CME

Callosal agenesis with cyst

A better understanding and new classification

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Article abstract—*Objective:* To analyze imaging studies of 25 cases of agenesis of the corpus callosum with interhemispheric cyst to assess this malformation itself and associated anomalies. *Methods:* CT (6 patients) and MRI (19 patients) were retrospectively reviewed. The patients were categorized according to morphologic and clinical characteristics. *Results:* Based on morphology, the patients were separated into two major types, each with subtypes. Type 1 cysts appear to be an extension or diverticulation of the third or lateral ventricles, whereas Type 2 are loculated and do not communicate with the ventricular system. Type 1a were associated with presumed communicating hydrocephalus but no other cerebral malformations. Type 1b were associated with hydrocephalus secondary to diencephalic malformations prohibiting egress of CSF from the third ventricle into the aqueduct of Sylvius. Type 1c were associated with small head size and apparent cerebral hemispheric dysplasia or hypoplasia. Type 2a (multiloculated cysts) were associated with no abnormalities other than callosal agenesis/hypogenesis. Type 2b were associated with deficiencies of the falx cerebri, subependymal heterotopia, and polymicrogyria (and were almost all in patients diagnosed with Aicardi syndrome). Type 2c were associated with subcortical heterotopia. Type 2d consists of interhemispheric arachnoid cysts. Other than those with Type 2b cysts, gender predominance was overwhelmingly male. *Conclusion:* Agenesis of the corpus callosum with interhemispheric cyst appears to consist of a heterogeneous group of disorders that have in common callosal agenesis and extraparenchymal cysts, both of which are among the commonest CNS malformations. This article proposes a classification system, based primarily on morphology, by which this complex group of disorders might begin to be better understood.

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The ability of MRI to show the gross morphology of the brain in vivo using thin sections in multiple planes has allowed the identification of previously unknown malformations,[1,2] a new appreciation of the frequency of malformations that were previously thought extremely rare,[3,4] and differentiation of malformations that were previously combined.[5] Although MR has been utilized to assess the agenetic/dysgenetic corpus itself and associated limbic system anomalies,[6-11] there has been little work analyzing the interhemispheric cysts that sometimes accompany callosal agenesis and hypogenesis.[12-16] In this study, the MRI characteristics of 25 patients with callosal agenesis with accompanying interhemisperhic cysts were retrospectively analyzed. Based on this analysis, a classification scheme is proposed.

Methods. A review of the teaching files and records in our department revealed 25 patients in whom imaging studies had revealed agenesis or hypogenesis of the corpus callosum associated with an interhemispheric cyst. The patients included 18 boys and 7 girls. Sixteen of the patients were initially imaged as neonates, four as infants (ranging from 2 to 10 months), and five as children (ranging from 2 to 7 years). Indications for imaging were macrocephaly in 15 patients, seizures in 6 patients (3 with partial motor seizures and 3 with infantile spasms), macrocephaly and dysmorphic features in 1 patient, macrocephaly with seizures in 1 patient, microcephaly with infantile spasms in 1 patient, and partial motor seizures with right spastic hemiparesis in 1 patient.

Imaging consisted of MR in 17 patients, X-ray CT in 6, and both MR and CT in 2. MR studies varied in technique, as they were performed at multiple institutions over a period of 16 years. However, all studies included sagittal T1 images, axial T1-weighted images, axial T2-weighted images, and coronal T1- or T2-weighted images. All CT scans included both axial and coronal images, although in three patients the coronal images were reformatted from 5-mm–thick axial sections. Paramagnetic contrast was administered in five of the MR scans and iodinated contrast was administered in two of the CT scans.

All of the scans were reviewed with particular attention to the degree of callosal abnormality (agenesis versus hypogenesis, severity of hypogenesis), character of the cyst (unilocular versus multilocular, intensity or attenuation as compared to CSF of the ventricles and subarachnoid space, location, communication with the ventricular system), and the presence and type of associated malformations. Clinical information was limited, as most of the patients were imaged as neonates because of macrocephaly or ultrasound findings of ventricular enlargement or cyst. When information from later in infancy or childhood was available, it was examined to determine neurologic status, developmental status, the presence or absence of seizures, type of seizures, and whether any anomalies were present outside of the nervous system. Based on these characteristics and

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the clinical characteristics, the cysts were separated into two major categories, with a total of seven subcategories.

Results. The major differentiation (Type 1 and Type 2) was based upon whether the cyst was in communication with the ventricular system; we define Type 1 cysts as those that communicate with the ventricles, whereas Type 2 are defined as loculated cysts that do not communicate. Type 1a interhemispheric cysts were associated with (presumed) communicating hydrocephalus but no other cerebral malformations. Type 1b interhemispheric cysts were associated with hydrocephalus secondary to malformations prohibiting egress of CSF from the third ventricle into the aqueduct of Sylvius. Type 1c interhemispheric cysts were associated with small head size and apparent cerebral hemispheric hypoplasia. Type 2a interhemispheric cysts (loculated) were associated with no abnormalities other than callosal agenesis/hypogenesis. Type 2b interhemispheric cysts were multiloculated cysts associated with deficiencies of the falx cerebri, subependymal heterotopia, and polymicrogyria. Type 2c interhemispheric cysts were associated with subcortical heterotopia. Type 2d interhemispheric cysts are arachnoid cysts; we did not have any such cysts in our series, but they are well described in the literature.[14]

Our patient group included seven patients with Type 1a interhemispheric cysts, six patients with Type 1b cysts, two patients with Type 1c cysts, two patients with Type 2a cysts, five patients with Type 2b cysts, and three patients with Type 2c cysts.

Type 1 cysts. Patients with Type 1a cysts included seven boys. All presented with macrocephaly during the first few days of life. All were diagnosed with hydrocephalus (presumably communicating); indeed, the three patients who were not immediately shunted showed progressive head enlargement and ventricular enlargement that was arrested by insertion of a ventriculoperitoneal shunt. Five of the patients had complete callosal agenesis, whereas the other two had callosal hypogenesis, with presence of the posterior genu only. Two patients had associated Dandy–Walker malformations. The falx cerebri appeared normal in four patients, was deficient anteriorly in two, and seemed to be completely absent in one. The cysts themselves were large, extending nearly the entire anteroposterior length of the calvarium, and in communication with at least one lateral ventricle and the third ventricle. One was in communication with a small parietal meningocele (figure 1). The structures of the roof of the third ventricle were laterally displaced by the cyst and in five of the patients a membrane that was considered the cyst wall could be identified near the inner table of the calvarium, particularly after shunting. Six of the seven cysts were predominantly on one side of the midline, even in those with a deficient anterior falx. The cyst in the seventh patient was in the midline; this patient had associated Dandy–Walker malformation and no appreciable falx cerebri. Contrast was administered in three patients; no enhancement of the cyst walls was seen.

Patients with Type 1b cysts by definition had an apparent obstruction to flow in the third ventricle. The obstruction appeared to result from fused thalami in five of the patients (figure 2). In the sixth patient, obstruction appeared to be the result of a hamartomatous-appearing mass that seemed to originate in the right thalamus and extend laterally across the posterior third ventricle. All patients in this group, which included four boys and two girls, were initially detected as neonates because of macrocephaly. Three of the patients had complete callosal agenesis whereas three had callosal hypogenesis; two showed presence of only the posterior genu whereas the third appeared to have both genu and anterior body. Two of the patients had parietal meningoceles in the regions into which their cysts extended. The falx cerebri appeared normal in two patients and absent in two patients. In the two remaining patients (with meningoceles), the falx was deficient in the area of the calvarial defect; in one, the falx was also hypoplastic anteriorly. The cyst itself occupied most of the anteroposterior diameter of the calvarium in three patients who were imaged prior to shunting but was more localized in the other three, imaged after treatment. In the two patients with cephaloceles, the cyst was localized to the parietal-occipital regions of the interhemispheric fissure. In the two patients with normal falx cerebri, the cyst was centered on one side of the falx, whereas the cyst was centered in the midline in the other four. Contrast was administered to two of the patients; no enhancement of the cyst wall was seen.

Group 1c was composed of two boys, who were imaged as neonates because of either microcephaly and neonatal seizures or ventriculomegaly detected on a routine prenatal sonogram. Both were microcephalic (head circumference more than two standard deviations below the norm). Both had complete callosal agenesis and both had inferior vermian hypogenesis. One had associated kinking of the brainstem (figure 3). The falx was normal in both. The cyst in both patients was continuous with the entire ventricular system. The affected hemicalvarium was slightly larger than the contralateral side despite the microcephaly and the fact that the ipsilateral hemisphere looked slightly small. No cyst walls were identified. Contrast was not administered to these patients.

Type 2 cysts. Group 2a was composed of two boys who were imaged for macrocephaly as neonates. Both had complete callosal agenesis and multiple loculated cysts of CSF intensity that did not communicate with the ventricular system (figure 4). In neither could the cingulum or medial ventricular walls be assessed because of severe distortion by the cysts and accompanying hydrocephalus. The cysts were on both sides of the midline. The falces cerebri had normal appearances. No other brain anomalies were identified. Contrast was not administered to these patients.

Group 2b was composed of five girls who were imaged as neonates or infants for either seizures or macrocephaly. Four had complete callosal agenesis whereas the fifth had callosal hypogenesis with presence of the posterior genu and anterior body. All patients in this group had frontal or frontoparietal polymicrogyria and subependymal heterotopia (figure 5). All had at least one dilated lateral ventricle that appeared to result from a diminished volume of adjacent white matter. All had a hypoplastic falx cerebri, with the posterior aspect being more severely involved. The interhemispheric cysts in this group extended across the midline and did not communicate with the ventricular system. All of the cysts had different signal from CSF; the fluid had higher attenuation on CT and shorter T1 relaxation time (see figure 5), which suggests higher protein content. The cyst walls appeared thick and manifested en-

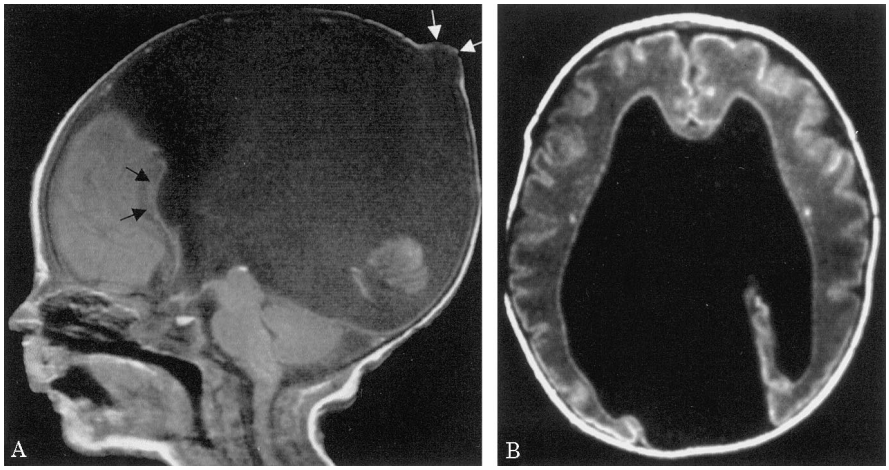

Figure 1. Type 1a cyst. (A) Sagittal spin echo (SE) 600/15 image shows nearly complete absence of the corpus callosum; only the genu (black arrows) is present. The anterior recesses of the third ventricle are dilated and the calvarium is expanded, indicative of hydrocephalus, with fluid filling nearly all of the posterior midline space. CSF extends beyond the calvarial borders in the parietal regions (arrows) forming a small cephalocele. The cyst exerts mass effect on the quadrigeminal plate and the cerebellum. (B) Axial SE 600/15 sequence shows that the cyst is continuous with both lateral ventricles.

hancement in the two patients in whom contrast was administered.

Group 2C was composed of three children who were imaged because of either epilepsy or craniofacial dysmorphism. All had complete callosal agenesis (figure 6). All patients in this group had large subcortical heterotopia involving a variable amount of one (two patients) or both (one patient) cerebral hemispheres. The patient with bilateral heterotopia had associated anomalies of the cerebellum (which had the appearance of diffuse cerebellar polymicrogyria) and a hypoplastic pons. The cysts in these patients were multilocular, slightly hyperintense to CSF on T1-weighted images, did not communicate with the ventricular system, and crossed the midline despite the normal-appearing falces cerebri.

Discussion. Although the association of interhemispheric cysts with absence of the corpus callosum has been recognized and reported may times since the 1920s,[15,17-19] a good deal of disagreement about these malformations persists in the literature. Are these arachnoid cysts,[14] neuroepithelial cysts,[12] or extensions of the third ventricle, lined by ventricular epithelium[20]? Are these malformations usually isolated[14] or are they associated with other malformations of the skull, meninges, and brain[15]? The purpose of this study was to try to answer these and other questions. We found that interhemispheric cysts associated with callosal anomalies had a variable appearance and that several brain malformations were present in some of the affected individuals.

It seemed that the best way to analyze the data we derived from our analysis was to separate the patients into groups based upon similar morphology. The determination of the system by which to classify these patients was difficult. Several other authors have offered classifications. One early classification divided the patients based on results of pneumoencephalograms and pneumoventriculograms into those with communicating (with the ventricular system) and noncommunicating cysts.[15] The communicating cysts were divided into "primary cysts," which were defined as being associated with a deficient falx cerebri, and secondary cysts, in which the falx was intact. This system did not work well for our series in that it did not account for the parenchymal abnormalities that we identified. Another author proposed separating intraparenchymal porencephalic cysts from extraparenchymal cysts and, within the latter group, midline cysts from parasagittal cysts.[14] How-

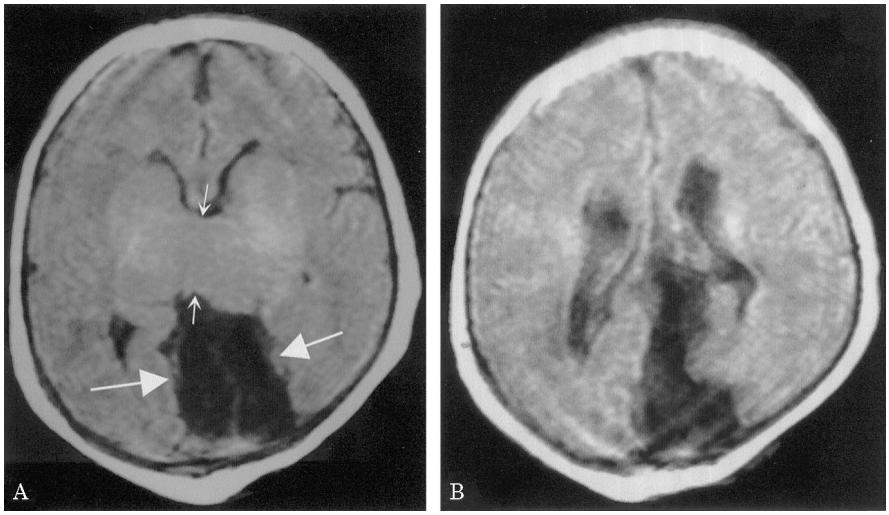

Figure 2. Type 1b cyst. (A) Axial spin echo (SE) 650/20 image shows fused thalami and a large posterior cyst (arrows) that is in communication with the posterior third ventricle. No callosal genu is present. (B) Axial SE 650/20 image at a slightly higher level shows better the absence of the corpus callosum.

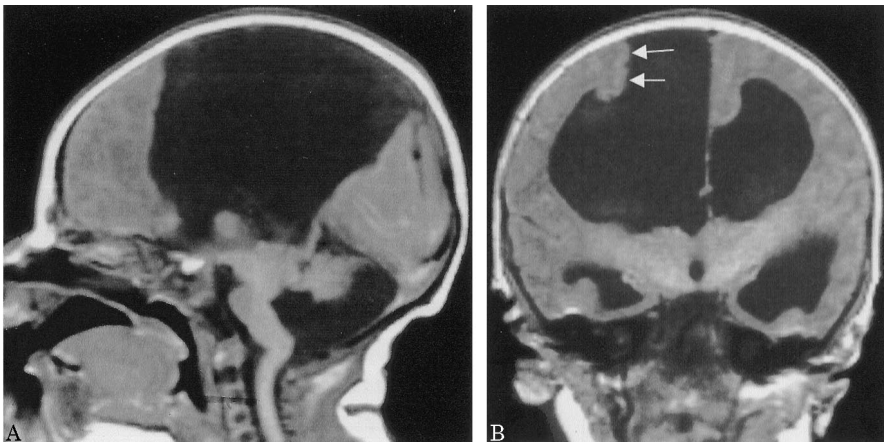

Figure 3. Type 1c cyst. (A) Sagittal spin echo (SE) 600/20 image shows absence of the corpus callosum and continuity of the third ventricle with a large CSF collection that seems to split the anterior and posterior portions of the cerebral hemispheres. The brainstem is kinked. The cerebellar vermis is hypogenetic. The craniofacial proportions are abnormal for a neonate (head relatively small), consistent with the clinical finding of microcephaly. (B) Coronal SE 650/20 image shows that the medial margin of the right cerebral hemisphere (arrows) is abnormally lateral in location. The ventricles are enlarged. The falx and septum pellucidum appear normal.

ever, this population was limited to cysts that did not communicate with the ventricles (two of the extraparenchymal cysts were identified histologically as arachnoid cysts). In addition, this classification also did not account for associated parenchymal anomalies. A more recent classification, proposed in 1998, is more sophisticated and proposes three categories.[10] Type 1 cysts were expansions of the ventricular system (similar to the communicating cysts group of the first classification system above); no other brain anomalies were identified in this group. Type 2 cysts were intraparenchymal, associated with polymicrogyria, heterotopia, and schizencephaly, and were postulated to be destructive lesions such as porencephalies. Type 3 cysts were multilocular, did not communicate with the ventricles, and appeared to have intra- and extraparenchymal components. Heterotopia, cortical malformations, and other extraparenchymal cysts were present in all patients with Type 3 cysts. We had problems incorporating our patients into this system, too, as it does not allow for the separation of patients with fusion of the diencephalon from those with diencephalic separation; these groups, as will be discussed below, seem to be different even though the cysts themselves appear similar. Thus, we elected to devise and propose a new classification system.

Our classification combines the approach of two of those described above. Our primary criterion for classification is whether the cyst appears to be in communication with the ventricular system (Type 1) or not (Type 2). Although we did not perform intrathecal or intraventricular contrast studies in the majority of our patients and, therefore, we cannot be absolutely certain as to whether communication was present, we believe that the identification of multiple loculations and visualization of the walls of the loculations is adequate evidence of lack of communication in Type 2. In addition, the loculated cysts typically had different signal intensity than the CSF in the ventricles. We are somewhat less certain that all of our "communicating" cysts were, indeed, in communication with the ventricles. Nonetheless, the lack of a visible wall between the cyst and the ventricles and the isointensity of the cyst fluid with that of the ventricles were used as the criteria for defining this group, which appears clearly different from the other.

After determining whether the cyst was Type 1 or Type 2, we further subdivided them by the other features. For example, we separated those patients in whom the hydrocephalus was presumably the result of diencephalic anomaly (Type 1b) from those in whom no cause for hydrocephalus could be identified

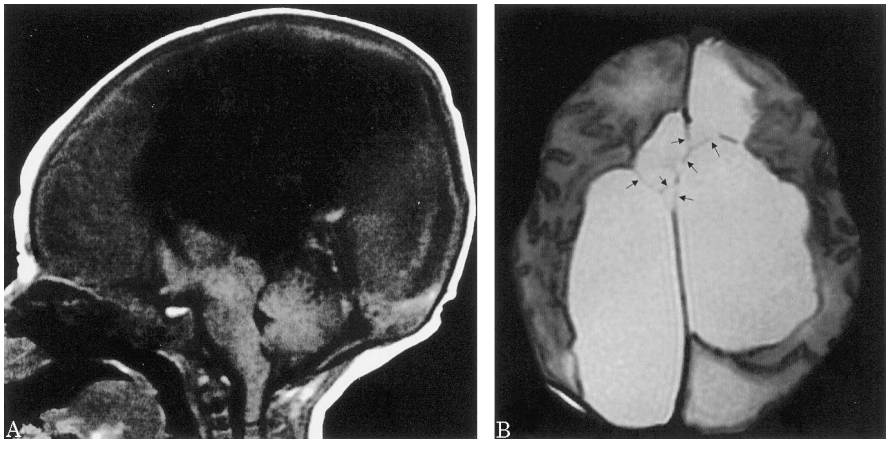

Figure 4. Type 2a cyst. (A) Sagittal spin echo 600/20 image shows complete callosal agenesis. (B) Axial spin echo 3000/120 image shows enlarged lateral ventricles and multiple loculations within and adjacent to the midline. Multiple small septa are seen (small black arrows).

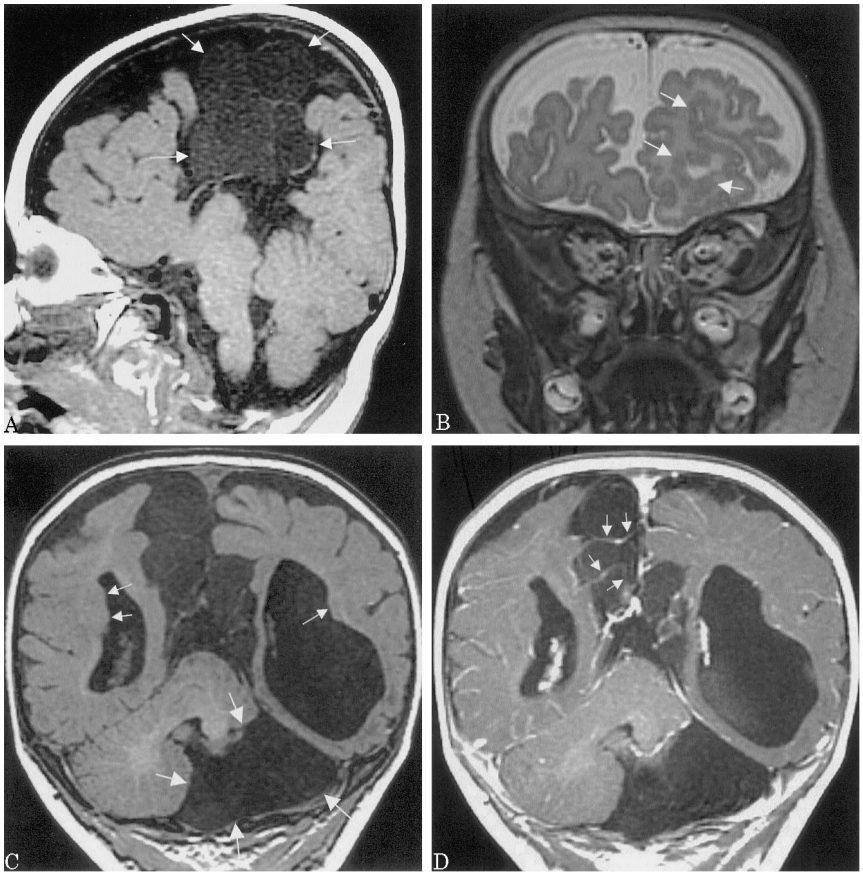

Figure 5. Type 2b cyst. (A) Sagittal spin echo (SE) 600/11 image shows absence of the corpus callosum and multiple dorsal cysts that are slightly hyperintense compared to CSF. (B) Coronal fast SE 4000/112 shows left frontal polymicrogyria (arrows). (C) Coronal SE 650/11 shows the multiloculated interhemispheric cysts crossing the midline. These are slightly hyperintense compared to CSF. Subependymal heterotopia (small arrows) are seen in the walls of the lateral ventricles. A posterior fossa cyst (large arrows) is present. (D) Postcontrast coronal SE 650/11 image shows that the septae between the loculations (or walls of the cysts, depending on perspective) enhance.

(Type 1a). Another reason to separate these groups was that the patients classified as Type 1a were all (7/7) boys, whereas those with Type 1b included four boys and two girls. Although this difference in sex distribution is not significant ($p = 0.19$), it is different enough to suggest that the genetic cause of the diencephalic anomaly (the presumed cause of hydrocephalus in Type 1b) may well be different from the cause(s) of hydrocephalus in the other group. We also created a separate group for the two patients with microcephaly, in whom the interhemispheric CSF collections are presumed to be continuous with the ventricular systems because of cerebral dysgenesis or prenatal injury (Type 1c). All other Type 1 patients were macrocephalic from hydrocephalus and their CSF collections are suspected to be diverticula of the expanded ventricular system, as suggested by previous authors.[15,20] Type 1c is, therefore, roughly analogous to Type 2 cysts of the 1998 classification system described above,[10] as it may be the result of in utero destruction.

Some would question whether the group with thalamic fusion and dorsal cysts might be better classified as having holoprosencephaly. A recent morphologic study of a large group of patients with holoprosencephaly, however, showed that the hypothalamus and caudate are fused in greater than 95% of affected patients, whereas the thalami were fused in only 67%.[21] Therefore, thalamic fusion is not a sensitive criterion for the diagnosis of holoprosencephaly. Neither is it specific, as thalamic fusion is seen in many conditions, such as Chiari II malforma-

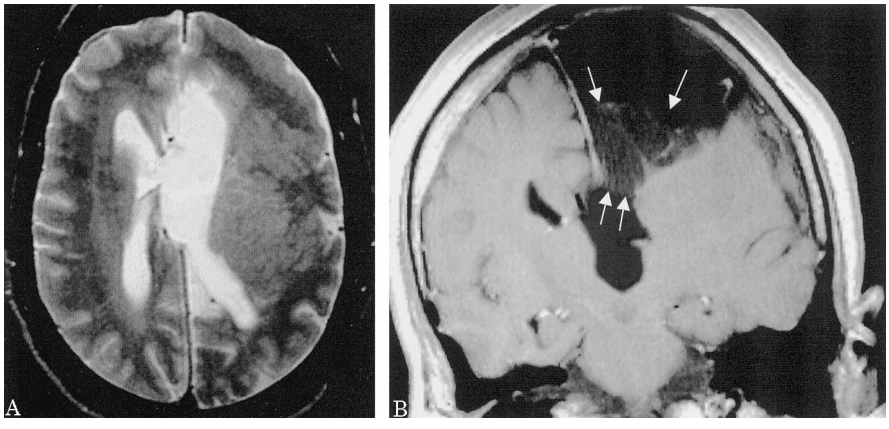

Figure 6. Type 2c cyst. (A) Axial spin echo (SE) 2500/80 image shows large right-sided mass of subcortical heterotopia. (B) Coronal SE 650/20 image shows the cyst (arrows) can be seen to be hyperintense compared to CSF. The heterotopia is difficult to see on this image, which was photographed to emphasize the cyst.

tions and X-linked hydrocephalus. Therefore, in the absence of more rostral fusions, such as in the hypothalamus and caudate, the presence of fused thalami does not qualify a malformation as being holoprosencephaly. We do not believe that our Type 1b cases, in which the malformation was limited to the thalami, should be classified as holoprosencephaly.

One might dispute the validity of including the patient with the diencephalic hamartoma in the group with thalamic fusion. We believe that more cases with diencephalic hamartomas and callosal agenesis will be found and that some of these will have interhemispheric cysts. At that time, a separate category might be established (Type 1d?), which will almost surely be genetically distinct from Type 1b. Similarly, the patient with cerebellar dysplasia may have a different underlying genetic defect than the other patients with Type 2c. For now, combining all patients with diencephalic anomalies that result in impaired flow of CSF through the third ventricle and combining all patients with subcortical heterotopia seems better than having categories with only one patient or having a wide variety of clearly different malformations lumped together in a Miscellaneous category. Ultimately, the different groups and subgroups will be definitively sorted out by observing and reporting more patients with these anomalies. Therefore, this classification can be considered an initial step in sorting out the different types of callosal agenesis with interhemispheric cyst. We believe that the framework of this classification, based upon the morphology of the cyst, will survive and remain useful as potentially many different categories are added.

Our Type 2 group was also subdivided based upon the presence or absence and the type of associated anomalies. Type 2a patients, with no apparent associated anomalies, were easy to separate from Types 2b and 2c. We separated Type 2b from the other Type 2 cysts because all five of the patients were female (in stark contrast to the 9:1 male:female ratio among the other 20 patients in this series) and because all had similar findings of frontal polymicrogyria, subependymal heterotopia, and deficiency of the falx cerebri. Indeed, we believe that all five of these girls had Aicardi syndrome[22] even though the

Table *Definition of cyst types*

Cyst type	Sex	Age, reason for presentation	Cyst characteristics	Associated anomalies
Type 1: Communication with ventricles				
1a	M	Neonate, macrocephaly	Isointense to CSF	Hydrocephalus
			Unilocular	
			Communicates with ventricles	
1b	M > F	Neonate, macrocephaly	Isointense to CSF	Thalamic fusion without subcortical heterotopia
			Unilocular	
			Communicates with third ventricle	
1c	M	Neonate, seizures, microcephaly	Isointense to CSF	Small ipsilateral cerebral hemisphere
			Unilocular	
			Communicates with lateral and third ventricle	
Type 2: No communication with ventricle				
2a	M	Neonate, macrocephaly	Isointense to CSF	Hydrocephalus
			Multilocular	
			No communication with ventricle	
2b	F	Infant, delay, seizures, micro/macrocephaly	Multiloculated	Subependymal heterotopia
			No communication with ventricles	Polymicrogyria
			Hyperdense on CT, hyperintense on T1 MRI	Deficient falx cerebri
2c	M	Child, seizures, delay	Isointense to CSF	Subcortical heterotopia
			Multilocular	
			No communication with ventricle	
2d	?	Macrocephaly	Arachnoid cyst	None
			Isointense to CSF	
			Unilocular	
			No communication with ventricle	

characteristic retinal lacunae were positively identified in only four of them. Examination of a cyst from a girl with similar associated brain malformations determined the cyst to be a neuroepithelial (glia-ependymal) cyst.[12] We believe that this histologic result further supports our classification of these as different types of cysts from those that are extensions of the ventricular system. The patients classified as Type 2c all had subcortical heterotopia, which is known to have a high incidence of callosal anomalies.[23] One of these three patients also had a hindbrain malformation and may, therefore, have a different underlying genetic defect from the other two. For reasons discussed above, we have chosen to classify this patient with the other patients with subcortical heterotopia for the present. Although we did not have any definite arachnoid cysts in our series, it is clear that histologically proven arachnoid cysts do occur in association with callosal agenesis.[14] These cysts do not communicate with the ventricular system and, therefore, we have included them in our classification as Type 2d. We would expect these cysts to have signal intensity identical to the CSF in the ventricles.

The use of our classification system allows several patterns to become clear. As stated earlier, the interhemispheric cysts in Types 1a and 1b seem to be ventricular diverticula. All of the patients in these groups presented with macrocephaly due to hydrocephalus. All had appearances quite similar to pneumoencephalograms,[15] which demonstrated that the cysts were extensions of the ventricular system. The cause of the hydrocephalus is unknown, but it is tempting to speculate that abnormalities in the embryonic mesenchyme inhibit expression of the Slit and Comm proteins, both of which are critical to normal midline crossing of callosal axons.[24,25] Disorders of dorsal embryonic mesenchyme could also result in dysplasia of the leptomeninges[26] with resultant impaired CSF resorption. It is tempting to speculate that the hydrocephalus is noncommunicating, as an animal model of callosal agenesis with interhemispheric cyst, the *hyh* (hydrocephalus with hop gait) mouse,[27] has noncommunicating hydrocephalus as a result of aqueductal stenosis. The hyh mice have dilated lateral ventricles and a large third ventricular diverticulum/cyst, narrowed rostral cerebral aqueduct, cystic caudal aqueduct, and no communication of the aqueduct with the fourth ventricle.[27] The cerebellum has a mild cortical malformation. The mutation that causes the malformation has been mapped to the proximal end of chromosome 7, close to the Gpi-1 locus. We did not identify abnormalities of the aqueduct in our patients, however, so we believe that the hydrocephalus could still be communicating. Either way, we believe that the hyh mice might prove a useful model for study of the development of Type 1 cysts.

All of the subgroups of patients with Type 2 cysts seem quite distinct. It is difficult to understand why multilobulated cysts develop in the interhemispheric region in association with callosal agenesis and hydrocephalus unless it is, again, related to abnormal differentiation of the primitive mesenchyme; the interhemispheric mesenchyme forms the permissive substrate for axonal crossing of the midline commissures and later differentiates into the subarachnoid space.[28,29] Regarding Type 2c cysts, a recent publication noted that 9/13 patients with subcortical heterotopia had callosal agenesis or hypogenesis.[23] Of these, three had an associated interhemispheric cyst. Thus, this group seems quite distinct from the others. However, a relationship between the presence of callosal agenesis and a multilocular interhemispheric cyst is easier to explain than the association with the heterotopia. Possibly, the same signaling molecules (e.g., integrins, semaphorins, netrins[30]) that guide the callosal axons to their midline crossing points also function to guide neurons in their migration from the germinal zone to the developing cerebral cortex. Supporting this concept is the fact that mutation of the netrin receptor Unc5h3 results in abnormal migration of cerebellar granule cells.[31] Likely candidate genes for mutations that lead to abnormal expression of mesenchyme in the interhemispheric fissure include the *Bmp*, *Pax*, and *Wnt* families, as well as the *Zic2* gene. All of these exert an influence on the normal differentiation of the dorsal structures of the neural tube.[32] In theory, mutations of genes guiding development of the dorsal mesenchyme could also lead to abnormal development of the subarachnoid space, resulting in arachnoid cysts in the interhemispheric fissure (Type 2d cysts).

The high incidence of male patients in this series is in agreement with a prior report.[13] However, as alluded to above, more careful analysis of the male: female ratio suggests that some types of callosal anomalies with interhemispheric cyst are more common in males whereas others are more common in females. This finding again emphasizes that callosal agenesis with interhemispheric cyst is not a single malformation, but a heterogeneous group of disorders that have in common callosal agenesis or hypogenesis and a midline cyst. It should be asked whether some of our patients (particularly in groups 1a and 2a) are a part of the disorder known as X-linked hydrocephalus.[33] X-linked hydrocephalus has become better understood recently as a result of the finding of its association with mutations of the *L1CAM* gene at Xq28.[34-36] Several studies have revealed that this disorder is complex, being associated with hypoplasia or absence of the corticospinal tracts, dysplasia of the cerebral mantle, a large massa intermedia, a small brainstem, atrophy of the anterior cerebellar vermian lobules, and diffuse hypoplasia of the cerebral white matter.[37] These features were not found in our patients, nor in other reported cases of callosal agenesis with interhemispheric cyst and male predominance.[10,13] Finally, interhemispheric cysts have not been reported in association with L1CAM mutation hydrocephalus. Thus, al-

though some of our patients are likely to have a form of X-linked hydrocephalus, it seems unlikely that they have the classic form associated with mutations of *L1CAM*.

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References

1. Barkovich AJ, Peacock W. Sublobar dysplasia: a new malformation of cortical development. Neurology 1998;50:1383–1387.
2. Guerrini R, Barkovich A, Sztriha L, Dobyns W. Bilateral frontal polymicrogyria. Neurology 2000;54:909–913.
3. Granata T, Battaglia G, D'Incerti L, et al. Schizencephaly: clinical findings. In: Guerrini R, ed. Dysplasias of the cerebral cortex and epilepsy. Philadelphia: Lippincott-Raven, 1996: 407–415.
4. Barkovich AJ, Kjos BO. Schizencephaly: correlation of clinical findings with MR characteristics. AJNR Am J Neuroradiol 1992;13:85–94.
5. Dobyns WB, Truwit CL, Ross ME, et al. Differences in the gyral pattern distinguish chromosome 17-linked and X-linked lissencephaly. Neurology 1999;53:270–277.
6. Atlas SW, Zimmerman RA, Bilaniuk LT, et al. Corpus callosum and limbic system: neuroanatomic MR evaluation of developmental anomalies. Radiology 1986;160:355–362.
7. Barkovich AJ, Norman D. Anomalies of the corpus callosum: correlation with further anomalies of the brain. AJNR Am J Neuroradiol 1988;9:493–501.
8. Barkovich AJ. Apparent atypical callosal dysgenesis: analysis of MR findings in six cases and their relationship to holoprosencephaly. AJNR Am J Neuroradiol 1990;11:333–340.
9. Raybaud C, Girard N. The developmental disorders of the commissural plate of the telencephalon: MR imaging study and morphologic classification. Nerv Syst Child 1999;24:348–357.
10. Raybaud CA, Girard N. Étude anatomique par IRM des agénésies et dysplasies commissurales télencéphaliques. Neurochirurgie 1998;44(suppl 1):38–60.
11. Kier EL, Truwit CL. The normal and abnormal genu of the corpus callosum: an evolutionary, embryologic, anatomic, and MR analysis. AJNR Am J Neuroradiol 1996;17:1631–1641.
12. Barth PG, Uylings HBM, Stam FC. Interhemispheral neuroepithelial (glio-ependymal) cysts, associated with agenesis of the corpus callosum and neocortical maldevelopment: a case study. Childs Brain 1984;11:312–319.
13. Lena G, van Calenberg F, Genitori L, Choux M. Supratentorial interhemispheric cysts associated with callosal agenesis: surgical treatment and outcome in 16 children. Childs Nerv Syst 1995;11:568–573.
14. Mori K. Giant interhemispheric cysts associated with agenesis of the corpus callosum. J Neurosurg 1992;76:224–230.
15. Probst FP. Agenesis of the corpus callosum. Acta Radiol 1973; suppl 331:1–150.
16. Young JN, Oakes WJ, Hatten HP. Dorsal third ventricular cyst: an entity distinct from holoprosencephaly. J Neurosurg 1992;77:556–561.
17. Jura A. Über einen mit Cystenbildung des Gehirns, Heterotopie des Plexus choroideus und Mikrogyrie verbundenen Fall von vollständigem Balkenmangel. Arch Psychiatr Nervenkr 1934;102:731–744.
18. Loeser JD, Alvord EC. Agenesis of the corpus callosum. Brain 1968;91:553–570.
19. Tretiakoff C, Balestra S. Absence congénitale du corps calleux sans troubles psychiques apparents chez une femme morte a l'âge de 32 ans. Bull Soc Clin Med Ment 1922;10:58–67.
20. Brihaye J, Gillet P, Parmentier R, Peetrons E. Agénésie de la commissure calleuse associé avec un kyst épendymaire. Schwietz Arch Neurol Psychiatr 1956;77:615–631.
21. Simon E, Hevner R, Pinter J, Kinsman S, Hahn J, Barkovich AJ. Assessment of deep gray nuclei in holoprosencephaly. AJNR Am J Neuroradiol 2000;21:1955–1961.
22. Aicardi J, Lefebre J, Lerrique–Koechlin A. A new syndrome: spasm in flexion, callosal agenesis, ocular abnormalities. Electroencephalogr Clin Neurophysiol 1965;19:609–610.
23. Barkovich AJ. Subcortical heterotopia: a distinct clinicoradiologic entity. AJNR Am J Neuroradiol 1996;17:1315–1322.
24. Battye R, Stevens A, Jacobs J. Axon repulsion from the midline of the Drosophila DNS requires slit function. Development 1999;128:2475–2481.
25. Kidd T, Russell C, Goodman C, Tear G. Dosage sensitive and complementary functions of roundabout and commissureless control axon crossing of the CNS midline. Neuron 1998;20:25–33.
26. O'Rahilly R, Müller F. The meninges in human development. J Neuropathol Exp Neurol 1986;45:588–608.
27. Bronson R, Lane P. Hydrocephalus with hop gait (hyh): a new mutation on chromosome 7 in the mouse. Brain Res Dev Brain Res 1990;54:131–136.
28. Truwit CL, Barkovich AJ. Pathogenesis of intracranial lipoma: an MR study in 42 patients. AJNR Am J Neuroradiol 1990;11:665–674.
29. Osaka K, Handa R, Matsumoto S, Yasuda M. Development of the cerebrospinal fluid pathway in the normal and abnormal human embryos. Childs Brain 1980;6:26–38.
30. Tessier–Lavigne M, Goodman CS. The molecular biology of axon guidance. Science 1996;274:1123–1133.
31. Goldowitz D, Hamre K, Przyborski S, Ackerman S. Granule cells and cerebellar boundaries: analysis of Unc5h3 mutant chimeras. J Neurosci 2000;20:4129–4137.
32. Sarnat H, Menkes J. How to construct a neural tube. J Child Neurol 2000;15:110–124.
33. Bickers DS, Adams RD. Hereditary stenosis of the aqueduct of Sylvius as a cause of congenital hydrocephalus. Brain 1949; 72:246–262.
34. Fransen E, Schrander–Stumpel C, Vits L, Coucke P, Van Camp G, Willems PJ. X-linked hydrocephalus and MASA syndrome present in one family are due to a single missense mutation in exon 28 of the *L1CAM* gene. Hum Mol Genet 1994;3:2255–2256.
35. Willems PJ, Dijkstra I, Van der Auwera BJ, et al. Assignment of X-linked hydrocephalus to Xq28 by linkage analysis. Genomics 1990;8:367–370.
36. Willems PJ, Vits L, Raeymaekers P, et al. Further localization of X-linked hydrocephalus in the chromosomal region Xq28. Am J Hum Genet 1992;51:307–315.
37. Yamasaki M, Arita N, Hiraga S, et al. A clinical and neuroradiological study of X-linked hydrocephalus in Japan. J Neurosurg 1995;83:50–55.