we followed up on our previous examination of brain structure in ICLP by exploring potential differences in brain structure in children with unilateral ICLP and age-matched comparison subjects. If differences exist, it is reasonable to expect that they would be most pronounced in tissue types and regions found to be abnormal in the study by Nopoulos et al,[12] including white matter, the cerebellum, frontal lobe, and occipital lobe. However, we did not have an a priori hypothesis as to which group may be more affected in terms of abnormal brain structure.

METHODS

PARTICIPANTS

ICLP Group

Individuals with clefts were recruited from the Cleft Lip/Palate Clinic at the University of Iowa Hospital and Clinics. To examine the significance of laterality of clefts on brain structure, the study group was limited to a total of 33 boys with unilateral clefts with an age range of 7 to 17 years (31 of these subjects were described in the study by Nopoulos et al[12]). Unfortunately, there were not enough girls with unilateral clefts for us to perform meaningful analyses. It should be noted that there is an approximate 2:1 male to female ratio for ICLP,[5] which may account for the low number of girls.

All the patients in the study had been previously examined by a trained medical geneticist to rule out other congenital syndromes. Medical records were reviewed to verify and document cleft status, including type of cleft and side of the cleft. With regard to type of clefts, only children with cleft lip only and children with cleft lip and palate were included. Children with cleft palate only and bilateral clefts were not included, as these defects are not typically lateralized. Of the boys with unilateral clefts, 14 had right clefts and 19 had left clefts. The distribution of boys with cleft lip only and cleft lip and palate was similar in the right and left cleft groups. Specifically, there were a total of 4 boys with cleft lip only and 10 boys with cleft lip and palate in the right-side group, and a total of 5 boys with cleft lip only and 14 boys with cleft lip and palate in the left-side group. There were no significant differences in number of children with cleft lip only and with cleft lip and palate between those with right or left clefts (χ^2_1=0.021, *P*=.89). To increase power, the subjects with cleft lip only and those with cleft lip and palate were combined into a single group.

Comparison Group

The comparison group was recruited form the community and included 57 healthy boys aged 7 to 17 years (48 of these age-matched subjects were described previously[12]). In both groups, individuals were excluded if they had a history of serious medical and neurological disease that required significant medical intervention. In addition, comparison subjects were also excluded if they had a history of a learning disorder or psychiatric disorder such as attention-deficit/hyperactivity disorder. Written informed consent was obtained for all subjects prior to participation. The study was approved by the University of Iowa Human Subjects institutional review board.

DEMOGRAPHICS

Demographic data included age, parental socioeconomic status, and handedness. Socioeconomic status was determined using a modified Hollingshead scale of 1 to 5 in which a lower number represents higher socioeconomic status.[32] A quantitative scale was used to determine handedness.[33] As can be seen in **Table 1**, the groups were fairly similar on these demographic variables.

STRUCTURAL IMAGING

Magnetic resonance imaging scans were obtained using a 1.5-T General Electric SIGNA System (GE Medical Systems, Milwaukee, Wisconsin). Three-dimensional T1-weighted 1.5-mm coronal images were acquired. Proton density– and T2-weighted images were also acquired.

Magnetic resonance imaging data were processed using BRAINS2.[34] T1-weighted images were bias field–corrected and resampled to 1.01-mm^3 voxels. The anterior-posterior axis of the brain was realigned parallel to the anterior commissure–posterior commissure line. The interhemispheric fissure was aligned by selecting points along the fissure in the coronal and

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Table 2. Global and Regional Brain Measures in the Different Groups

Measure, cm³	Adjusted Mean: Right Cleft (n = 14)	Adjusted Mean: Left Cleft (n = 19)	Adjusted Mean: Comparison Subjects (n = 57)	*F*	*P* Value	Mean Difference (95% CI): Right vs Left Cleft	Mean Difference (95% CI): Right vs Comparison	Mean Difference (95% CI): Left vs Comparison
Intracranial volume[a]	1368.9	1402.8	1447.4	2.69	.07	−33.9 (−118.7 to −51.0)	−78.5 (−151.7 to −5.3)	−44.6 (−108.5 to 19.0)
CSF[b]	56.6	50.2	46.1	2.17	.12	6.4 (−5.5 to 18.4)	10.5 (0.2 to 20.9)	4.1 (−4.8 to 13.1)
Gray matter[b]	928.9	911.9	918.3	2.28	.11	17.0 (1.1 to 32.9)	10.6 (−3.1 to 24.3)	−6.4 (−18.4 to 5.5)
White matter[b]	440.1	463.5	461.3	4.06	.02[c]	−23.4 (−41.7 to −5.2)	−21.2 (−36.9 to −5.4)	2.3 (−11.4 to 16.0)
Cerebellum								
Total[b]	133.2	138.0	142.8	6.25	.003[c]	−4.8 (−11.5 to 1.7)	−9.6 (−15.4 to −3.9)	−4.8 (−9.7 to 0.2)
Gray matter[d]	115.7	113.0	113.6	1.63	.20	2.7 (−0.3 to 5.7)	2.1 (−0.7 to 4.7)	−0.6 (−2.9 to 1.6)
White matter[d]	24.0	26.8	26.9	2.90	.060	−2.8 (−5.6 to −0.04)	−2.9 (−5.4 to −0.4)	−0.1 (−2.2 to 1.9)
Cerebrum								
Total[b]	1198.1	1200.8	1198.7	0.13	.88	−2.7 (−14.8 to 9.4)	−0.6 (−11.1 to 9.9)	2.1 (−7.1 to 11.2)
Gray matter[e]	793.9	779.8	784.5	1.71	.19	14.1 (−1.2 to 29.3)	9.3 (−3.8 to 1.2)	−4.7 (−16.2 to 6.7)
White matter[e]	397.5	418.2	416.8	4.02	.02[c]	−20.7 (−37.2 to −4.2)	−19.3 (−33.4 to −5.0)	1.4 (−10.9 to 13.9)
Frontal lobe[e]								
Gray matter	293.0	289.3	292.5	0.97	.38	2.9 (−3.3 to 9.1)	−0.32 (−5.6 to 5.0)	−3.2 (−7.9 to 1.4)
White matter	156.0	166.3	164.5	4.49	.01[c]	−10.3 (−17.6 to −2.9)	−8.5 (−14.8 to −2.3)	1.7 (−3.8 to 7.2)
Parietal lobe[e]								
Gray matter	164.6	161.3	161.9	0.92	.40	3.3 (−1.8 to 8.4)	2.7 (−1.7 to 7.1)	−0.6 (−4.4 to 3.3)
White matter	100.1	103.4	102.7	1.07	.35	−3.4 (−8.3 to 1.4)	−2.7 (−6.8 to 1.5)	0.7 (−2.9 to 4.4)
Temporal lobe[e]								
Gray matter	191.0	185.8	186.0	4.2	.02[c]	5.2 (1.0 to 9.3)	5.0 (1.4 to 8.5)	−0.2 (−3.3 to 2.9)
White matter	65.5	66.8	67.3	.76	.47	−1.4 (−4.8 to 2.1)	−1.8 (−4.8 to 1.1)	−0.5 (−3.1 to 2.1)
Occipital lobe[e]								
Gray matter	86.6	83.7	85.7	1.6	.21	3.0 (−0.7 to 6.6)	0.9 (−2.2 to 4.0)	−2.0 (−4.7 to 0.7)
White matter	35.1	39.5	38.6	5.93	.004[c]	−4.4 (−7.0 to −1.7)	−3.4 (−5.7 to −1.2)	0.9 (−1.1 to 2.9)

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid.
[a] Covariates are height and age.
[b] Covariates are intracranial volume and age.
[c] Significant at $\alpha \leq .05$.
[d] Covariates are total cerebellum and age.
[e] Covariates are total cerebrum and age.

axial views. T2- and proton density–weighted images were aligned to the spatially normalized T1-weighted image[34] to allow the use of a multimodal discriminant classifier. The resulting classified image was used for the application of an artificial neural network that creates an automated brain mask.[35] Results of this procedure were visually inspected, and greater than 90% of the scans passed all stages successfully. The most common reason for failure was poor coregistration of the multiple modes. If the automated processing failed, the scan was either rejected owing to quality issues (motion, artifacts, etc) or manually corrected and processed completely. For successful scans, the resulting ICV mask includes all brain tissue and both internal and surface cerebrospinal fluid. General brain measures included total gray matter, total white matter, and total cerebrospinal fluid. Regional measures included the cerebrum (divided by the Talairach atlas into 4 lobes) and the cerebellum. Each of these regions was then segmented into component gray and white tissue.

STATISTICAL ANALYSIS

All analyses were performed with SPSS 17.0 for Windows. Structural measures in centimeters squared were compared using analysis of covariance (ANCOVA). All the analyses were corrected for total volume, as this affects the size of individual brain regions. Age was included as a covariate because it has a considerable effect on brain size in children and adolescents.[36] To verify whether group effects were more notable on a certain side of the brain, we performed a 2 (left and right sides of the cranium) × 3 (right cleft, left cleft, and comparison group) repeated-measures ANCOVA, with age and total volume as covariates, and evaluated the side × group interaction.

Analysis of covariance is a robust technique for small sample sizes like ours, provided that the data are normally distributed. Therefore, distributions of the residuals for a model were checked for normality in each group. When the data were somewhat skewed, a natural log transformation was performed, and the results were checked with the log-transformed variables.

RESULTS

The results of the structural analyses are summarized in **Table 2**. Both cleft groups had somewhat lower ICVs; however, this effect did not reach significance ($P = .07$). When the separate tissue types were evaluated (ICV and age as covariates), it appeared that white matter volumes were lower in boys with right clefts, while cerebrospinal fluid and gray matter volumes were somewhat larger. The group difference reached significance for white matter ($F_{2,85} = 4.06$, $P = .02$). Specifically, white matter volume was significantly reduced in boys with right clefts compared with boys with left clefts ($P = .01$) and healthy boys ($P = .009$), whereas volumes were similar in the latter 2 groups ($P = .74$). The side × group interaction was not

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significant ($P=.39$), suggesting that white matter on the left and right sides of the brain was equally reduced in boys with right clefts.

Next, gross regional measures including the cerebellum and the cerebrum were examined. Group differences were detected in total cerebellum tissue volume with ICV and age as covariates ($F_{2,85}=6.25$, $P=.003$). The 2 cleft groups did not differ in terms of cerebellar volume ($P=.15$). However, boys with right clefts did significantly differ from the healthy boys ($P<.001$), whereas the difference in total cerebellum tissue volume between boys with left clefts and healthy boys was a trend ($P=.06$).

Cerebellar gray and white matter were then examined separately, with total cerebellum volume and age as covariates. Cerebellar gray matter was similar between the 3 groups ($P=.20$); however, there was a marginally significant effect for cerebellar white matter ($P=.06$; Table 2). This effect was driven by boys with right clefts, who had lower cerebellar white matter volumes compared with boys with left clefts and healthy boys (both, $P<.05$). The latter 2 groups on the other hand, did not differ from each other ($P=.90$). Again, the side × group interaction effect was not significant ($P=.27$).

The effect for total cerebrum tissue volume with ICV and age as covariates was not significant ($P=.88$). Closer inspection revealed that this finding was probably due to a distribution shift of gray and white matter in boys with right clefts. Specifically, the ANCOVA for cerebral gray matter with total cerebrum and age as covariates suggested that cerebral gray matter was somewhat enlarged in boys with right clefts compared with the other groups, though this pattern did not reach significance ($P=.19$; Table 2). However, group differences were significant for cerebral white matter. Boys with right clefts had lower volumes compared with boys with left clefts ($P=.02$) and healthy boys ($P=.009$), whereas the latter 2 groups were similar in terms of cerebral white matter ($P=.81$). The side × group interaction was not significant ($P=.81$).

Separate ANCOVA for frontal, temporal, parietal, and occipital gray and white matter volume then examined whether group differences were more pronounced in certain regions. Although cerebral gray matter was somewhat higher in boys with right clefts in all these regions, differences only reached significance for temporal gray matter ($P=.02$; Table 2). Specifically, larger temporal gray matter volumes were evident in boys with right clefts compared with boys with left clefts ($P=.02$) and healthy boys ($P=.007$), while the latter 2 groups were similar ($P=.90$).

In terms of regional cerebral white matter volume, group effects were found in the frontal lobe ($F_{2,85}=4.49$, $P=.01$) as well as the occipital lobe ($F_{2,85}=5.93$, $P=.004$; Table 2), whereas white matter morphometry of the parietal lobe and temporal lobe was very similar between the groups (both, $P>.35$). Frontal and occipital white matter was significantly lower in boys with right clefts compared with boys with left clefts (both, $P<.01$) and healthy boys (both, $P<.01$); however, the latter 2 groups did not differ from each other (both $P<.36$). The side × group interaction for frontal and occipital white matter was not significant (both, $P>.31$).

In this sample, differences in white matter were most pronounced; however, our results suggest that gray matter may be somewhat larger in the right cleft group compared with the other groups. To examine the possibility of a distribution shift in gray and white matter in boys with right clefts, the proportion of total cranial gray matter over total cranial white matter was calculated. The ANCOVA with age as covariate was indeed significant ($F_{2,86}=5.57$, $P=.005$). Pairwise comparisons revealed that boys with right clefts had proportionally more gray matter than white matter, and this was significantly different from boys with left clefts ($P=.01$) and healthy boys ($P=.001$), whereas gray and white matter distribution was similar between the latter 2 groups ($P=.70$).

To take into account multiple comparisons, the analyses were repeated with the Bonferroni correction. All the reported results remained similar, with the exception of cerebellar white matter. That is, the reduction in cerebellar white matter in boys with right clefts was not different from boys with left clefts ($P=.1$) and only marginally different from healthy boys ($P=.06$).

COMMENT

These results demonstrated that right-sided clefts in boys are associated with more abnormalities in brain structure, in particular white matter volume, regardless of the side of the brain. Within the cerebrum, reduced white matter volumes were evident in the frontal lobes and the occipital lobes. It should be noted, however, that there may be a tissue distribution shift in boys with right clefts, characterized by more gray matter and relatively less white matter. Our findings are the first to suggest that laterality of clefts does have a differential effect on brain structure and related behavior.

These results underscore the significance of the laterality of a birth defect on the brain. Asymmetry of structure and function is indeed a common theme in human biology and development.[31] For example, the right superior frontal and temporal gyri appear earlier than their counterparts on the left side.[37] The mechanisms behind these asymmetries lie in left-right asymmetry in gene expression during prenatal development.[38] Interestingly, the frontal and striate extrastriate areas are the most asymmetric during fetal brain development,[39] and these regions were also most abnormal in boys with right clefts. Furthermore, there is an interesting sex difference in asymmetric growth of the brain. That is, growth of the male fetal cerebrum is characterized by more rapid development of the right hemisphere, whereas female fetuses are more likely to have equally sized hemispheres or a slightly larger left hemisphere.[39] On a final note, the right and left halves of the body have markedly different risks of some congenital disorders.[30] In other words, laterality of a certain defect may have a significant and differential impact on the (developing) brain.

Interestingly, right-sided insults to the brain appear to have more detrimental effects for adult men. Specifically, lesion studies show that men with right-sided damage to

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the amygdala or ventral medial prefrontal cortex have greater deficits in social/emotional conduct than matched men with comparable damage to these regions in the left hemisphere. In contrast, women with left-sided damage show functional impairments, while the women with right-sided lesions were functionally normal.[40-43]

In our study, there was no evidence that one side of the brain was affected more severely than the other. On the contrary, our findings suggest that an anomalous developmental program may manifest unilaterally in one structure (ie, a unilateral orofacial cleft) but manifest bilaterally or more globally in another (ie, global brain tissue distribution). Potentially these different outcomes are related to the patterns of gene expression specific to each of these regions or to the specific events occurring at the affected stage of development, which may differ and be specific to each region, or perhaps some complex combination of both factors. Given the work done in adult patients with lesions, there appears to be a compelling case that not only intact right cerebral structures but also proper right-sided development, including structures outside of the brain, is critical for normal function in males.

An important next step in understanding the importance of laterality of clefts on brain structure will be to test girls and women with unilateral ICLP. Lesion work suggests that left-sided insults to the brain have a more detrimental effect on females.[40,41] Therefore, it may be the case that in girls, left-sided clefts are more detrimental for development of the brain. Unilateral ICLP can be an important tool for the investigation of laterality patterns in development.

In conclusion, right-sided clefts appear to have more detrimental effects on certain brain structures than left-sided clefts, which is particularly evident in white matter. Laterality of a defect is therefore not merely a mundane feature or clinical anomaly, but may be an important factor affecting central nervous system development. However, the functional significance is largely unexplored, and it is therefore, as of yet, difficult to understand the potential clinical significance. At the least, these outcomes underscore a need for more research on laterality in birth defects to shed more light on this issue. Isolated cleft lip and palate may prove to be a valuable model to study morphological and functional asymmetry in the brain.

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