



Anomalies of the Corpus Callosum: An MR Analysis of the Phenotypic Spectrum of Associated Malformations

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OBJECTIVE. We sought to categorize the structural brain anomalies associated with abnormalities of the corpus callosum and anterior and hippocampal commissures in a large cohort.

MATERIALS AND METHODS. Brain MR images of adult and pediatric patients from our institution and from a national support organization (the ACC Network) were retrospectively evaluated for the type and severity of commissural anomalies and the presence and type of other structural abnormalities.

RESULTS. Of 142 cases that were reviewed, 82 patients had agenesis of the corpus callosum (ACC), while 60 had hypogenesis of the corpus callosum (HCC). Of the overall cohort, almost all had reduced white matter volume outside the commissures, the majority had malformations of cortical development (most commonly heterotopia or abnormal sulcation), many had noncallosal midline anomalies (including abnormal anterior or hippocampal commissures and interhemispheric cysts and lipomas), and several patients had abnormalities of the cerebellum or brainstem. Sixty-six patients had Probst bundles, which were more common in patients with ACC than in those with HCC. Probst bundles were present in all four patients who had ACC or HCC but no other midline, cortical, or posterior fossa anomalies.

CONCLUSION. Isolated commissural anomalies were rare in the populations of patients examined. Most cases of ACC and HCC were associated with complex telencephalic, diencephalic, or rhombencephalic malformations. Reduced cerebral hemispheric white matter volume and malformations of cortical development were seen in more than half of the patients, suggesting that many commissural anomalies are part of an overall cerebral dysgenesis. ACC and HCC appear to lie along a dysgenetic spectrum, as opposed to representing distinct disorders.

MRI shows CNS anatomy in exquisite detail, permitting *in vivo* characterization of human brain anomalies previously incompletely evaluated using CT and sonography. Accordingly, certain anomalies previously thought to be isolated have proven to be associated with one or more other brain malformations [1–7]. MRI thus sheds new light on a fundamental problem in clinical neurology: explaining disparate outcomes in patients who heretofore were thought to have identical CNS malformations. Equally, MRI can reveal disparate structural anomalies leading to similar clinical outcomes such as seizures and developmental delay.

The corpus callosum is the principal supratentorial cerebral commissure (interhemispheric white matter tract). It has traditionally been separated into four segments: the rostrum, genu, body, and splenium (Fig. 1). Two smaller interhemispheric connections are located near the corpus callosum: the anterior

commissure, which runs between the amygdaloid nuclei, and the hippocampal commissure or psalterium, which connects the fornices and blends with the ventral aspect of the callosal splenium. Prior work has shown that anomalies of the corpus callosum, including agenesis (absence) and hypogenesis (presumed later-formed segments missing but earlier-formed segments present, sometimes referred to as “partial agenesis of the corpus callosum”), may be associated with a variety of other brain malformations [1, 2, 5, 8–10].

For this study, we compiled MRI data from the largest extant cohort of patients with callosal anomalies and attempted to sort patients into discrete groups based on the morphology of the cerebral commissures and associated malformations of the midline, of cortical development, of white matter, and of the diencephalon and rhombencephalon. The focus of this article is to describe the noncallosal anomalies present in patients with callosal

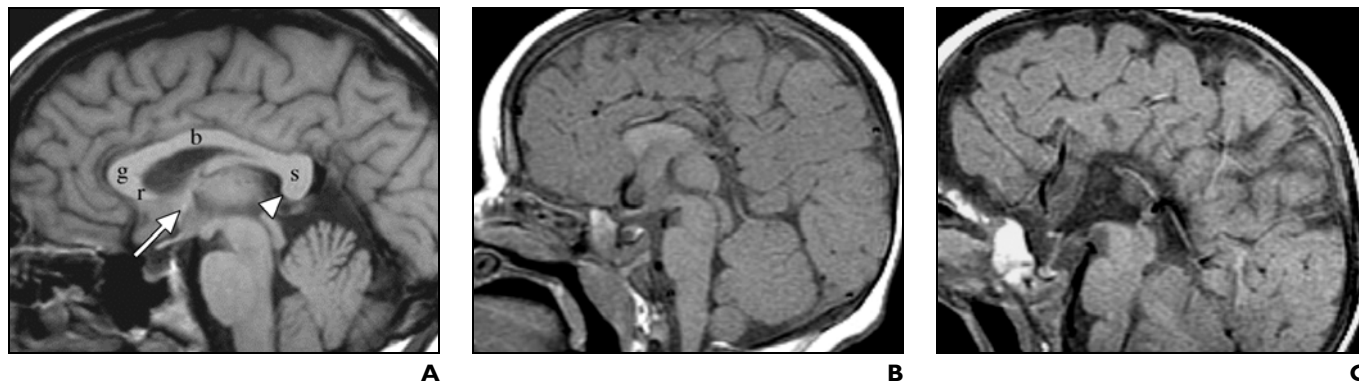


Fig. 1—Midline sagittal MR images of normal cerebral commissures, callosal hypogenesis, and callosal agenesis. **A**, Sagittal T1-weighted image in 20-year-old woman shows normal cerebral commissures, including fully formed corpus callosum with rostrum (r), genu (g), body (b), and splenium (s). Anterior commissure is denoted by arrow, and hippocampal commissure is denoted by arrowhead. **B**, Sagittal T1-weighted image in 12-year-old boy shows callosal hypogenesis, with genu and anterior body present, but posterior body, splenium, and rostrum absent. **C**, Sagittal T1-weighted image in 10-year-old girl shows agenesis of corpus callosum, with concomitant medial hemispheric sulci oriented perpendicular to third ventricular roof.

malformations, to examine the radiologic differences between patients with ACC and those with HCC, and to identify the radiologic differences between patients with callosal anomalies examined at a major tertiary care referral center and patients who are members of the ACC Network (a national support group for patients with callosal anomalies). This constitutes the first step in a long-term project to perform genetic analysis on anatomically discrete subgroups of patients with commissural anomalies.

Materials and Methods

Potential subjects for this retrospective cohort study were obtained from a search of the radiology database for all MRI examinations of the brain performed between 1985 and 2003 at our institution, a major tertiary care university medical center. The database of 66,736 examinations was queried with “callosum” and “hypogenesis” or “dysgenesis” or “agenesis.” This search yielded 198 patients. Dictations were reviewed to identify all likely cases of agenesis of the corpus callosum (ACC) or hypogenesis of the corpus callosum (HCC), yielding 167 cases; the remaining 31 patients were excluded because the callosum was described as not abnormal in the dictations. An additional 85 cases were excluded because the studies could not be located.

Images from the 82 remaining MRI studies were evaluated by two neuroradiologists and a pediatric neurologist. Further exclusion criteria included inadequate scan quality; commissural dysmorphisms interpreted as being secondary, such as those from congenital hydrocephalus, Chiari II malformations (most which were associated with open neural tube defects), or large destructive injuries to the brain;

holoprosencephaly, in which commissural anomalies are believed to result from incomplete induction of associated regions of brain; and those that are part of known multiple congenital anomaly (MCA) syndromes (e.g., Aicardi’s syndrome) for which underlying genetic causes have been identified previously [11, 12]. These excluded patients (except those with inadequate scans) are considered as distinct groups and will be evaluated in separate studies. Additional reasons for exclusion were identification of a normal corpus callosum on MRI and presence of a normal corpus callosum other than a nonvisualized rostrum, which can indicate a true absence or merely an inability to detect that small structure on an MR image obtained with a sagittal slice thickness of ≥ 4 mm.

The scans of included patients were evaluated for type and severity of commissural anomalies; presence and type of interhemispheric cyst; presence and type of malformations of cortical development; distortions of the cerebral ventricles; anomalies of white matter (normal or reduced volume, location of reduced volume, and state of myelination); presence or absence of Probst bundles (collections of axons running anteroposteriorly lateral to the lateral ventricles, thought to represent axons that would have crossed the midline if a callosum were present); presence of microcephaly; and anomalies of the cerebellum, brainstem, orbits, and olfactory apparatus. With regard to qualitative white matter volume, the three expert observers subjectively compared the size of the centrum semi-ovale to the overall size of the brain and reached a consensus as to whether the volume of white matter was qualitatively normal, increased, or mild, moderately, or severely decreased as compared with age-matched control subjects (from our institution’s

database of normal brain MRI examinations) who were imaged for reasons other than developmental delay. The cerebellar size and folial pattern and the size and location of the fourth ventricle were similarly qualitatively assessed to determine whether foliation was normal and whether segmental or overall hypoplasia was evident. In the category labeled abnormalities of sulcation were included cortical malformations, such as pachygyria and polymicrogyria, as well as oversulcation (defined as the presence of too many sulci in the absence of identification of the sulci normally present in that region). Similarly, other qualitative and quantitative anomalies were determined by consensus of the three observers. A subset of scans from our hospital was also reviewed by a neuroradiologist blinded to the first consensus interpretation. The findings of this additional evaluation were compared with the consensus findings in order to calculate kappa statistics for interobserver consistency (MacKappa [computer software], Watkins MW).

Eighty-seven additional cases were obtained from an ongoing prospective cohort of individuals with anomalies of the corpus callosum. Families learned of the study through the National Organization of the Corpus Callosum and the ACC Network, national family support organizations for individuals with ACC. Membership in these organizations is based on self-referral by patients or the families of patients who have been diagnosed with agenesis or abnormalities of the corpus callosum. Seizures and developmental delay are the most common reasons these patients initially came to clinical attention. MRI examinations of patients in the ACC Network were subjected to the same exclusion criteria and analyses as outlined for patients from our institution, leaving 85 for inclusion. ACC Network pa-

MRI of Anomalies of the Corpus Callosum

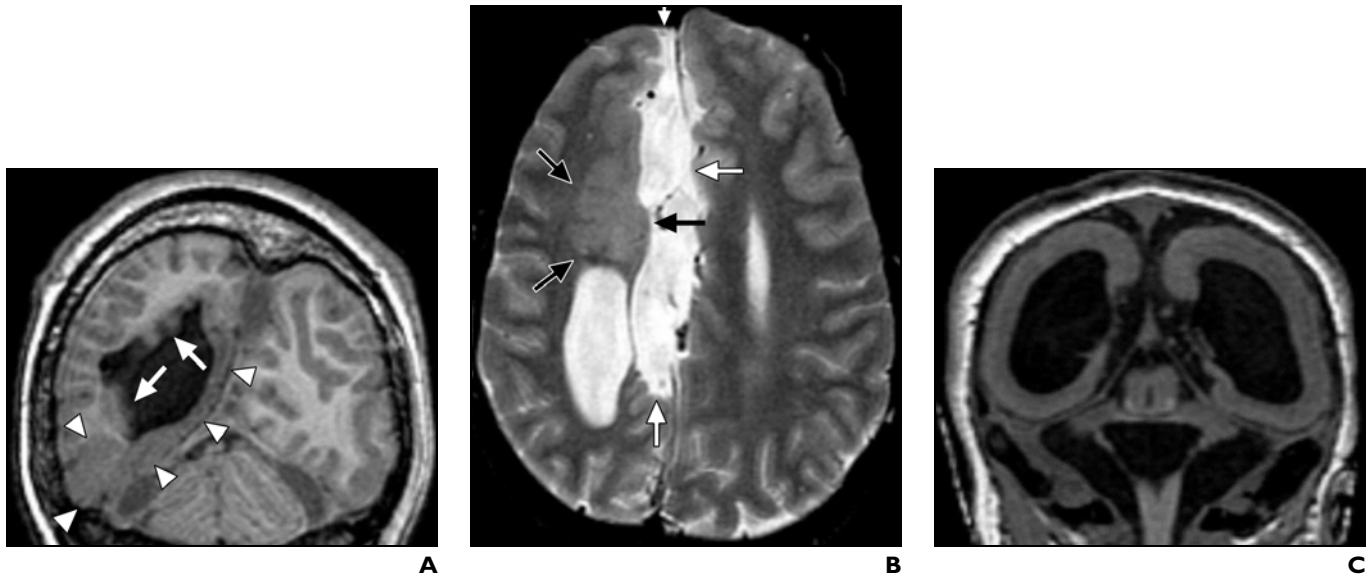


Fig. 2—Malformations of cortical development of varying extent and severity were found in patients with callosal hypogenesis or agenesis. **A**, Coronal T1-weighted image in 4-year-old boy shows periventricular nodular heterotopia (*arrows*) and dysplastic occipital cortex (*arrowheads*) in addition to dysplastic cerebellum. **B**, Axial T2-weighted image in 17-year-old boy shows dysplastic frontal and cingulate cortex (*black arrows*) adjacent to interhemispheric cyst (*white arrows*). **C**, Coronal T1-weighted image in 6-year-old girl shows lissencephaly with four-layer cortex.

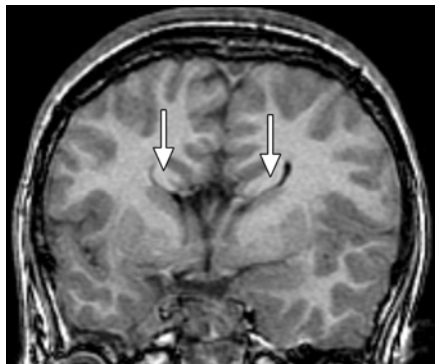


Fig. 3—Probst bundles. Coronal T1-weighted image in 14-year-old girl shows lateral callosal bundles of Probst (*arrows*) indenting superomedial margins of lateral ventricles.

tients had MRI examinations of highly variable quality, at times limiting their evaluation.

Chi-square analyses of all patients were conducted using Microsoft Excel for Macintosh (Apple Computer), 2001 edition, for bivariate comparisons between patient groups with regard to key radiologic findings. Two-tailed Student's *t* tests were used to compare ages between cohorts, also using Microsoft Excel.

Results

The prevalence of callosal agenesis or dysgenesis in patients undergoing brain MRI at

our tertiary care referral institution was 0.25% (167 of 66,736). Eighty-two cases from our institution and 87 outside studies were reviewed. Eighty-two patients had callosal agenesis, 60 callosal hypogenesis, and 27 were excluded from further review (normal callosa, known multiple congenital anomaly syndromes, or technically limited studies). Of the remaining 142 patients, 73 had malformations of cortical development (Fig. 2), with heterotopia and abnormal sulcation as the most common. The anterior commissure was absent in 48 patients and abnormal in size in 46 (10 enlarged and 36 small). The hippocampal commissure was absent in 107 patients and abnormal in size in four. Cerebral ventricles were abnormal in 128 patients, white matter volume was reduced in 134, and myelination was delayed in 32. Probst bundles were identified in 66 patients (Fig. 3), interhemispheric cysts in 20 (11 patients had cysts in communication with the ventricular system and nine had cysts that did not communicate), and interhemispheric lipomas in three. Anomalies of the cerebellum, brainstem, orbits, and olfactory apparatus were also evident in many patients.

The patients with ACC and those with HCC were compared. The mean ages (\pm SD) of ACC and HCC patients were different ($p = 0.04$), being 4.0 ± 7.1 years (range, 1 day–39 years)

and 7.8 ± 13.7 years (range, 2 days–68 years), respectively. Forty-seven percent of ACC patients and 37% of HCC patients were female ($p = 0.78$). ACC patients constituted a lesser proportion of patients (28%) from our tertiary care hospital cohort than from the ACC Network cohort (57%; $p < 0.001$).

Interhemispheric cysts were similar in frequency between the two groups (17% of ACC patients and 10% of HCC patients; $p = 0.23$), as were interhemispheric lipomas (2% in both ACC and HCC patients). Abnormalities of the anterior commissure (71% ACC, 67% HCC; $p = 0.65$) and hippocampal commissure (95% ACC, 88% HCC; $p = 0.1$) were similar in frequency between the two groups. The presence of any cortical malformation (51% ACC, 55% HCC; $p = 0.65$) and of gray matter heterotopia (29% ACC, 21% HCC; $p = 0.28$) was not significantly different in frequency between ACC and HCC patients.

Abnormal cerebral ventricles were more frequently present in ACC patients (96%) than in HCC patients (83%, $p < 0.01$). Abnormalities of the orbits (6% ACC, 13% HCC; $p = 0.14$), pituitary (13% ACC, 19% HCC; $p = 0.31$), state of white matter myelination (25% ACC, 22% HCC; $p = 0.62$), cerebellar hemispheres (18% both ACC and HCC), cerebellar vermis (30% ACC, 33% HCC; $p = 0.71$), and brainstem (22% ACC, 27% HCC; $p = 0.51$) were

similar in frequency between the ACC and HCC patients. Abnormalities of the olfactory sulci (33% ACC, 15% HCC; $p = 0.03$) were more frequent in ACC patients. Reductions in extracallosal white matter volume (98% ACC, 92% HCC; $p = 0.1$) and the presence of moderately or severely reduced extracallosal white matter volume (69% ACC, 58% HCC; $p = 0.16$) differed for the two groups, but that difference did not reach statistical significance. The most statistically marked difference between ACC and HCC patients was the frequency of lateral callosal bundles of Probst (59% ACC, 30% HCC; $p < 0.001$).

Comparison was also made between patients examined at our tertiary referral university hospital with those who underwent MRI examinations at outside hospitals and were enrolled in our prospective study through the ACC Network. These groups differed both demographically and anatomically. The mean age (\pm SD) of patients examined at our hospital was 8.3 ± 15.2 years (range, 2 days–68 years) versus 4.3 ± 3.6 years (range, 1 day–19 years) for patients examined elsewhere and enrolled through the ACC Network ($p < 0.01$). Sixty-nine percent of patients referred through the ACC Network had absence of the corpus callosum versus 40% of our patients ($p < 0.001$); the remaining patients in both groups had callosal hypogenesis. The ACC Network prospective cohort patients were more likely to be young children than those examined at our university hospital.

Our hospital's patients were more likely to have abnormal anterior commissures (78% tertiary hospital, 63% ACC Network; $p = 0.05$), cortical malformations (64% tertiary hospital, 45% ACC Network; $p = 0.027$), abnormal ventricles (82% tertiary hospital, 95% ACC Network; $p = 0.013$), moderately to markedly reduced white matter volume (76% tertiary hospital, 56% ACC Network; $p = 0.016$), abnormal (delayed or incomplete) myelination (32% tertiary hospital, 17% ACC Network; $p = 0.024$), and anomalies of the cerebellar vermis (42% tertiary hospital, 24% ACC Network; $p = 0.027$) and brainstem (34% tertiary hospital, 17% ACC Network; $p = 0.023$). Probst bundles, however, were far more common among ACC Network prospective cohort patients (66%) than among patients from our hospital (18%, $p < 0.001$).

ACC and HCC patients were also categorized by the presence of Probst bundles, midline anomalies, malformations of cortical development, and other anomalies (primarily rhombencephalic and diencephalic anomalies

and known multiple congenital anomaly syndromes, such as Aicardi's syndrome). Callosal agenesis and hypogenesis were usually accompanied by other abnormalities. Only three patients had isolated ACC without other anomalies, and only one patient had isolated HCC without other anomalies; all four of these patients had Probst bundles. Midline anomalies (primarily cysts, lipomas, anomalies of the anterior or hippocampal commissures) were the most common supratentorial abnormalities. Whereas the majority (22/25) of patients with ACC and other midline anomalies had Probst bundles, the majority of patients (13/21) with HCC and other midline anomalies did not have Probst bundles. Patients with rhombencephalic or diencephalic abnormalities (14/61) were less likely to have identifiable organized bundles of Probst than patients without such anomalies (53/81).

A subset of scans from our university hospital was also reviewed by a neuroradiologist blinded to the first consensus interpretation. Comparison of this observer's findings with the consensus results showed a high degree of interobserver consistency, with kappa statistics for interobserver agreement ranging from 0.89 to 1.0 for examined parameters. The kappa statistic for agreement was 0.89 when categorizing extracallosal supratentorial white matter volume as normal versus reduced to any degree. Similarly, when white matter was categorized into two groups—normal or mildly reduced versus moderately or markedly reduced—the kappa statistic for agreement remained 0.89.

Discussion

Agenesis or hypogenesis of the corpus callosum is a feature in more than 50 different human congenital syndromes, with clinical manifestations ranging from mild to devastating [13–18]. In several prior studies, researchers have used CT, sonography, and MRI to analyze patients with callosal anomalies [1, 2, 9, 15, 16, 19]. Our current study includes the largest MRI-proven collection of patients with callosal anomalies (excluding hypoplasia, in which all segments are present but small). Although there was considerable heterogeneity in our populations of patients, certain themes emerged.

An abnormality or the absence of cerebral commissures was almost always accompanied by other brain malformations. The type, number, and severity of associated anomalies, however, differed between the retrospective cohort from our university hospital and the

prospective ACC Network cohort. These differences underscore the selection biases inherent in drawing patients from a tertiary referral center and from a support group for individuals or families of individuals with a specific anomaly. Our university patients tended to have more complex and extensive anomalies, but fewer had ACC and fewer had identifiable Probst bundles; neonates with multiple congenital anomalies were more prevalent in our university cohort than in the ACC Network cohort. The relative lack of such patients in the ACC Network may reflect early mortality (patients not surviving long enough for their parents to join a support group) or that patients with multiple anomalies may be categorized principally by a diagnosis other than their callosal anomaly (e.g., parents of patients with lissencephaly associated with callosal hypogenesis might seek association with a support group for lissencephaly instead of the ACC Network). Despite the relative lack of neonates in the ACC Network cohort, on average patients were younger in this group than in our university's cohort. To our knowledge, this is the first documentation in the literature that cohorts of patients examined for the presence of a specific congenital malformation might differ only because of the source of referral.

Beyond the difference between patients from the ACC Network and our university hospital, there is also an inherent selection bias toward patients with clinical symptoms. The relative dearth of patients with isolated ACC or HCC may reflect either rare prevalence of isolated callosal anomalies or that people with isolated callosal anomalies do not have clinical symptoms that bring them to the attention of physicians. Neuropsychologic testing of patients with callosal agenesis has previously revealed subtle deficits of higher cognitive function not evident on routine clinical examinations [20, 21]. Another study reported that the only individuals with normal neurodevelopment were those with isolated callosal hypogenesis [22]. Only a large population-based MRI screening study could sort this out, and that task is beyond the scope of our current study.

An abnormality or the absence of cerebral commissures was rarely isolated in our study. Barkovich and Norman [2] examined 68 adult and pediatric patients with brain anomalies using MRI. Of these, 32 had ACC or HCC, but only one had isolated ACC, similar to the current study. Byrd et al. [9] later performed a retrospective and prospective analysis of

105 children with ACC in which all participants were examined on X-ray CT, 60 also on MRI, and 15 also on sonography. The 105 patients were sorted into seven nonexclusive groups (10 patients were counted twice), including 26 with isolated ACC. Of note, however, in the "isolated" ACC group, eight of 26 had Aicardi's syndrome, which always includes heterotopia and polymicrogyria among other characteristic features [23–25]. The inability to detect associated brain anomalies in these patients likely reflects the known lack of sensitivity of CT and sonography in detecting malformations of cortical development [7]. This limitation is compounded by a lack of sensitivity and specificity of CT in the analysis of the corpus callosum itself.

Midline anomalies, including interhemispheric cysts and lipomas, were present in several patients in this study and have been noted on prior studies of patients with commissural anomalies. Byrd et al. [9] found that 35 of 105 children with callosal agenesis had interhemispheric cysts, of which 31 communicated with the ventricles (type 1) and four did not communicate (type 2). In our study, 20 patients (14%) with ACC had interhemispheric cysts, of which 11 communicated with the ventricles and nine did not. Approximately 3% of the patients in the current study and in the prior study of Byrd et al. [9] had interhemispheric lipomas.

Malformations in cortical development are frequently associated with commissural anomalies. Gray matter heterotopia was the most common malformation of cortical development in our study, present in 29% of subjects with ACC and 21% of those with HCC. This compares with two of 68 patients with heterotopia in the study of Barkovich and Norman [2] and 18 of 105 patients with "migration disorder" in the study of Byrd et al. [9]. In the current study, 17 patients had polymicrogyria and 35 had abnormal sulcation, with similar frequencies in the ACC and HCC cohorts (Table 1).

Classic lissencephaly, cobblestone lissencephalies, polymicrogyria, schizencephaly, and heterotopia have all been described previously in conjunction with anomalies of the cerebral commissures. The current study documents the frequency of such associated anomalies and reveals that many patients with ACC or HCC have abnormal gyral patterns that do not fit into one of the classic categories (30 of 35 with abnormal sulcation, as described earlier and in Table 1). Beyond the expected eversion of the cingulum and radial orientation of paramedian gyri that routinely accompany

TABLE 1: Malformations of Cortical Development in Patients with Agenesis of the Corpus Callosum (ACC) and Patients with Hypogenesis of the Corpus Callosum (HCC)

Type of Malformation of Cortical Development	No. of Patients	
	ACC	HCC
Any malformation of cortical development	41	32
Gray matter heterotopia	23	12
Polymicrogyria	9	8
Total no. of patients with abnormal sulcation	20	15
Abnormal sulcation subtype		
Lissencephaly	1	0
Pachygyria	1	1
Bilateral schizencephaly	0	2

callosal agenesis, abnormalities of sulcation ranged from overly shallow olfactory sulci to frank hemispheric dysplasia. We speculate that abnormal sulcation may reflect a more generalized developmental disorder of the cerebral white matter because white matter has been postulated to contribute to normal sulcation and, by definition, commissural anomalies are abnormalities of white matter [26]. The abnormality of sulcation may possibly be associated with the decreased volume of white matter so commonly found in our subjects.

Given that the corpus callosum is the principal transverse white matter tract connecting the cerebral hemispheres, it is not surprising that reduced extracallosal supratentorial white matter volume was identified in nearly all patients. In fact, only one of 81 patients with ACC and five of 59 patients with HCC were found to have normal white matter volume. Reductions in extracallosal white matter may represent a primary dysplasia or hypogenesis, with fewer axons forming during development, or a secondary regression, possibly due to retraction of axons that do not find their way across midline to synapse with their homologues and thereby gain the neurotrophic support necessary for survival [27]. Alternatively, the number of axons in white matter tracts that do not cross midline could be similar, but have relatively less myelin than is seen in normal commissures. The normal-appearing signal intensity of the hemispheric white matter in our patients makes this possibility unlikely. Diffusion tensor MRI is an

emerging tool for mapping white matter tracts in vivo [28]; in the next phase of this project, patients with commissural anomalies will undergo diffusion tensor MR tractography to better assess the presence, location, and organization of white matter tracts.

The lateral callosal bundles of Probst indent the superomedial aspect of the lateral ventricles and are postulated to represent the axons that would have crossed the midline [29, 30]. Our study shows that Probst bundles are about twice as common in patients with ACC (59%) as in patients with HCC (30%). This may reflect a genuine biologic difference or may simply be a result of the technique used to analyze the brains: The human eye can more easily detect a long, wide, continuous, well-organized Probst bundle running the entire length of the lateral ventricle (ACC) than a narrower tract running only a short distance (HCC). Byrd et al. [9] also commented on 26 children with ostensibly isolated ACC, remarking that "in children with true ACC, Probst bundles are present." Whereas Probst bundles were uncommon in patients with anomalies beyond the midline and malformations of cortical development (principally malformations of the diencephalon and rhombencephalon), all three of the isolated ACC cases and one isolated HCC case had Probst bundles, perhaps portending a more organized brain overall. Further studies comparing MR appearance, including diffusion tensor tractography, with clinical outcome will address this important question.

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