Abnormal Brain Structure in Children With Isolated Clefts of the Lip or Palate

Peg Nopoulos, MD; Douglas R. Langbehn, MD, PhD; John Canady, MD; Vincent Magnotta, PhD; Lynn Richman, PhD

Objective: To evaluate brain structure in a sample of children with isolated clefts of the lip and/or palate (ICLP).

Design: Case-control study.

Setting: Tertiary care center.

Participants: A large sample of 74 children aged 7 to 17 years with ICLP was compared with a healthy control group, matched by age and sex.

Main Exposure: Isolated cleft lip and/or palate.

Outcome Measures: General measures of height and head circumference were obtained. Brain structure was evaluated using magnetic resonance imaging, generating both general and regional brain measures (volumes).

Results: Height was significantly lower in the ICLP group ($F = 4.83, P = .03$). After controlling for this smaller body size, children with ICLP had abnormally small brains with both cerebrum ($F = 4.47, P = .04$) and cerebellum ($F = 14.56, P < .001$) volumes substantially decreased. Within the cerebrum, the frontal lobe was preferentially decreased ($F = 7.22, P = .008$) and subcortical nuclei were also substantially smaller ($F = 4.18, P = .003$). Tissue distribution of cortical gray matter and white matter within the cerebrum were abnormal in boys with ICLP (larger cortical volume, smaller volume of white matter) but proportional to controls in girls with ICLP.

Conclusions: Children with ICLP have abnormal brain structure, potentially due to abnormal brain development. The fact that the pattern of brain abnormalities in children with ICLP is dramatically different from the pattern of brain abnormalities seen in adults with ICLP suggests that brain growth and development trajectory is also abnormal in subjects with ICLP.

Arch Pediatr Adolesc Med. 2007;161(8):753-758

CLEFTS OF THE LIP AND/OR palate are among the most common congenital anomalies, occurring in 1 of 600 newborns worldwide. These oral clefts are developmental craniofacial abnormalities that result, at least in part, from a failure of neural crest cells to migrate properly. As a group, 70% of clefting disorders comprise those that are isolated to facial clefts only (nonsyndromic) and 30% are those in which the facial cleft is part of a well-defined syndrome of additional anomalies.1

For editorial comment see page 811

Cognitive deficits in syndromic clefting are frequent and often severe (mental retardation). The cognitive deficits associated with isolated clefts of the lip and/or palate (ICLP) are less severe, but the functional consequences of these deficits should not be underestimated. The pattern of cognitive deficits reported in ICLP is a lower than average general IQ2 with specific deficits in language function.3 Furthermore, these language deficits have been shown to produce reading and memory deficits similar to those found in children with developmental dyslexia and developmental dysphasia.4,5 These deficits are severe enough that reading disabilities have been reported to be 6 to 10 times more prevalent in children with ICLP compared with the general population.6,7

The etiology of these cognitive deficits has most commonly been cited as due to secondary factors such as hearing and/or speech deficits (chronic otitis media being very common in this population) or even to the social effects of facial disfigurement.8,9 However, more recently, the notion that these deficits could be a primary problem related to abnormal brain structure and function has been considered. The development of the brain and face are intimately related in both normal and pathologic conditions10,11 and suggest that abnormal brain development might accompany an abnormality in facial development.

Author Affiliations:
Departments of Psychiatry (Drs Nopoulos and Langbehn), Otolaryngology (Dr Canady), Radiology (Dr Magnotta), and Pediatrics (Dr Richman), University of Iowa Carver College of Medicine, and Department of Biostatistics, University of Iowa School of Public Health (Dr Langbehn), Iowa City.
In previous studies from our laboratory, men with ICLP were found to have abnormal brain structure and function.12-15 The brain of adults with ICLP showed normal cerebral volumes, but an abnormality in tissue distribution in which the frontal and parietal lobes were substantially increased in volume compared with normal, and the temporal and occipital lobes were significantly decreased in volume. The cerebellum was also decreased in volume in the subjects with ICLP.

Our previous study was performed on men with ICLP, limiting the interpretation as to what potential developmental processes were involved and whether there were any differences between the sexes in regard to brain structure abnormalities. The current study was designed therefore to evaluate brain structure in children (boys and girls) with ICLP. Brain structure was evaluated using magnetic resonance imaging. Our hypotheses were that children with ICLP would, like the adults we studied, have abnormal brain structure, further supporting the notion that the brain structure abnormalities are present early in life and are likely due to abnormal brain development.

### METHODS

**SUBJECTS**

All children with ICLP were recruited from our University of Iowa Cleft Clinic. Any child with ICLP in whom there was a suspicion of genetic syndrome was evaluated by a clinical geneticist and included in the study only if the child was deemed nonsyndromic based on that evaluation. Exclusion criteria for the ICLP subjects included presence of braces (which create artifact in magnetic resonance imaging scan) and a known IQ less than 70 (mental retardation). As mentioned previously, mental retardation is common in syndromic clefting, and although it has been also documented in ICLP, we chose to exclude children with known mental retardation to protect against enrolling subjects with syndromic clefts that had not previously been diagnosed. The sample consisted of 50 boys and 24 girls with ICLP. Cleft type was categorized into clefts of the lip only (CLO) (n=18), clefts of the lip and palate (CLP) (n=33), and cleft palate only (CPO) (n=23).

Healthy normal controls were recruited from the community via local newspaper advertisements. Exclusion criteria for this group included presence of braces; major medical, neurologic, or psychiatric illness; or history of learning disability (information obtained from parents during screening process). Healthy controls were matched to the ICLP group by age (within 1 year) and sex.

**IMAGING METHODS**

Images were obtained on a 1.5-T GE Signa magnetic resonance scanner (General Electric, Milwaukee, Wisconsin). Three different sequences were acquired for each subject: T1, T2, and proton density. Images were obtained on a 1.5-T GE Signa magnetic resonance scanner (General Electric, Milwaukee, Wisconsin). Three different sequences were acquired for each subject: T1, T2, and proton density. Processing of the images after acquisition was done using a locally developed family of software programs called BRAINS (acronym for Brain Research: Analysis of Images, Networks, and Systems). Details of the image analysis are published elsewhere.10-23

Intracranial volume is subdivided into total brain tissue and cerebrospinal fluid (CSF). Brain tissue is subdivided into the cerebrum and cerebellum. The cerebrum is then divided further into its 4 lobes (frontal, parietal, temporal, occipital). Subcortical structure volumes are obtained using an automated neural net.24 Regions reliably obtained by this method include the caudate, putamen, globus pallidus, and thalamus. To break down the cerebrum into the component tissue parts (gray matter and white matter), a fully automated method based on discriminant function analysis is used, incorporating data from the T1 and the proton density/T2 sequences. The details of this method are published elsewhere.23 Measures obtained for analysis included total cerebral gray matter volume and cerebral white matter volume. Total cerebral gray matter is further divided into volume of the cortex and the gray matter volume comprising the 4 subcortical nuclei obtained via the neural net described here. Technologists performing image analysis were blind to any demographic characteristics of the brain they were working on.

**STATISTICAL ANALYSIS**

All analyses were performed using the SAS language with SAS STAT procedures (SAS Institute Inc, Cary, North Carolina). All parent socioeconomic status of all participants was obtained using a modified Hollingshead Scale of 1 to 5 with a lower number corresponding to higher socioeconomic status.16,17 Race of both groups was mostly white (ICLP group: 67 white, 6 Asian American, 1 Hispanic; control group: 65 white, 4 Asian American, 5 Hispanic). All participants signed informed consent prior to enrolling in the protocol, which was approved by the local investigational review board. In addition, all participants received compensation for their participation in the study.

Using a Wilcoxon rank sum test to compare parental socioeconomic status between the ICLP subjects and healthy controls, the mean score for the controls was significantly lower (meaning higher social status) compared with that of the ICLP group (mean [SD] for controls, 2.32 [0.53], and for ICLP group, 2.69 [0.59]; P < .001). It has been previously shown that lower socioeconomic status is associated with higher incidence of ICLP16,18; thus, this difference was expected. Demographic information for the 2 study groups appears in Table 1.

**MEASURES OF COGNITIVE FUNCTION, HEIGHT, AND HEAD CIRCUMFERENCE**

Each child was assessed using a battery of neuropsychological tests to measure IQ as well as several other cognitive domains. The results from this assessment appear elsewhere (A. Conrad, PhD; L. Richman, PhD; P. Nopoulos, MD; unpublished data, November 2006). Similar to other studies, subjects with ICLP performed lower on standardized measures of verbal IQ, rapid verbal labeling, verbal fluency, and verbal memory. Nurses in our General Clinical Research Center assessed all participants and obtained measures of height (in centimeters) and head circumference (in centimeters).

Parental socioeconomic status of all participants was obtained using a modified Hollingshead Scale of 1 to 5 with a lower number corresponding to higher socioeconomic status.16,17 Race of both groups was mostly white (ICLP group: 67 white, 6 Asian American, 1 Hispanic; control group: 65 white, 4 Asian American, 5 Hispanic). All participants signed informed consent prior to enrolling in the protocol, which was approved by the local investigational review board. In addition, all participants received compensation for their participation in the study.

Using a Wilcoxon rank sum test to compare parental socioeconomic status between the ICLP subjects and healthy controls, the mean score for the controls was significantly lower (meaning higher social status) compared with that of the ICLP group (mean [SD] for controls, 2.32 [0.53], and for ICLP group, 2.69 [0.59]; P < .001). It has been previously shown that lower socioeconomic status is associated with higher incidence of ICLP16,18; thus, this difference was expected. Demographic information for the 2 study groups appears in Table 1.
controls of type I errors in hypothesis testing.27
rected, we then examined the individual outcomes and reported uncor-
association between ICLP and all outcome variables in the model,
overall ICLP effect to control for multiple outcome compari-
brain regions. Within each MANOVA, we used a Wilks
and the need for different covariate control for various types
separate models based on both logical groupings of outcomes
without reference to regional lobe distinctions. We created these
4 examined proportional cortical gray and cerebral white matter
age of cerebral volume. Model 3 examined ICLP influence on
parietal, temporal, and occipital lobes, measured as a percent-
white matter. Model 2 examined ICLP influence on the frontal,
adjusted MANOVA models. Model 1 simultaneously examined
outcome variables were grouped into 4 separate covariate-

Although the difference in mean values of parental socio-
conomic status between the 2 groups was less than 1 point,
preliminary analysis showed this difference to be statistically
significant by the Wilcoxon rank sum test (Table 1).29 More-
over, social class has been shown to be related to measures such as
brain size.30 Other factors known to influence general and
growth measures include age and sex. Therefore, parental so-
ocioeconomic status, age, and sex were used as covariates in the
analysis of all measures, including general measures of height,
head circumference, and all brain measures. Finally, potential
sex × diagnostic interactions were explored for all analyses. If
they were found (model 4), we did not attempt interpretation of
diagnostic effect in the absence of sex considerations.

Our grouping of brain measures was systematic, starting with
the analysis of more general measures in our first model and mov-
ing through increasingly smaller portions or regions of the brain.
The covariates used in the analyses of the brain measures (in ad-
tion to age, sex, and parental socioeconomic status) varied with
the size of the structure. That is, for the general measures in model
1, height was used as an additional covariate. To investigate cor-
tical lobes within the cerebrum (model 2), subcortical struc-
tures (model 3), and proportional cerebral gray vs white matter
(model 4), cerebral volume was used as an additional covariate.
Cerebral volume was used as covariate even for the propor-
tional measures to control for the possibility that the propor-
tion of cerebral volume occupied by each of the structures may
influence regional measures. We used cerebral volume as covari-
ate even for the proportional measures because it is a
structural measure that provides an estimate of the total volume
occupied by brain tissue. Our grouping of brain measures was
systematic, starting with general measures, including height and
circumference, and all brain measures. In this study, we used
the analysis of general measures to control for multiple outcome
comparisons. If only one covariate was added to the model,
results were no longer significant. We examined the individual
outcomes and reported uncorrected P values. This method has been
shown to effectively achieve model-level control of type I errors in hypothesis testing.27

We checked all models for appropriate parametric assumptions
during examination of residuals, DDFIT (difference in fits, standardized) statistics, and predicted v
observed response patterns.28 In 2 cases involving subcortical nu-
clei, an extreme outlier (likely due to measurement failures) was identified and removed.

Although the difference in mean values of parental socio-
conomic status between the 2 groups was less than 1 point,
preliminary analysis showed this difference to be statistically
significant by the Wilcoxon rank sum test (Table 1).29 More-

### RESULTS

Table 2 displays the results from the general body size (height and head circumference) and all brain measures compared across study groups. Adjusted means within the table list estimated means for the ICLP and controls given

<table>
<thead>
<tr>
<th>Measure</th>
<th>ICLP Subjects</th>
<th>Controls</th>
<th>ICLP Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Adjusted Mean</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Height, cm^c</td>
<td>148.5 (18.6)</td>
<td>148.3</td>
<td>152.6 (17.3)</td>
</tr>
<tr>
<td>Model 1, general head/brain measures^d</td>
<td>54.5 (2.68)</td>
<td>54.6</td>
<td>55.6 (2.07)</td>
</tr>
<tr>
<td>Intracranial volume, cm^3</td>
<td>1378 (125)</td>
<td>1377</td>
<td>1449 (109)</td>
</tr>
<tr>
<td>Total brain tissue, cm^3</td>
<td>1312 (133)</td>
<td>1310</td>
<td>1394 (114)</td>
</tr>
<tr>
<td>Total CSF</td>
<td>67.0 (44.5)</td>
<td>66.7</td>
<td>55.0 (30.6)</td>
</tr>
<tr>
<td>Total gray matter</td>
<td>892 (6.5)</td>
<td>890</td>
<td>934 (74.2)</td>
</tr>
<tr>
<td>Total white matter</td>
<td>420 (61.3)</td>
<td>419</td>
<td>459.2 (54.6)</td>
</tr>
<tr>
<td>Cerebral volume, cm^3</td>
<td>1198 (112)</td>
<td>1195</td>
<td>1253 (96)</td>
</tr>
<tr>
<td>Cerebellar volume, cm^2</td>
<td>128 (13.0)</td>
<td>127</td>
<td>138 (13.1)</td>
</tr>
<tr>
<td>Model 2, cerebral regions, % cerebral volume^e</td>
<td>38.6 (1.3)</td>
<td>38.5</td>
<td>39.1 (1.1)</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>22.8 (1.4)</td>
<td>22.8</td>
<td>22.4 (1.0)</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>19.7 (1.0)</td>
<td>19.8</td>
<td>19.7 (0.9)</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>10.9 (0.7)</td>
<td>11.0</td>
<td>10.7 (0.8)</td>
</tr>
<tr>
<td>Model 3, subcortical structures, cm^2</td>
<td>5.65 (0.82)</td>
<td>5.77</td>
<td>6.12 (0.73)</td>
</tr>
<tr>
<td>Caudate</td>
<td>8.97 (0.96)</td>
<td>9.08</td>
<td>9.63 (0.89)</td>
</tr>
<tr>
<td>Globus pallidum^g</td>
<td>2.70 (0.45)</td>
<td>2.73</td>
<td>2.98 (0.35)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>12.9 (1.10)</td>
<td>13.1</td>
<td>13.6 (1.13)</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; ICLP, isolated cleft lip and/or palate.
^a Mean adjusted by covariates.
^b All univariate F tests had df = 1,134. Wilks λ test of ICLP in model 1 had df = 6,128. Models 2 and 3 both had df = 4,131.
^c Covariates were age, sex, and parental socioeconomic status.
^d Covariates were height, age, sex, and parental socioeconomic status.
^e Covariates were cerebral volume, age, sex, and parental socioeconomic status.
^f One extreme outlier (volume < 5.5 cm^3) was removed.
^g One extreme outlier (volume > 9.0 cm^3) was removed.
mean values for all other covariates used in each analysis. With the exception of total CSF, the children with ICLP were substantially smaller than normal controls on all general measures, including height (F = 4.83, P = .03), head circumference (F = 4.30, P = .04), intracranial volume (F = 5.79, P = .02), total brain tissue (F = 7.50, P = .007), both total gray matter (F = 3.97, P = .048) and total white matter (F = 10.11, P = .002), cerebral volume (F = 4.47, P = .04), and cerebellar volume (F = 14.36, P < .001). It is important to note that the measures of head size and brain volumes were abnormally small, even after controlling for the significantly lower body size (height).

To evaluate tissue distribution of the cerebrum, proportions of cortical gray matter and cerebral white matter were measured after controlling for total cerebral volume. There were marginally significant sex × diagnostic interactions for both measures (F = 1.99, P = .05, for gray matter interaction and F = 1.92, P = .06, for white matter interaction). The percentages of cortex and cerebral white matter across groups and broken down by sex are listed in Table 3. In regard to cerebral cortex, the relative volume in boys with ICLP is significantly increased compared with controls while there is no significant difference in this measure between the girls with ICLP and healthy controls. In addition, the proportional volume of cerebral white matter is significantly decreased compared with controls in the boys with ICLP while, again, this measure shows no significant difference between the girls with ICLP and their control group. These findings suggest that both boys with ICLP and girls with ICLP have lower than normal volumes of the cerebrum (there was no sex × diagnostic interaction for the measure of cerebral volume itself). Yet boys with ICLP manifest a further abnormality in that there is a tissue distribution shift with proportionately larger cortical volumes and proportionately smaller white matter volumes compared with controls. In girls with ICLP, the cerebrum is smaller than normal, but volumes of cortex and white matter are proportional to those seen in healthy controls.

Is the decrement in the volume of the cerebrum global or regionally specific? The measures of the 4 regions of the cerebrum are displayed in Table 2. Consistent with overall smaller cerebral volumes, the unadjusted volumes of each lobe is smaller in the ICLP group compared with controls. Thus, like the cerebral tissue segmentation analysis, we investigate this question by comparing the proportion of cerebral volume occupied by the various lobes in ICLP subjects and controls. The standard deviations for the measures of the cerebral regions expressed as a percentage of cerebral volume were quite small; thus, these measures with little variance are sensitive to what appear to be modest differences in proportional measures. The frontal lobe was substantially decreased in volume compared with controls (F = 7.22, P = .008). There was equivocal evidence that the occipital lobe occupies a larger portion of total brain volume (F = 3.91, P = .05). The parietal and temporal lobes showed no differences between the groups. There were no sex × diagnostic interactions for this analysis. Therefore within a smaller than normal cerebrum in children with ICLP, the frontal lobe is preferentially decreased in volume.

Comparison of volumes of the subcortical nuclei is also listed in Table 2. Again, after controlling for cerebral volume, the volumes of the caudate (F = 4.94, P = .03), putamen (F = 8.26, P = .005), and globus pallidus (F = 8.84, P = .004) are all significantly smaller in comparison with healthy controls. The volume of the thalamus, although smaller in the ICLP group, was not significantly different than controls (F = 2.02, P = .16). There were no sex × diagnostic interactions for this analysis.

In our previous study of men with ICLP, there was a spectrum of severity of in brain structure and function across craniofacial phenotype in which severity of structure and function abnormality was found to be stratified by type of cleft: bilateral cleft lip/palate was associated with the most severe abnormalities and was followed by unilateral cleft of the lip/palate, cleft palate only, and no cleft (controls).14,15 In light of these findings, a post hoc analysis was run, evaluating 1 measure, total brain tissue (to limit the number of comparisons), across the 3 subgroups of ICLP (CLO, CPO, CLP) compared with controls, using the same MANOVA structure as done previously (covariates were height, parental socioeconomic status, age, and sex) with type of cleft (CLO, CPO, CLP, none [controls]) as the between-subjects variable. Overall effect of type of cleft was significant (F = 4.37, P = .005). In review of the post hoc analyses, we once again observed a spectrum of severity in which brain volume, compared with the control group, was stratified by type of cleft: none (controls) larger than CLO, CPO, and then CLP. Adjusted mean volume of total brain tissue in controls was 1366 cm³ and that of the CLO subgroup (n = 18)
was not significantly different (adjusted mean = 1360 cm³, \( t = 0.21, P = .84 \)). Adjusted mean volume for the CPO group was 1310 cm³, which was marginally significantly lower than controls (\( t = 1.99, P = .048 \)) while the adjusted mean volume in the CLP group was substantially smaller than controls (volume = 1261 cm³, \( t = 3.74, P = .003 \)).

**COMMENT**

It is a commonly believed, even among medical professionals, that an isolated cleft of the lip and/or palate is a birth defect limited to a facial deformity, which is surgically corrected early in life. Even for those professionals who understand that children with ICLP often suffer from additional problems such as cognitive deficit, the etiology of these deficits has been considered secondary to other factors and the scientific research to investigate the neurobiology of these deficits has been limited. The current study provides evidence that ICLP is not limited to a facial defect but is accompanied by abnormalities in both general growth and development with specific structural abnormalities of the brain.

**GENERAL GROWTH**

The current study found that school-aged children with ICLP are substantially smaller in stature compared with their matched healthy control group. At least 3 previous studies have examined height in school-aged children with ICLP, all of them reporting lower than normal measures for the ICLP group. Cunningham and Jerome found that the growth trajectories of boys with ICLP are such that although in childhood this group is smaller than expected, normal height could eventually be reached. This is supported by our previous study of men with ICLP, which found the height of the ICLP group to be no different than healthy controls (and in fact, nonsignificantly taller). A similar trajectory was seen in females. The adjustment of mean body size (height) for the ICLP group was 1310 cm³, which was marginally significantly lower than controls (\( t = 1.99, P = .048 \)) while the adjusted mean volume in the CLP group was substantially smaller than controls (volume = 1261 cm³, \( t = 3.74, P = .003 \)).

**BRAIN STRUCTURE**

This study finds children with ICLP to have significant abnormalities in the structure of the brain. After controlling for smaller body size (height), children with ICLP had reduced head circumference with smaller volumes of brain tissue, both in the cerebrum and cerebellum. Moreover, within the small cerebrum, the frontal lobes and subcortical nuclei of the caudate, putamen, and globus pallidus are preferentially affected.

**SEX DIFFERENCES IN TISSUE DISTRIBUTION**

Although both male and female children with ICLP had reduction in the volume of the cerebrum, boys with ICLP had an additional abnormality in that the tissue distribution within the cerebrum was abnormally compared with controls. Specifically, boys with ICLP had proportionately more cortical volume than controls and less cerebral white matter compared with controls. This tissue distribution shift was not seen in girls with ICLP. Although the notion of abnormally increased volumes of cortex seems counterintuitive, the phenomenon of “pathologic enlargement” of cortex has been previously well documented. Specifically, this phenomenon has been seen almost exclusively in neurodevelopmental disorders, including autism. Moreover, in our previous study of men with ICLP, there was abnormal enlargement in the frontal and parietal cortex as well as in the superior temporal plane. In addition, these enlargements were truly pathological in that the volume of these cortical regions was inversely correlated with IQ: the larger the volume, the lower the IQ.

Sex differences in diseases that affect brain development are common, and in fact almost all neurodevelopmental disorders are more common and more severe in male subjects, including mental retardation, autism, attention-deficit disorder, dyslexia, all developmental reading disorders, and schizophrenia. Isolated cleft lip and/or palate is no exception with the incidence of CLP nearly 2:1 men to women (although CPO is more common in female subjects). With the etiology of the brain abnormalities in ICLP hypothesized to be due to abnormal brain development, the sex findings of the current study (boys manifesting more severe brain abnormalities than girls) are not unexpected.

**GROWTH TRAJECTORIES OVER TIME**

Although it is suggested that for height, boys with ICLP may eventually catch up and attain normal height, this is not expected for brain morphology. The pattern of abnormal brain morphology in our previous study of men with ICLP is substantially different from the pattern of abnormalities seen in the childhood sample. The children with ICLP have smaller brain volume, preferentially in the frontal lobe and subcortical gray matter. In men with ICLP, volumes of total brain and cerebrum are normal. Within the cerebrum, the frontal and parietal lobes are enlarged and there is decrement in size of the temporal and occipital lobes. No studies of brain morphology have been completed in women. How can the different patterns of brain abnormalities between children and adults with ICLP be reconciled? The growth and development of the human brain is very protracted. Although the volume of the cerebrum reaches 95% of adult volume by age 5 years, the changes in volumes of the gray and white matter within the cerebrum undergo substantial changes, especially during puberty, and continue through the second decade of life. Although the volume of the ICLP cerebrum may eventually reach a normal measure, the tissue distribution within the cerebrum is abnormal both in childhood and in adulthood, suggesting that later phases of growth and development, from school age to age 30 years, has an abnormal trajectory in subjects with ICLP compared with normal. One region of the brain, the cerebellum, is abnormally small in the childhood sample and remained abnormally small in the adult sample. Longitudinal assessment of both girls and boys with ICLP would be useful in better understanding the pattern of brain growth and development in ICLP and how it differs from healthy controls and by sex.
Accepted for Publication: February 8, 2007.
Correspondence: Peg Nopoulos, MD, University of Iowa Hospitals and Clinics, 200 Hawkins Dr, W278 GH, Iowa City, IA 52242 (peggy-nopoulos@uiowa.edu).

Author Contributions: Study concept and design: Nopoulos and Langbehn. Acquisition of data: Nopoulos, Canady, and Magnotta. Analysis and interpretation of data: Nopoulos, Langbehn, Magnotta, and Richman. Drafting of the manuscript: Nopoulos, Langbehn, and Magnotta. Critical revision of the manuscript for important intellectual content: Nopoulos, Langbehn, Canady, Magnotta, and Richman. Statistical analysis: Nopoulos and Langbehn. Obtained funding: Nopoulos and Langbehn. Administrative, technical, and material support: Nopoulos, Magnotta, and Richman. Study supervision: Nopoulos and Magnotta.

Financial Disclosure: None reported.

Funding/Support: This study was supported by grant 5 R01 DE014309-05 from the National Institutes of Dental and Craniofacial Research.

REFERENCES