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DEVELOPMENTAL DIFFERENCES OF THE MAJOR FOREBRAIN COMMISSURES IN LISSENCEPHALIES

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Abstract

Background and purpose—Changes of the major forebrain commissures in lissencephaly have not been systematically studied. This study investigated the developmental differences of the commissures in patients with varying types of lissencephaly to determine whether specific commissural features may help in distinguishing among lissencephaly phenotypes.

Materials and methods—MRI of 124 patients were retrospectively reviewed. Patients were classified as classic(cLIS), variant(vLIS) and Cobblestone lissencephaly(CBSC) according to cortical phenotype; few patients had genetic diagnoses. Abnormalities of the corpus callosum, anterior (AC), and hippocampal commissures (HC) were recorded, and the overall shape was regarded as hypogenetic, hypoplastic, dysmorphic, angled splenium and convex corpus compared with ge matched controls. Correlations between commissural characteristics and cortical patterns were analyzed using Monte Carlo simulation of chi-square, ‘extention to mxn table’, and Fisher’s exact tests as appropriate ($p<0.05$).

Results—Patients were classified as cLIS (57.4%), vLIS (38.4%) or CBSC (4.2%). The most common callosal developmental anomaly was hypogenesis with absent rostrum, small inferior genu and small splenium. An angled (90°) splenium was found to be significantly associated with cLIS; and excessively convex corpus callosum with VLDLR mutations. ACC with enlarged anterior commissure was found in all ARX mutations.

Conclusion—Specific patterns of the commissure anomalies were associated with certain types of lissencephaly. Callosal anomalies were more common than those of AC or HC. Developmental differences of commissures may be useful as an imaging criterion in differentiating the groups of lissencephalies and may give insight into the processes causing these malformations.

INTRODUCTION

Cerebral corticogenesis includes three major steps: 1) cell proliferation, 2) cell migration and differentiation and, 3) cortical organization with formation of mature cortex (1). Lissencephalies result from impaired migration of neurons from germinal matrices to the developing cerebral cortex (1–4). Disruption of normal neuronal migration can result from

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many different genetic and environmental disturbances; the result is usually a major brain malformation, including many types of heterotopia, lissencephaly, and cobblestone malformations (also called dystroglycanopathies because they result from abnormal glycosylation of alpha-dystroglycan) (4–9).

Lissencephalies were previously divided into 2 distinct groups: type I (classic) and type II (cobblestone). Recently, this classification has been expanded and the groups separated on the basis of pathologic, imaging, and genetic features (4,8,10). A recently proposed classification includes: *LIS1* and *DCX*, mutations causing classic lissencephalies; *ARX*, *RELN*, and *VLDLR* mutations and 2-layered cortex causing vLIS; and *FCMD, FKRP, LARGE, POMT1, POMT2*, and *POMGnT1* mutations causing CBSC (10). Almost all patients have neonatal hypotonia, epilepsy, and little developmental progress. The diagnosis is difficult when based only on clinical and laboratory findings, which are time-consuming and expensive. Fortunately, typical imaging features have been described in association with many mutations causing lissencephalies. This imaging phenotypic characterization may help in differentiating among these malformations (11–35).

Various anomalies of the major forebrain commissures, namely the CC, the AC and the HC, are commonly observed in human lissencephalies. The aim of our study was to investigate and categorize the developmental differences of the forebrain commissures in a large group of patients encompassing all lissencephaly types (classical, variant and cobblestone) to determine if specific features of size and shape may help to distinguish among the lissencephaly phenotypes.

MATERIALS AND METHODS

MRI scans or portions of MRI scans of 124 patients were retrospectively reviewed. The scans were acquired from the private teaching collection of the senior author, acquired over 23 years, from the teaching file of the Radiology Department at our institution (searching using lissencephaly, agyria, pachygyria, band heterotopia, cobblestone malformation, and congenital muscular dystrophy as key words), and from MRIs reviewed for a grant studying the genetics of epilepsy. The MRIs were included only if they had good quality images through the cerebrum (to assess the type and severity of the cortical malformation) and through the cerebral commissures as determined by a consensus of the authors. All studies included T1-weighted and T2-weighted images with scans performed in at least two planes (sagittal and axial). All cases included were confirmed unanimously by the authors to show agyria, pachygyria, or cobblestone cortex in some part of the cerebrum. As the cases were largely from radiological referrals, clinical information was usually rather sparse (typically including only a short report describing developmental delay, seizures, and family history) or, in some cases, completely absent. Sixteen cases without midsagittal images, and six with only CT images were excluded. Eight patients with Walker-Warburg disease who had severe hydrocephalus limiting assessment of some commissural structures were also excluded. The available data of the remaining 94 patients showed a mean age of 5.5 ± 7.5 years (range: 1 day to 32 years;, median: 2 years) at the time of imaging. The group included 33 females, 44 males, and 17 with unavailable gender information.

MRIs of 50 gender- and age-matched patients who were scanned for headaches, suspected macrocephaly, or epilepsy and interpreted as normal by a board-certified neuroradiologist were reviewed as controls. The lack of abnormality was confirmed unanimously by all authors in all cases. These control MRIs established the normal appearance of the forebrain commissures for comparison with our patients. All control MRIs had sagittal T1-weighted images, axial T1-weighted images, and axial and coronal T2-weighted images with slice thickness of 3–5 mm.

The authors reviewed the cases jointly with special attention to the cortical involvement. The patients were then classified to a presumed genotype based upon the imaging phenotype. Information about genotype was available only for a small percentage of our patients, because most were studied before the genetic tests for lissencephalies (*LIS1, DCX, TUBA1A, ARX, VLDLR, RELN*) or cobblestone malformations (*FCMD, FKRP, POMT1, POMT2, LARGE, POMGnT1*) were available. These many patients were classified as presumed (p) genotypes, (p)LIS1, (p)DCX, (p)ARX, (p)RELN, (p)VLDLR, if the imaging findings were highly suggestive of a specific gene mutation as detailed in a previous paper (10). Cobblestone malformations were not subclassified, since it has been well established that mutations of many glycosyltransferase enzyme genes can cause any of the clinical phenotypes; the clinicoradiologic phenotype is more dependent on the severity of the mutation (and presumably other, still unknown causes) than on the gene that is mutated (9, 34–36). All cases with ARX had a genetically proven diagnosis. All mutations (proven and presumed) were further grouped together into the three *main groups* such as cLIS, vLIS and CBSC for comparisons of imaging features.

We assessed the forebrain commissures, white matter volume, and myelination for each patient and compared these features with respect to main groups. We compared the shapes of the CC in the midsagittal plane with those in the control group. The shape and size of each commissure was determined by visually comparing each subject with age-matched controls. As there is significant variation in the size of the callosal components and of the commissures with age, as well as some variation among controls of the same age, only those commissures and callosal components judged unanimously by the three authors as significantly different from controls were graded as abnormal. The CC was categorized as follows.

1. Developmental appearance

   Agenesis (absence of the entire CC), *hypogenesis* (absence of the rostrum associated with small or absent splenium, small or absent inferior genu), *hypoplasia* (all parts formed, but decreased thickness, presumably due to reduced number of crossing axons, of any part of the CC), *dysmorphic* (abnormal shape of any part of the CC, presumably due to abnormal development).

2. Size of parts (rostrum, genu, body, splenium) and overall shape of the CC

   Changes in size and shape of at least one part or another of the CC led us to observe mainly two recurrent overall callosal shapes in a large number of patients. Some had an absent rostrum, small inferior genu, and small splenium with a convex upward shape and a sharp angle at the level of the midcallosal body (Fig. 4). Other patients had absence of the rostrum, small inferior genu, abnormally thin flat callosal body, and a sharp angle (about 90 degrees) between the body and a vertical splenium (Fig. 5). These specific features were reminiscent of a hypogenetic dysmorphic CC.

The HC and AC were assessed on midsagittal T1 and coronal T1 or T2 weighted images. Coronal images were particularly helpful for assessment of the HC as it connects the fornices and is usually largest immediately anterior and inferior to the callosal splenium. The size of the commissures was graded by visual assessment as small, normal or enlarged compared with the control group.

The degree of myelination was reviewed and compared with the standards for the patient's age (36). For patients less than one year old, myelination more than 2 months below standards for age was considered as delayed. For infants between one- and two years old, myelination more than 3 months below standards was considered as delayed. For children

beyond their second birthday, only grossly reduced cerebral myelination was recorded as delayed. When a patient's age could not be determined or the images were insufficient for reviewing the myelination, it was recorded as non-assessed (NA). White matter volume was visually assessed by the authors and considered as normal or reduced. The proximity of cortical sulci to the lateral margins of the cerebral ventricles and the relative ratio of white matter to ventricular size after comparison with normal controls were the criteria used for this assessment. Consensus was achieved among the authors for all cases; patients with questionable findings but close to normal status were considered to be normal.

Statistical comparisons of overall callosal shapes between classical and variant groups were carried out by the 'extension to mxn table, Monte Carlo simulation of chi-square and Fisher's exact tests as appropriate. ACC, hypogenesis, hypoplasia, angled splenium, convex corpus and normal shape underwent statistical comparisons. A p value less than 0.05 was considered as significant. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS, version 15.0, Chicago, IL, USA).

RESULTS

Among our 94 patients, 23 (24.46%) patients had a confirmed genetic diagnosis. 57.4% were classified as cLIS (LIS1=3.7%, (p)LIS1=53.7%, DCX= 11.1%, (p)DCX= 29.6%, and 1 patient with no mutation), 38.4% as vLIS (ND= 58.3%, RELN= 2.8%, (p)RELN= 5.5%, ARX=11.1%, VLDLR= 5.5%, (p)VLDLR= 16.6%), and 4.2% had cobblestone complex (CMD-ND= 50% and *MEBD*= 50%).

Most of the cases had developmental abnormalities of the forebrain commissures. The CC was more commonly affected than the AC and HC. The CC was most often hypogenetic and dysmorphic. This appearance of CC clearly differed from that seen in the control group. Combining the proven and presumed same mutation groups, we applied statistics to evaluate group differences based on the forebrain developmental abnormalities.

In cLIS, most of the LIS1 patients (70.9%) had callosal hypogenesis (Fig. 1) with a thin flat body and vertical splenium shape in about half cases (48.4%) (Fig. 5), which made a significant difference between LIS1 and other groups (p=0.011). The AC and HC were normal in most of the cases. In DCX patients, we found hypogenetic CC (68.1%) with no specific dysmorphic shape. The AC and HC were mostly normal.

In vLIS group, all ARX patients had ACC with enlarged AC (Fig. 6). The patients with RELN mutation phenotype had a hypoplastic CC in all cases with absent (33%) or small (66%) inferior genu. The AC was absent in 66% while the HC was normal in all. The VLDLR phenotype was significantly associated with a hypogenetic convex upward CC body which differed from other groups (p=0.011). The AC was predominantly small (62.5%) and the HC was mostly non assessed (75%). The shape of the CC showed a significant difference between the cLIS and vLIS groups (p=0.017). The CBSC patients typically had absent rostrum (75%), a thin or normal genu (75%), a thin or normal body (75%), and a thin splenium (50%). Because many of these patients had hydrocephalus or shunted hydrocephalus, the CC was often distorted and had variable general appearances. Patients without severe hydrocephalus often had a smoothly arched callosal body (Fig. 4). The AC and HC were normal in half of the cases.

Myelination was normal in 43.6% of all lissencephaly cases. Sixty-four percent of cLIS and 18.9% of vLIS patients showed normal myelination. Delayed myelination was found in half of the vLIS cases. The white matter volume was regarded as normal in only 6.4% of cases who had a normal CC (Fig. 7). The remaining patients (93.6%) had differing severities of reduced white matter volume. All cases in vLIS group showed reduced white matter volume.

Considering the components of the CC, the rostrum was absent in 70.3% of cLIS and in 75% of vLIS cases. The genu was absent in only 7.4% of cLIS but in 30.6% of vLIS. A small inferior part of the genu was found in 59.3% of cLIS and in 38.9% in of vLIS patients. A thin flat body was seen more commonly in cLIS; it was frequently convex upward in vLIS patients (as stated above). The splenium was normal in only 18% of all patients. When it was not associated with a particular overall shape of the CC as previously defined, it appeared small in all other cases when seen. Statistical results are summarized in Table 1.

DISCUSSION

This detailed review of a large number of MRI scans of patients with various types of lissencephaly showed developmental abnormalities of the major forebrain commissures almost in all patients ; the CC was the commissure most commonly involved. This result is not surprising, as the CC is composed of axons from cerebral cortical neurons which are abnormal in location and possibly in function in lissencephalies (37). Neurites from these abnormal neurons might be expected to experience errors in pathfinding through the many signals that normally guide them across the midline in the developing brain (38–39). Although many variations were seen, the most common anomaly consisted of absent rostrum, small inferior genu, and small or abnormally shaped splenium: this configuration has been defined as hypogenetic (36,40). In addition, malformations secondary to specific mutations and presumed mutations seemed to have a characteristic overall shape of the CC.

The LIS1 patients had predominantly callosal hypogenesis with thin flat body and vertical splenium shape (Fig. 5) while the DCX phenotype was significantly associated with hypogenetic CC without any specific overall CC shape. ARX mutation with the XLAG phenotype is known to have callosal agenesis in nearly all cases (by definition). Therefore, finding ACC in our ARX patients was expected. ACC was also found in other vLIS cases and could potentially be used to differentiate cLIS from vLIS. The RELN patients mainly had a hypoplastic CC (Fig. 2), while the CC in VLDLR patients was generally hypogenetic with a convex upward body shape (Fig. 4). The CBSC patients were included even though they have distinctive characteristic MRI features of the cerebral cortex and posterior fossa structures, because we aimed to explore the forebrain commissures within the full range of lissencephalies. We thus propose to include our findings in the differential criteria of various lissencephaly MRI phenotypes.

The AC and the HC were assessed along with the CC since all are composed of axons from cortical neurons crossing through the cerebral midline (40). Thus, some developmental disturbances affecting the midline crossing callosal axons might be expected to involve the other commissures as well. Absence of the AC was common in patients with vLIS, and its enlargement was consistently detected in ARX (along with ACC). The significance of such enlargement is unclear. Regarding the HC, it was enlarged in some vLIS patients, but this appearance was not helpful in differentiating among the lissencephalies groups.

The developmental differences of forebrain commissures in various types of lissencephalic cortical malformations are likely related to the causes of these malformations, which means the effects of gene mutations on neurogenesis, neuronal migration, and neurite development. Axons from abnormal neurons or from neurons in abnormal locations are less likely to navigate normally across the midline via the cerebral commissures. As the physiological basis of neuronal and neurite development and migration is complex and incompletely understood to date, it is not helpful to speculate on the physiologic and molecular biologic differences that have resulted in the commissural anomalies described in this study. Nonetheless, a few general concepts seemed to emerge. Patients with the LIS1 pattern of cortical involvement (pachygyria gradient more severe posteriorly, involving parietal and

occipital lobes) had a more vertical splenium (Figs. 1, 5), while those with the DCX pattern (more severe anteriorly involving posterior frontal lobes) more often had normal or slightly thin splenium. Patients with the vLIS patterns of lissencephalic cortical malformations, which, other than VLDLR, have less organized cortical histology than the cLIS patterns (8), had the most severe commissural anomalies with frequent ACC or CC hypoplasia. Although VLDLR patients sometimes had nearly normal CCs, they more commonly had a relatively sharp upward angle of the midcallosal body, giving them the convex upward body shape. The cause of this angle is not clear but, if confirmed in other studies, it may be a useful imaging marker for this unusual disorder. Overall, our findings indicate that the appearance of the CC does not simply derive from the pattern of cortical involvement in lissencephalies but is likely the result of impaired neuronal and axonal migration at some step.

This study contains a number of assumptions and limitations. It is limited by the small number of cases with established genetic diagnoses. An attempt was made to increase this number by classifying studies as having a “presumed” genetic classification based upon characteristic MRI features and their correlation with known pathology, such as cell-sparse zones, associated cerebellar anomalies, and cortical thickness. In a previous study, we showed that the genetically-proven and presumed groups showed considerable homogeneity of MRI morphology (10). Thus, we believe that this classification as “presumed” mutations was both useful and justified. Many patients in the vLIS group were classified as ND because of lack of part or total clinical information. Some of these were likely to be the two-layered lissencephaly described by Forman (2005) or a result of *TUBA1A* mutations (41–44). We did not presume the diagnosis of *TUBA1A* mutation in any patient because the phenotypes associated with this mutation were not disclosed at the time of the study and are still not fully established. From current literature, it appears that *TUBA1A* mutations may result in either cLIS or vLIS patterns (41–44). It may be useful to reassess these cases in several years when these and other new causes of lissencephaly are better established. Despite these obvious deficiencies, this study has yielded important information for physicians and scientists interested in corticogenesis by adding to the knowledge of associated malformations.

CONCLUSION

Anomalies of the cerebral commissures are common in the lissencephalies and likely result from impairment of migration of cortical neurons and of navigation of their axons through the developing cerebrum. Looking at the commissures in lissencephalies may help to differentiate among lissencephaly phenotypes and hopefully, in the future, among genotypes. The information provided by our study will hopefully lead to further studies of the molecular disorders involved in brain anomalies associated with agyria and pachygyria and, ultimately, a better understanding of the mechanisms of normal and abnormal brain development.

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Abbreviations

cLIS	Classical lissencephaly
vLIS	Variant lissencephaly
CBSC	Cobblestone complex

LIS1	lissencephaly with mutated *LIS1* gene
DCX	lissencephaly with mutated *DCX* gene
ARX-XLAG	lissencephaly with *ARX* mutation, and an absent callosum, ambiguous genitalia
RELN	lissencephaly with *RELN* mutation
TUBA1A	lissencephaly with *TUBA1A* mutation
VLDLR	lissencephaly with *VLDLR* mutation
CMD	Congenital muscular dystrophies
WWS	Walker-Warburg syndrome
MEB	Muscle-eye-brain disease
FCMD	Fukuyama congenital muscular dystrophy
FKRP	lissencephaly with *FKRP* mutation
LARGE	lissencephaly with *LARGE* mutation
POMT1, POMT2, and POMGnT1	lissencephalies with *POMT1*, *POMT2*, *POMGnT1* mutations
(p)	Presumed
ND	Not determined
ACC	Agenesis of the corpus callosum
CC	Corpus callosum
AC	Anterior commissure
HC	Hippocampal commissure

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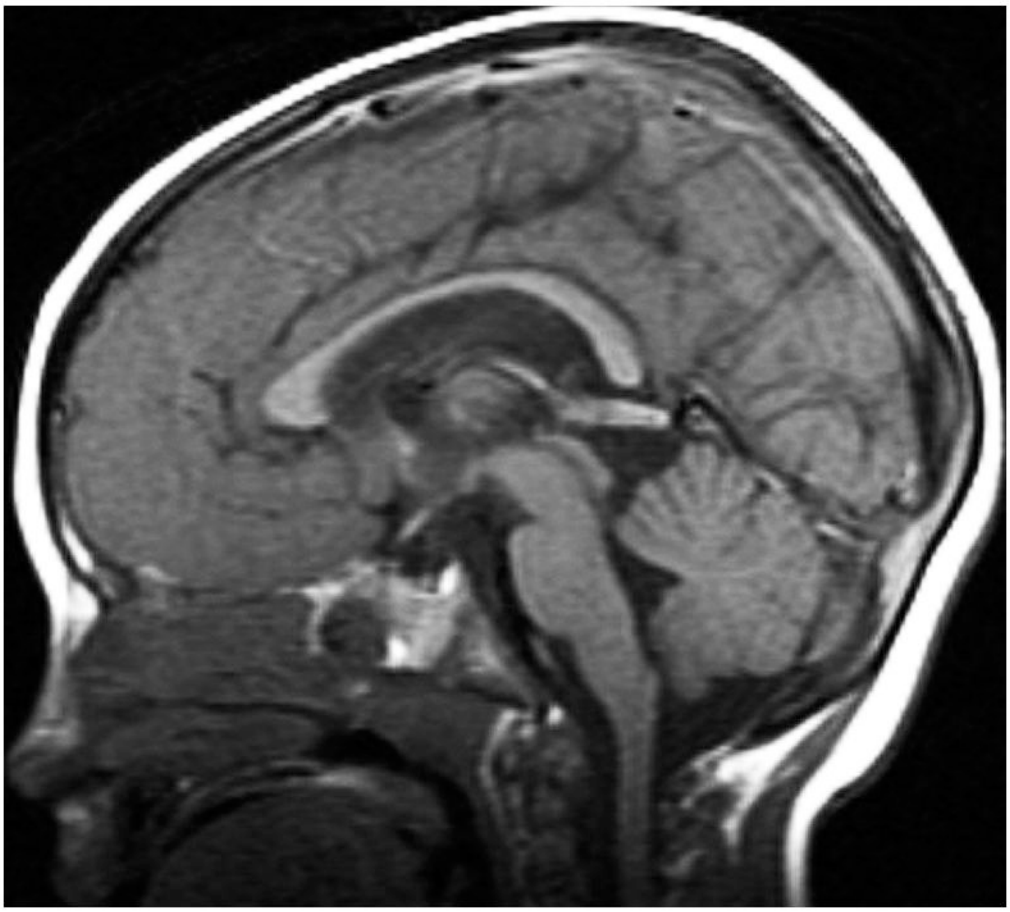


Figure 1.

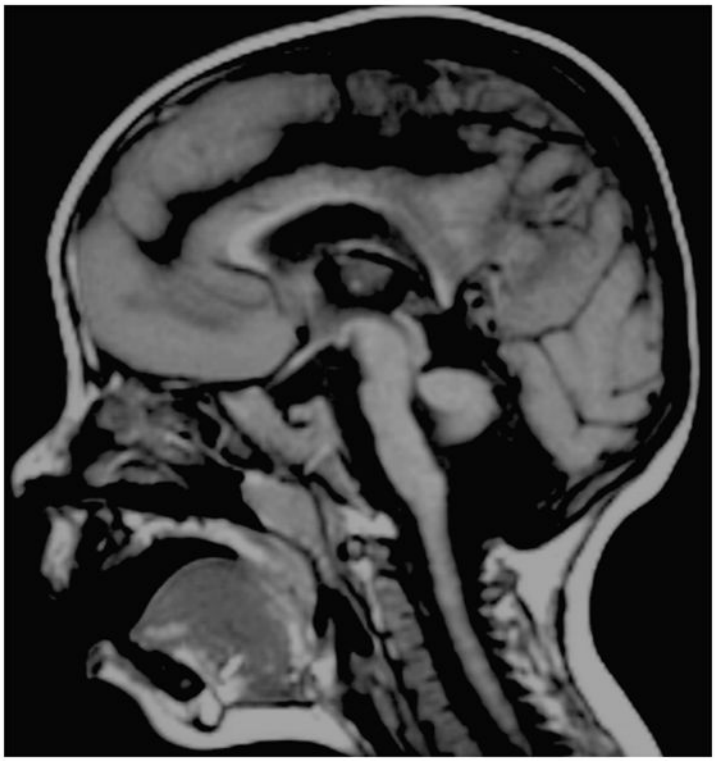


Figure 2.

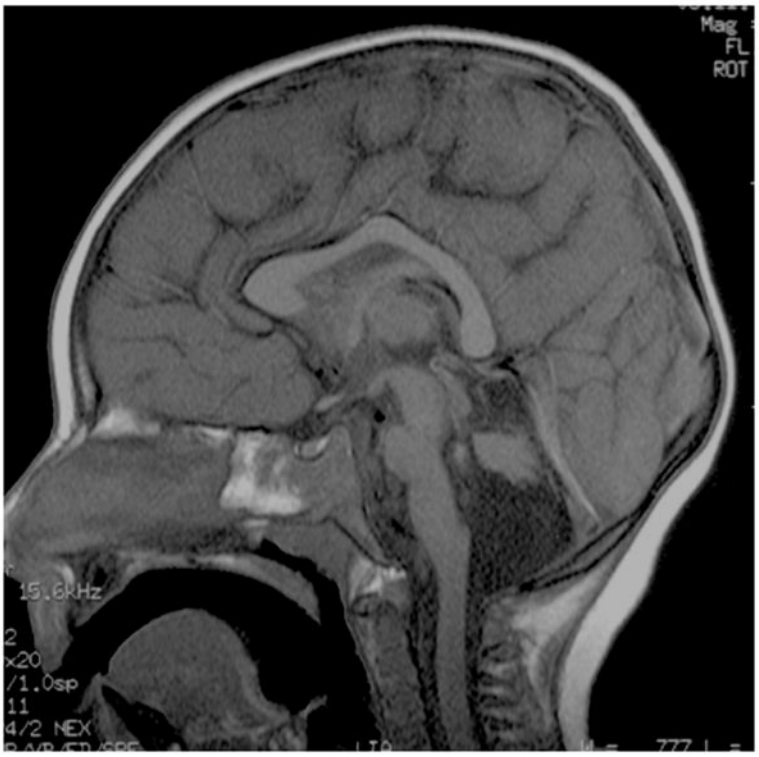


Figure 3.

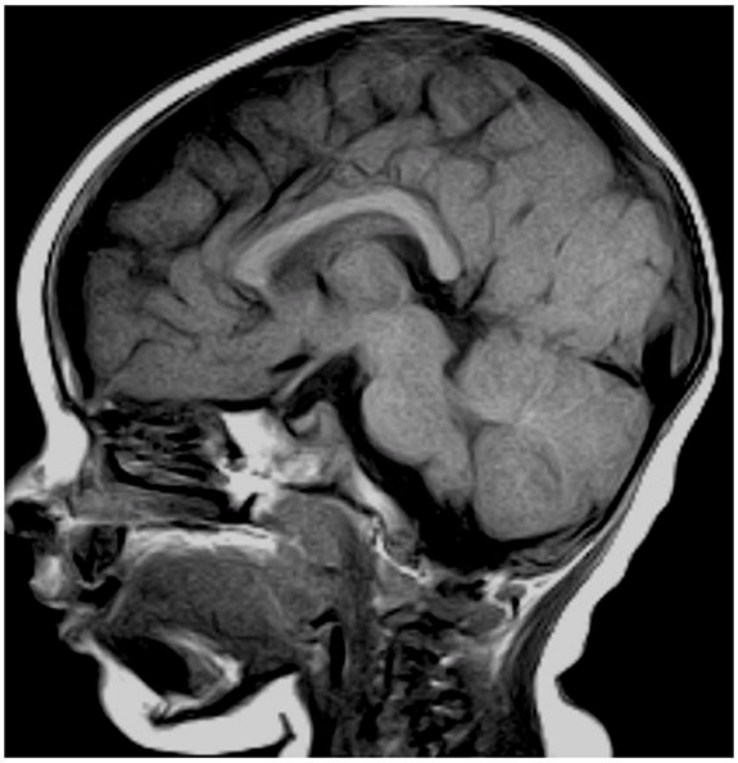
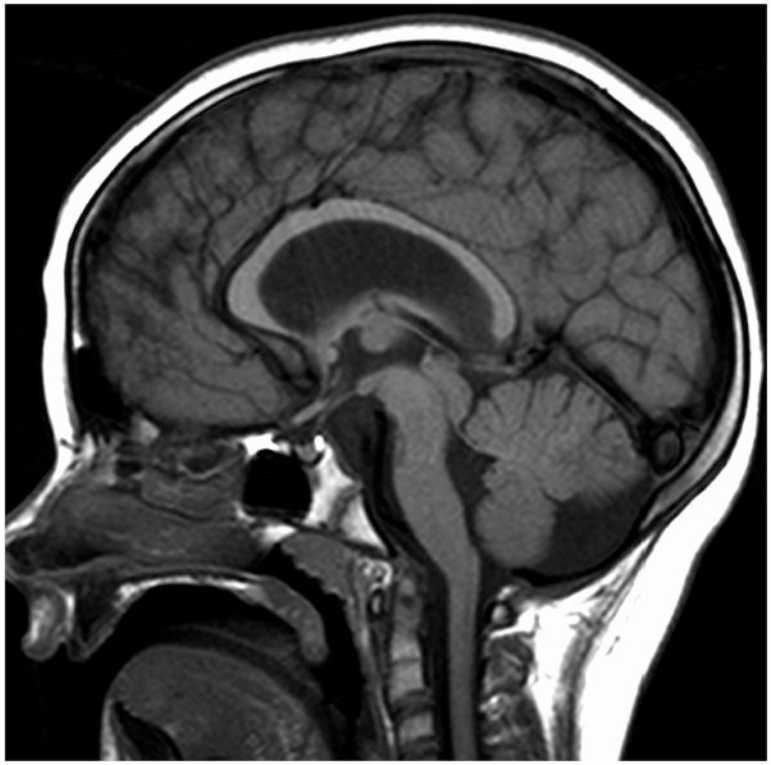


Figure 4.



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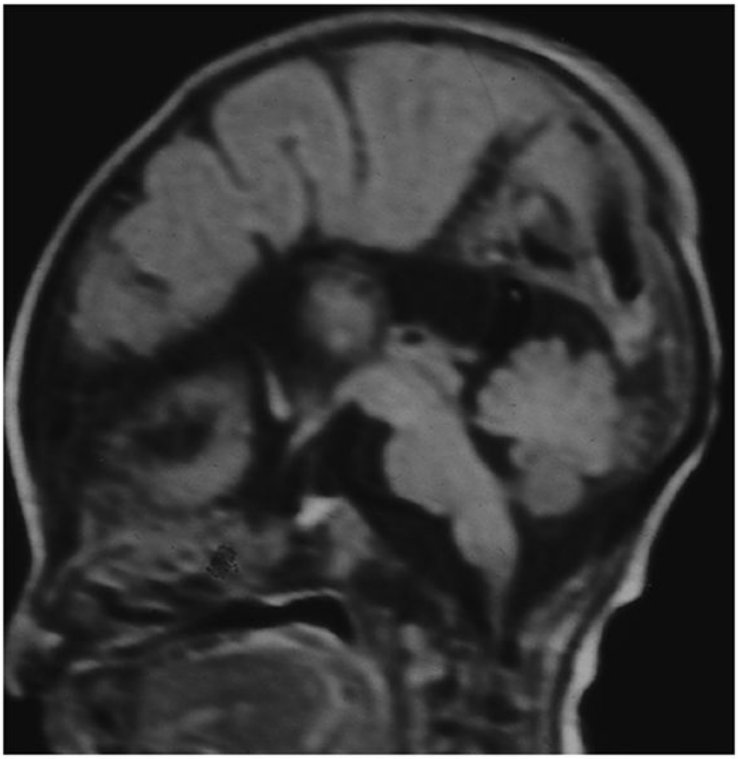

Figure 6.

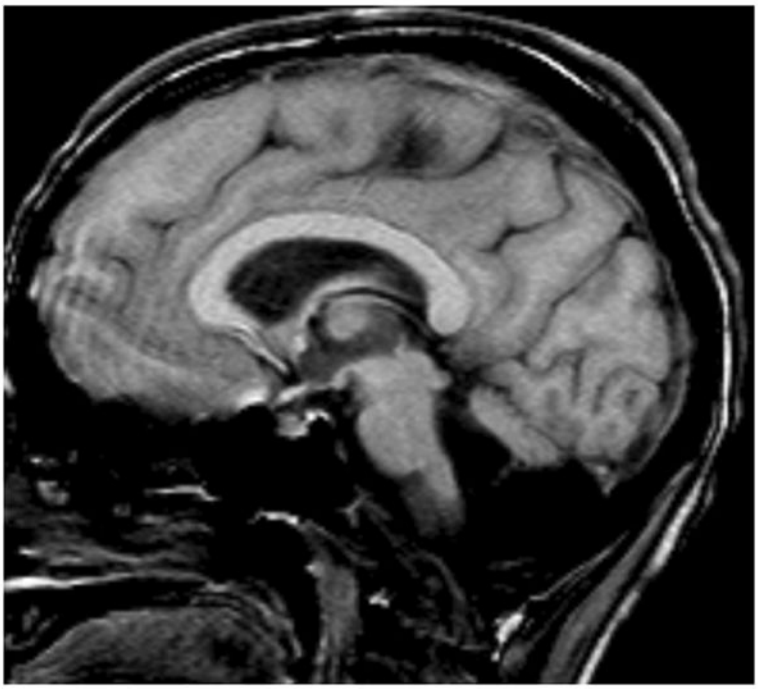

Figure 7.

Table 1

Significant differences between the major types of lissencephaly for each structure and specific features.

Structure	Groups compared and associated features	*p* value
Splenium	cLIS – vertical or thin vLIS – absent or thin, and small	p< 0.001
Brain involvement	cLIS – pachygyria (P>A, central, A>P) vLIS – pachygyria entire brain	p< 0.001
Myelination	cLIS - normal vLIS – delayed	p< 0.001
CC genu	cLIS – small inferior or N vLIS – absent or small inferior CBSC – normal genu	p= 0.002
HC	cLIS – normal	p= 0.003
AC	cLIS – normal or small vLIS – absent	p= 0.047
CC body	cLIS – normal or flat thin vLIS – convex upward	p= 0.011