July 2007

Recurrent pineal apoplexy in a child

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MONOZYGOTIC TWINS WITH MIRROR IMAGE CYSTS: INDICATION OF A GENETIC MECHANISM IN ARACHNOID CYSTS?

Arachnoid cysts are benign, congenital malformations of the arachnoid. The mechanism of cystogenesis remains unclear.

In other diseases with cysts in various organs as a hallmark of the disease, such as autosomal dominant polycystic kidney disease (ADPKD), a genetic basis for the disease has been described.[1] In ADPKD, arachnoid cysts have been reported to co-exist.[2]

The observations of familial occurrence of arachnoid cysts,[2,3] in combination with the observed co-existence of arachnoid cysts and genetically determined cystic diseases,[2,3] indicate a genetic component in the cystogenesis of at least some of the arachnoid cysts.

In this article, we present the first report of mirror image arachnoid cysts in the cerebellopontine angle in a pair of monozygotic twins and discuss the implications this might have for a possible genetic component in the development of arachnoid cysts.

Case report. These 12-year-old twins were born by vaginal delivery at 40 weeks' gestation after the uneventful pregnancy of a healthy 24-year-old mother. Both had Apgar score 9/9 at 1 and 9/9 at 5 minutes. The placenta was examined and described as monochorionic. Twin 1 was slightly smaller than Twin 2: weight 2,900 and 3,370 g, length 50 and 51 cm, and head circumference 34 and 34 cm, respectively.

Twin 1 was examined by a physiotherapist owing to a tendency of rotating her head to the right during the first three months of life.

The two sisters have had a normal psychomotor development and did not differ much in their early achievements. They are now attending seventh grade in the Norwegian school system, normal for their age.

One of the twins (Twin 1) was referred for neurosurgical evaluation owing to a severe headache following a minor head trauma without loss of consciousness (playing soccer). An initial CT scan was normal, with the exception of an arachnoid cyst in the right cerebellopontine angle. This observation was later verified by MRI (figure, A and B). The headache remained intense for several weeks, and she was therefore operated with extirpation and fenestration of the cyst without complications. An MRI of her twin sister revealed a mirror image arachnoid cyst in the left cerebellopontine angle (figure, C and D).

Discussion. Twin studies are often used to determine the genetic component in various diseases, with the basic assumption that monozygotic twins are genetically identical and hence that concordance is indicative of a genetic component of the disease. Previous twin studies on brain structure have demonstrated a highly heritable component in cerebral and hemispheric volumes,[4] but a structural–functional variation in brain structure in monozygotic twins has also been described.[5] This variation can also be in the form of mirror imaging,[6] a chirality that might result from enantiomer information in the very early mammalian embryo.[7]

For some locations, arachnoid cysts have been reported to have a familial occurrence, either as an isolated entity, or in covariation with other diseases.[2,3]

In our total surgical material of patients with arachnoid cysts (n = 299), only 5.4% of the cysts are located in the cerebellopontine angle. The rarity of this location makes it very unlikely that this co-occurrence in a pair of monozygotic twins had arisen by chance.

The association of arachnoid cysts with other diseases where a genetic basis of cystogenesis have been discovered and the current finding of mirror imaging of arachnoid cysts in the cerebellopontine angle in monozygotic twins indicate that, for at least some cysts, the cystogenesis may have a genetic component.

(A and B) Coronal and axial MR images of symptomatic twin with an arachnoid cyst of the right cerebellopontine angle. (C and D) Coronal and axial MR images of asymptomatic sister with an arachnoid cyst of the left cerebellopontine angle

Figure   MRI of the twins
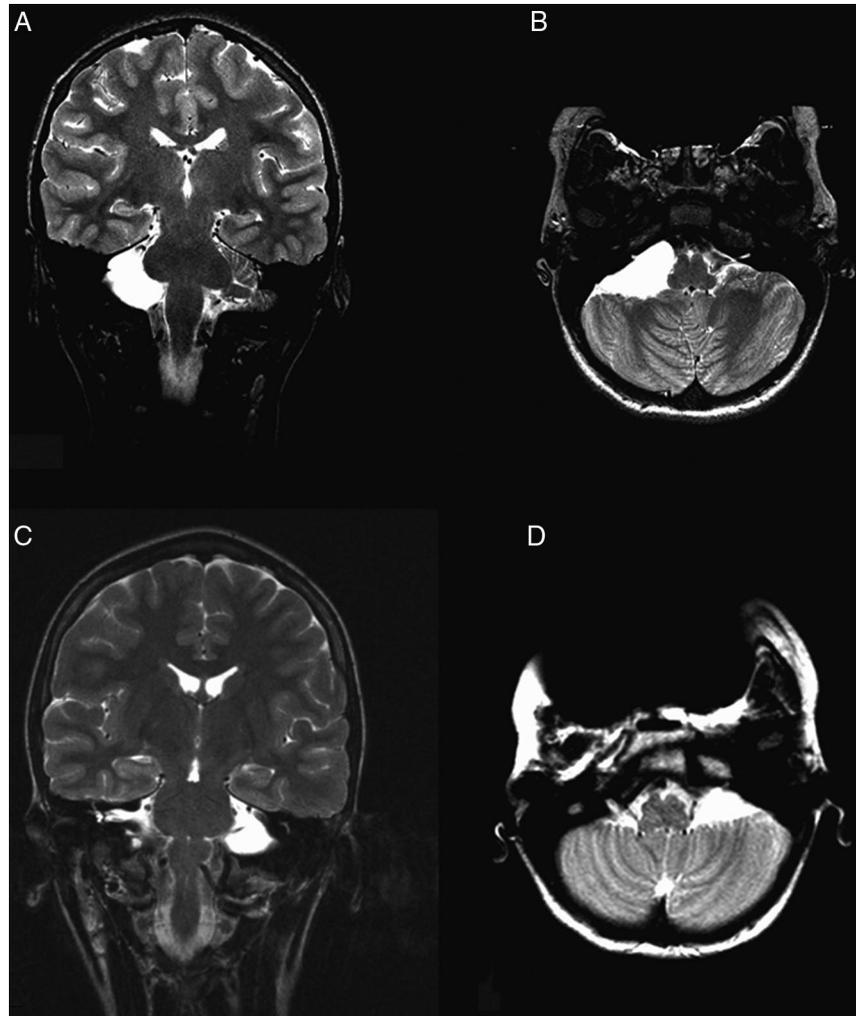
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REPORTING AND INTERPRETATION OF GENETIC VARIANTS IN CASES AND CONTROLS

When a new gene for a disease is reported, of course, the investigators in every lab with DNA samples relevant to that finding go to their freezers and get out their samples and begins to sequence that gene. Typically, they screen control series for those variants they find, but do not sequence their control samples. Whereas these studies are straightforward, their definitive interpretation is often problematic, especially in cases where mutations may not be fully penetrant. An excellent proven example of this is the recent identification of a clearly pathogenic progranulin mutation in case of ubiquitin-positive frontal dementia in which a presenilin variant had been previously described[1]; and an earlier example was the realization that the presenilin 1 E318Y was a harmless polymorphism and not disease causing.[2]

When performing this type of screening study or reading a manuscript that describes this approach, there are some straightforward considerations.

First, strictly, the pathogenicity of each individual mutation (especially missense changes) should be proven by either of the two standard genetic tests: segregation or association. Some changes may be rare variants or private polymorphisms (occurring only in a single family), which, though they may not be found by the authors in large numbers of controls, are nevertheless not pathogenic.

Second, the interpretation of the occurrence of mutations in samples labeled as controls is often not straightforward: Volunteers for genetic studies are often family members, and inexperienced collection of such samples can lead to misleading data. In addition, sample labeling is subject to human error at appreciable rates, and if a finding is unexpected, it should ideally be checked by resampling.

Third, especially in recessive diseases, where there is loss of function, nongeneticists need to be aware that there are many mutation types that can be difficult to identify (such as deletions). Identification of individuals with single mutations in such cases is very problematic. A recent example of this is the unresolved debate on the pathogenicity of single parkin mutations.[3]

Although these are simple rules, they are often difficult to follow in practice. Family structures are usually not ideal for genetic analysis, and resampling can be problematic for practical and ethical reasons. Ideally, a large number of controls from several ethnic backgrounds should be sequenced rather than the common practice of screening for mutation occurrence in a single ethnic background. However, this is often too expensive or arduous to be practical. When these strictures have not been followed, authors should explain why they were not, so that the scientific community can have a true value of their clinical worth: Caveat lector! Authors must discuss the realistic possibilities relating to their finding, without a bias toward the most attractive option (usually one of causality).[4] Likewise, editors of all journals must recognize the value of clarity in reporting these types of finding: While pathogenicity is a more saleable entity, it can mislead a field for many years and result in wasted time and resources.

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RECURRENT PINEAL APOPLEXY IN A CHILD

Pineal apoplexy denotes sudden hemorrhage occurring into the pineal gland or a cyst or a mass in pineal region. In clinical neuroscience, pituitary apoplexy is a well established entity. Hemorrhage into a pineal gland is, however, extremely uncommon. The first case of pineal apoplexy was reported in 1976 following use of anticoagulation medications.[1] Since then, 12 cases have been described in the literature (table).[2] Repeated bleeding into the pineal gland has been considered a possible risk, but no such case has been reported previously.[3]

Surgical intervention is usually recommended for pineal apoplexy; however, conservative management has also been tried.[2] Acute hydrocephalus that may result in pineal apoplexy can be taken care of by a ventriculoperitoneal (VP) shunt. Hemorrhagic mass into the pineal gland can then be managed expectantly and has been suggested.[2] However, recurrence of benign apoplexy necessitates surgical evacuation of hematoma to prevent compression of brain stem. In this article, the authors present a case of recurrent pineal apoplexy into a pineal cyst in a child. To the authors' knowledge, this is the first reported case of recurrent pineal apoplexy.

Case report. *History and examination.* A previously well young girl presented to the emergency room (ER) with worsening headache and vomiting. Two weeks earlier, she had developed neck pain, which gradually turned into diffuse headache. A day before coming to the ER, she had impaired mentation. On presentation she had severe headache followed by six episodes of vomiting. Her general and systemic examination was unremarkable except that she had bilateral horizontal gaze nystagmus and an

Table	Reported cases of pineal apoplexy	
Case no./age, y/sex	Clinical presentation	Pathology
1/56/M[1,7]	Acute severe headache, disorientation, eye signs	Pineal cyst
2a*/13/M[7]	Episodic severe headache, sudden death	Pineocytoma
2b/18/F[7]	Episodic severe headache, eye signs later	Pineocytoma
3*/54/M[7]	Progressive headache, eye signs, sudden collapse and death	Ganglioglioma
4/51/F[7]	Acute severe headache, loss of consciousness	Pineal cyst
5*/20/F[7]	Sudden death	Pineal cyst, AVM
6/30/M[7]	Progressive headache	Pineal cyst
7/9 mo/M[7]	Sudden onset of vomiting, irritability	Rhabdoid tumor
8/35/F[7]	Episodic headache, sudden collapses, papilledema	Pineal cyst
9* [7]	Not spontaneous although reported after Au implant, sudden loss of consciousness, death	Ectopic pinealoma
10/58/F[7]	Worsening following VP shunt, drowsiness, eye signs	Pineocytoma
11+/71/F [2]	Drowsiness, vomiting, headache, unsteadiness	Pineal cyst
12/11/F[3]	Headache, lethargy	Cavernous angioma
13‡/10/F	Worsening headache, impaired concentration, and gaze paresis	Pineal cyst‡

*Cases with sudden death.
+The only patient who was managed conservatively. The rest had surgery.
‡Recurrent pineal apoplexy in a child.
AVM = arteriovenous malformation;VP = ventriculoperitoneal.

upward gaze paresis. She was conscious, alert, and oriented. Her routine laboratory investigations were all normal.

Imaging. MRI scan revealed a well defined non-enhancing mass in the posterior half of the third ventricle measuring 2.3 × 2.7 cm. It was hyperintense on T1- and hypointense on T2-weighted images (figure 1). The lesion was pressing onto the tectal plate, obstructing CSF flow leading to hydrocephalus.

Course of disease. A VP shunt was inserted. Her CSF examination and levels of human chorionic gonadotrophin and α-fetoprotein were normal. Her symptoms improved subsequently. A CT scan obtained before discharge revealed mixed hypo- and hyperdense signals depicting a resolving subacute hemorrhage (figure 2A).

She presented again with neck pain after 5 days. On her second day of admission, she became very drowsy and irritable and developed an upward gaze paresis. CT scan was consistent with recurrent hemorrhage into a pineal cyst (figure 2B).

Surgery and postoperative course. She underwent sub-occipital craniotomy for excision of cyst and evacuation of hematoma. The diagnosis of pineal cyst was confirmed on histopathologic examination of the specimen. Her postoperative course was uneventful. Her immediate postoperative CT scan and a follow-up MRI scan 3 months later did not reveal any residual or recurrent lesion in the pineal region. The child was normal neurologically. She went back to school and adjusted well.

Discussion. Symptomatic pineal apoplexy is extremely rare. Only four cases have occurred in the pediatric population, and none of them had recurrence (table). The hematoma recurred in this case while she was still under conservative care.

Figure 1	MRI scans of pineal apoplexy at presentation
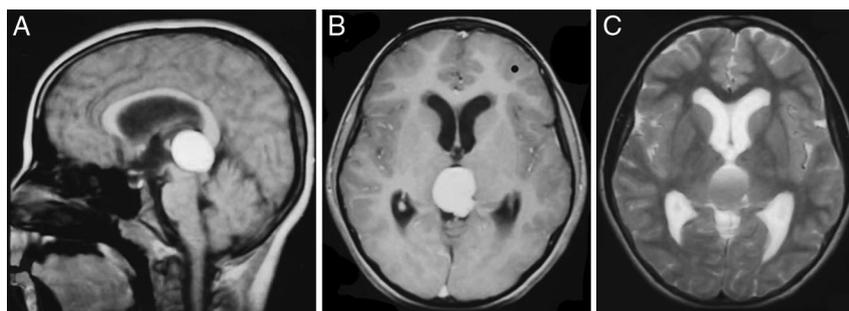
Sagittal T1-weighted image (A) and axial contrast-enhanced Tl-weighted image (B) show hyperintense lesion without any contrast enhancement. The lesion shows low attenuation on T2-weighted images (C).

CT scans demonstrating partial resolution of pineal hematoma 13 days after the initial presentation (A) and recurrence of hematoma evident as hyperdense signal in the pineal region 20 days after initial presentation (B).

Figure 2   CT scan on recurrent pineal apoplexy on follow-up
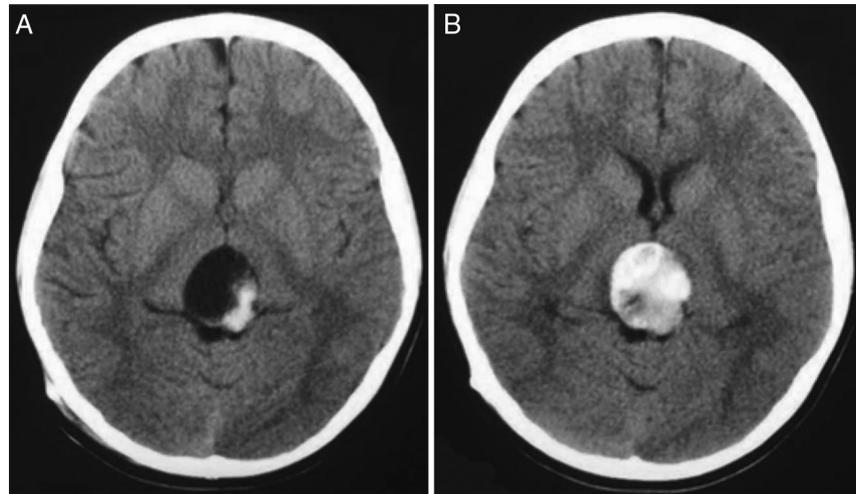
Apart from pineal cysts, other pathologies that may precipitate pineal apoplexy are pineal gland tumors and hemorrhage from the adjacent vascular malformations.[4,5] Spontaneous hemorrhage into the cystic gland parenchyma due to anticoagulation use has also been reported.[1] The mortality of pineal apoplexy is high; 4 of the 12 reported patients died of massive hemorrhage (table).

Pineal cysts present in three clinically distinct syndromes: paroxysmal headaches with gaze paresis; chronic headache, gaze paresis, papilledema, and hydrocephalus; and pineal apoplexy with acute obstructive hydrocephalus, the most uncommon presentation of a symptomatic pineal cyst.[3,6] Patients with symptomatic pineal apoplexy can be categorized into two groups (table): those presenting with rapid deterioration in consciousness and headache and those who present with sudden coma leading to death.[7]

Almost half (46.1%) the cases of pineal apoplexy were due to pineal cysts (table). The rest had different precipitating factors. No association was noted between pineal apoplexy and the age of the patient as all four cases in pediatric patients had different underlying lesions. Four of the 13 cases had had sudden death where the diagnosis was confirmed post mortem.

Surgical extirpation is considered mandatory in all cases to prevent the life-threatening hemorrhage which can compress the brainstem, causing death.[3] Additionally, specimens can be obtained for histopathologic examination because a confirmed diagnosis can prevent unnecessary treatment for a benign lesion.[5]

Conservative management of pineal apoplexy lacks sufficient evidence. Besides, it can recur, as happened in this case. Therefore, we propose that surgery should be performed early to save these patients from the life-threatening hemorrhage.

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