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CASE-BASED UPDATE

Pineal cysts in children: case-based update

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Abstract
Purpose Pineal cysts (PC) are found in children as often asymptomatic and without change in their size over the time. However, there are some debatable issues about their evolution and management in the pediatric population. The aim of the present paper is to update the information regarding pathogenesis, clinical presentation, and management of these lesions.
Methods All the pertinent literature was reviewed, and a meta-analysis of operated on cases was carried out. An illustrative case regarding the clinical evolution of a 13-year-old girl is also presented.
Results and conclusions PC are often asymptomatic and do not evolve over the time. However, since there is a certain risk of clinical and/or radiological progression, or even sudden and severe clinical onset (apoplexy), both a clinical and radiological follow-up is recommended in the pediatric age. The surgical excision is usually limited to symptomatic patients or to cases with clear radiological evolution.

Keywords Pineal cyst · Pineal gland · Management · Surgery · Children

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Introduction

Epidemiology

Pineal cysts (PC) occur in all ages. Their prevalence ranges from 1 to 10 % in adults [11, 16, 64, 80], being more close to 1 % in large series [4]. However, in autoptic series, this rate is significantly higher, ranging between 25 and 40 % [11, 41, 64]. Currently, PC are more and more diagnosed thanks to the advances and the diffusion of neuroimaging tools [namely, magnetic resonance imaging (MRI)] [4, 9, 16, 53, 57, 80].

According to some series, PC are rare in children younger than 10 years of age, since they are thought to appear during the adolescence [72, 76]. However, in the Al-Holou and cow-orkers' series, children and young adults (under 25 years) showed a 2 % prevalence, which is as high as in adults [2, 4]. In this group of patients, the female prevalence was higher (2.4 %) than in males (1.5 %) [2]. Such difference between the two sexes has been confirmed by other authors [72].

Pathogenesis and pathology

The natural history of PC is unknown [41] and the etiology still unclear [11], even though several theories have been propounded to explain their pathogenesis. According to some of them, PC would result from a focal degeneration of the pineal gland (PG), being composed by gelatinous material surrounded by a wall consisting of three layers: outer fibrous layer, middle layer of parenchymal cells with possible calcifications, and inner layer of hypocellular glial tissue [19, 86]. Based on other hypotheses, since the PG develops by the proliferation of the walls of the third ventricle diverticulum in the diencephalic roof, the remnants of the pineal diverticulum or the distention of its obliterated portion would result in PC [6, 72]. During this process, the cavity is lined by cells that can differentiate

into ependymal cells [55]. In some instances, however, PC are not lined by ependymal cells but they are surrounded by a glial scar [2, 19]. On these grounds, Laure-Kamionowska et al. hypothesized that PC may evolve from necrotic and hemorrhagic lesions found in the fetal PG [39]. Hirato and Nakazato, moreover, classified PC as non-neoplastic, tumor-like lesions surrounded by normal pineal parenchyma or lined by glial tissue (see also "Illustrative case") [27]. Finally, to summarize the variability of the composition of PC, Taraszewska et al. reported on two operated symptomatic patients and three asymptomatic incidental autopsy examinations: even though histological findings of symptomatic and asymptomatic cysts were essentially the same, one operated cyst was unilocular and partially lined with ependymal cells, whereas the other cysts were multilocular, showing cavities of various sizes consisting, in the central part, of gliotic tissue or pineal parenchyma and did not present ependymal lining [84].

Clinical presentation

The clinical spectrum is wide, varying from absence of symptoms to sudden death. Also the symptoms and signs attributed in the presence of PC vary considerably in the different reports. Headache is most common symptom both in children and adults [4, 6, 11, 18, 38, 44, 46, 57]. In the Mandera et al. series, indeed, headache burdened 14 out of 24 children [41]. Similarly, Al-Holou et al. found headache as the most common symptom in their series of young adults (under 25 years old) [3, 57]. An association with nocturnal headache and melatonin deficiency has been noticed [30]. However, a casual relationship between headache and PC can be suspected in some cases [58, 74, 75]. Headache is usually chronic with subtle onset, but sudden onset or acute worsening are not exceptional [58]. In some instances, severe frontal or occipital headache is not isolated but associated with gaze paresis and visual fields defect, hearing loss, nausea or vomiting, and syncope [5, 43, 49, 69, 81].

Other possible symptoms of pediatric PC are oculomotor nerve paresis, Parinaud's syndrome, lethargy, gait disturbances, vertigo, visual disturbances, anorexia, hemiparesis, epilepsy, nausea and/or vomiting, bradycardia, and papilledema [41, 46, 57, 89]. Hydrocephalus is an obvious complication in the case of compression and occlusion of the Sylvius's aqueduct. PC apoplexia and hemorrhage are rare but potentially dangerous [43, 50, 69] being responsible, together with acute hydrocephalus, of sudden death [47, 67].

The relationship between the size of the cyst and the onset of symptoms is still debated. Actually, the diameters of asymptomatic cysts are usually less than 10 mm or, at most, between 10 and 20 mm; however, though the diameters of the symptomatic cysts are usually more than 20 mm, symptomatic subjects with even 7 mm diameter PC have been described [6, 11].

PC have been found in coincidental association with retinoblastoma [3, 31, 61, 62], precocious puberty [14, 37, 68], idiopathic scoliosis [13], resting tremor [48], Aicardi syndrome [51], infantile spasm [56], hot water epilepsy [82]. Although postulated, there is no definite relationship between bipolar disorder and PC based on MRI exploration of the pineal volume [70]. Similarly, the association with endocrinologic dysfunctions seems to be occasional, since they do not improve after surgery [71].

Diagnosis

PC are often incidentally diagnosed because of the wide diffusion of the neuroimaging tools [16, 17, 53, 75]. PC are frequently detected with computerized tomography (CT scan) performed for other reasons (mainly head injury) [19, 74, 83]. On CT scan, they appear as a hypodense, grossly round mass [11, 19]. Small areas of hyperdensity can be detected because of hemorrhage or calcification; approximately, 30 % of PC contain micro-calcifications along their walls [11, 19, 22, 44]. MRI is the gold standard examination for both diagnosis and follow-up [9, 11, 20, 22, 25, 35, 53, 57, 64, 79, 80, 83]. On MRI, PC appear as a round or ovoid mass, hypo-/isointense or slightly hyperintense on T1-weighted and fluid-attenuated inversion-recovery images, and iso-/hyperintense on T2-weighted images [6, 11, 83]. The cyst wall is never thicker than 1–2 mm. The sagittal section is useful to visualize the surrounding anatomical structures, namely the aqueduct [6, 11, 59]. Lacroix-Boudhrioua et al. demonstrated that PC often contain septations by using high-resolution MRI. According to the authors, this finding is a normal variant and do not require additional follow-up imaging [38]. In PC with apoplexy and hemorrhagic areas, the diagnosis can be obtained by integrating MRI and CT scan [34, 52]. Cerebral angiography may be considered when associated vascular malformations are suspected [34, 67]. Serial MRI is used to follow indeterminate PC [9].

Transcranial ultrasonography (TUS) may represent a further diagnostic option [8, 24]. Budisic et al. studied the TUS characteristics of 14 PC patients (nine children and five adults) and their correlation with MRI [8]. Since there were not significant differences between TUS and MRI about the size and content of the PC, the authors propounded to use TUS for radiological follow-up. The major limit of the technique is the possible absence of an adequate temporal bone window.

Melatonin can be used as laboratory marker as for other pineal pathologies [30, 40]. According to Mandera et al., high night melatonin levels indicate a tumor

lesion, while normal or depressed levels suggest the presence of PC [41].

Management

The management of PC varies from the observation alone to the surgical excision. Observation is usually recommended for asymptomatic patients. A conservative management has been proposed also in selected symptomatic cases, as for example, those patients with PC apoplexy [5, 52]. However, Patel et al. recommended the surgical treatment of PC apoplexy to minimize the risk of complications and the possible recurrence of this phenomenon, which is common among children and young adults [58]. Melatonin therapy has been successfully used in some symptomatic subjects (headache) without hydrocephalus [18, 60].

In adults, surgery is generally not recommended unless there are neurosurgical signs resulting from the compression on the quadrigeminal plate, the aqueduct, or the vein of Galen [82]. Based on the largest available mixed series (151 adult and 288 pediatric cases), Al-

Table 1 Synopsis of the operated on cases reported in the literature

No.	Year (reference)	Age	Sex	Clinical presentation	Surgical approach	Cyst diameter	Surgical outcome
1	1914 [63]	14 years	M	Headache, gaze paresis, Hy	N/A	N/A	Death
2	1987 [89]	19 months	F	N/A	Transventricular	N/A	STR
3	1987 [89]	1 years	M	N/A	Transventricular	N/A	STR
4	1987 [89]	16 years	M	N/A	Infratentorial supracerebellar	N/A	STR
5	1989 [32]	12 years	M	Headache, gaze paresis, Hy	N/A	N/A	N/A
6	1991 [54]	10 years	M	N/A	N/A	N/A	N/A
7	1992 [90]	14 years	F	Headache, gaze paresis	Occipital transtentorial	N/A	GTR
8	1992 [90]	16 years	F	Headache, gaze paresis	Occipital transtentorial	N/A	GTR
9	1992 [90]	14 years	F	Headache, gaze paresis	Occipital transtentorial	N/A	STR
10	1992 [90]	5 years	F	Headache, gaze paresis	Occipital transtentorial	N/A	GTR
11	1993 [50]	16 years	F	Headache, nausea/vomiting, visual deficits, Hy	Stereotactic aspiration	27 mm	STR
12	1993 [50]	13 years	F	Headache, vomiting, diplopia, papilledema, Hy	Stereotactic aspiration	22 mm	STR
13	1995 [56]	3 months	F	Intractable flexor spasms	Suboccipital supratentorial	N/A (huge)	GTR
14	1997 [44]	7 years	M	Headache, nausea/vomiting, Hy	Infratentorial supracerebellar	6 mm	GTR
15	1997 [44]	15 years	M	Headache, diplopia, papilledema, ataxia, PS, Hy	Infratentorial supracerebellar	40 mm	GTR
16	2001 [15]	16 years	F	Headache, papilledema Hy	Endoscopic third ventriculostomy	25 mm	Disappeared
17	2002 [46]	4 years	F	Headache, vomiting, lethargy, Hy	Endoscopic marsupialization	N/A	GTR
18	2003 [43]	12 years	F	Headache, nausea/vomiting, syncope, Hy	Infratentorial supracerebellar	14 mm	GTR
19	2003 [41]	15 years	F	Headache, blurred vision, PS, Hy	Infratentorial supracerebellar	>20 mm	GTR
20	2003 [41]	12 years	F	Headache, blurred vision,	Infratentorial supracerebellar	>20 mm	GTR
21	2003 [41]	15 years	F	Headache	Infratentorial supracerebellar	<20 mm	GTR
22	2003 [41]	10 years	F	Headache, nausea/vomiting, abducent palsy	Infratentorial supracerebellar	<20 mm	GTR
23	2007 [13]	12 years	M	N/A	N/A	N/A	N/A
24	2007 [78]	13 years	F	Headache	Infratentorial supracerebellar	N/A	GTR
25	2008 [48]	18 years	F	Headache, nausea/vomiting	Bilateral suboccipital	13 mm	N/A
26	2008 [84]	17 years	M	Headache, vomiting, syncope	Infratentorial supracerebellar	16 mm	GTR
27	2008 [84]	18 years	F	Headache, nausea/vomiting, syncope	Occipital transtentorial	14 mm	GTR
28	2009 [69]	16 years	F	Headache, Hy	Infratentorial supracerebellar	18 mm	GTR
29	2009 [69]	16 years	F	Headache, diplopia, papilledema	Infratentorial supracerebellar	14 mm	GTR
30	2012 (present case)	13 years	F	Headache, visual deficits	Occipital transtentorial	16 mm	GTR

Cases without at least information on patient's age have not been included

M male, *F* female, *N/A* not available, *Hy* hydrocephalus, *PS* Parinaud's syndrome, *GTR* gross total resection, *STR* subtotal resection

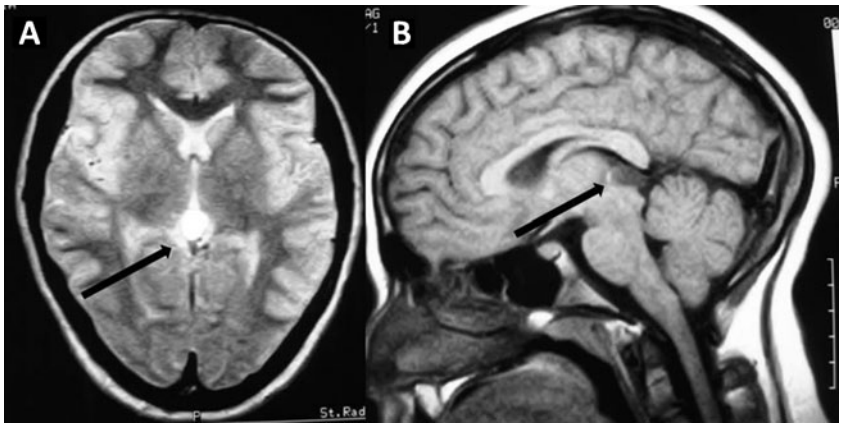

Fig. 1 First brain MRI showing a 13-mm-diameter pineal cyst (see arrow), hyperintense in T2-weighted axial view (**a**) and isointense in T1-weighted sagittal view (**b**)

Holou et al. did not consider clinical and radiological follow-up as mandatory in adults with asymptomatic PC [2, 4] as proposed also by others [8, 9]. Differently, the authors recommended both clinical and radiological follow-up in children, especially in older subjects [2, 3]. Such a strategy was adopted also in other studies [41, 46, 50, 90].

Surgery is required in patients with symptomatic and/or increasing size of PC [13, 19, 41, 42, 69, 84, 88]. Sitting, semi-sitting, prone, or modified prone positions are standardly used for the open surgical approach to pineal region [7], which includes the supracerebellar infratentorial [19, 33, 41, 43, 44, 46, 65, 84], the occipital transtentorial [29, 49, 65, 84, 90], the supratentorial infraoccipital [44], and the transcallosal interforniceal route [28]. Mini-invasive approaches are represented by stereotactic [26, 36, 50, 77] or endoscopic marsupialization [21, 46, 85, 87]. Endoscopic-assisted microsurgery is a further option [23, 45]. A singular mini-invasive option is represented by the neuronavigation-guided insertion of a clear plastic tubular retractor to reach the pineal region [66]. Anyway, according to the literature concerning the pediatric age, the most used approach is the supracerebellar infratentorial one [19, 41, 43, 44, 69, 84, 88, 89].

Neuro-endoscopy allows to obtain tissue samples for the pathological diagnosis as well as the fenestration of the cyst and, if needed, the treatment of associated hydrocephalus (third ventriculostomy) at the same time [10]. Frameless computerized neuronavigation system may be helpful in assisting endoscopic procedures [1, 12, 73].

Meta-analysis of literature on surgically managed children

There are no large series on operated children since only 30 cases were reported in the literature (including the present one) (Table 1). Accordingly, there were 21 girls (70 %) and nine boys (30 %). The mean age at surgery was 11 years (range, 3 months–18 years). Headache was the most common symptom (24 patients, 80 %). Other common clinical and neurological signs were vomiting (23 %), gaze paresis (20 %), nausea (16 %), papilledema (13 %), diplopia, and syncope (10 % each). Hydrocephalus was observed in 11 out of 25 children (44 %); data on hydrocephalus were unavailable for the remaining five cases. The diameter of PC was over than 20 mm in seven children and less than 20 mm in ten children (unavailable data in three cases).

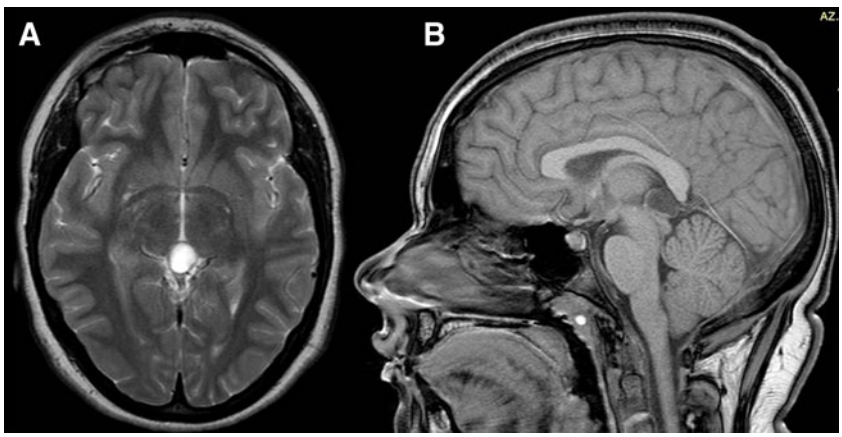

Fig. 2 Preoperative MRI, performed 3 years later, demonstrating a slight enlargement of the cyst (diameter, 16 mm). The signal characteristics were unchanged in both T2-weighted (**a**) and T1-weghted sections (**b**)

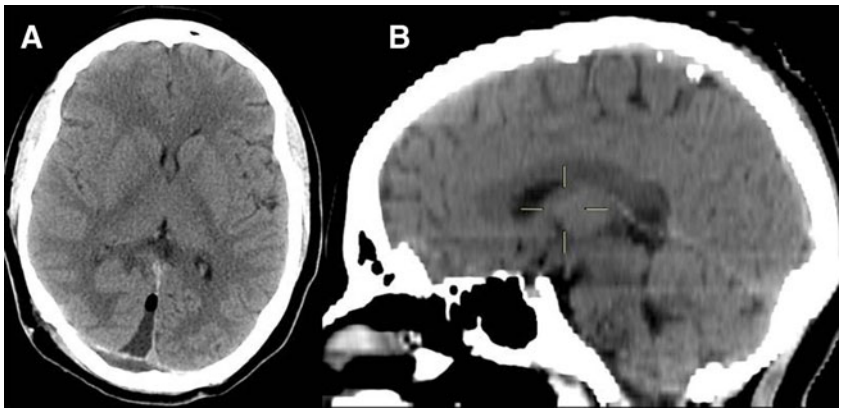

Fig. 3 Axial (**a**) and sagittal reconstruction (**b**) of the immediate postoperative CT scan confirming the excision of the cyst. The surgical route is still evident as consequence of the retraction of the right occipital lobe (**a**)

The most common surgical approach was infratentorial–supracerebellar approach, which was used in 12 cases (40 %), and occipital transtentorial approach, which was utilized in 6 cases (20 %). Transventricular, stereotactic (two patients each), suboccipital supratentorial, and bilateral suboccipital routes (one patient each), third ventriculostomy, and endoscopic marsupialization were the other surgical approaches (surgical technique was not reported in four cases).

A subtotal excision of PC was obtained in six children (20 %), mainly belonging to the oldest series. Actually, the advances in microsurgery allowed a total resection in 17 patients (56 %). In these series, there were no permanent complications after surgery. One transient complication (delayed lateral rectus muscle palsy) was reported following pneumocephalus due to the sitting position during the operation [78]. The only one reported death dates back to the pre-microsurgical era [63]. In one child with recurrent headache and associated hydrocephalus, PC disappeared with indirect surgery; after endoscopic third ventriculostomy, indeed, serial MRI demonstrated both the resolution of hydrocephalus and the regression of the PC so that the authors postulated the presence of a to-and-from movement of fluid through the cyst wall, the direction of which depends on the equilibrium existing between the inner pressure of the cyst and the outer cerebrospinal fluid pressure [15].

Illustrative case

This 13-year-old girl was admitted to our department because of chronic occipital headache worsening during the night. Three years before, she was suffering with sporadic episodes of diffuse headache, sporadically associated with photophobia and subjective visual disturbances. The MRI performed at that time showed a 13-mm pineal cyst (Fig. 1). Because of the low frequency of headache episodes, the absence of physical and neurological signs, and the absence of hydrocephalus, it was decided to follow the patient with a close clinical and radiological observation prior to considering a surgical operation. In the follow-up period, no neurological worsening or variations of the MRI image occurred. However, 3 years later, the headache episodes became frequent and more intense. MRI demonstrated a small increase in size of the cyst, which reached a 16-mm diameter (Fig. 2). On these grounds, the excision of the cyst was performed through a transtentorial suboccipital approach. The postoperative course was uneventful except for transient visual impairment which resolved in 24 h. Early postoperative CT scan did not show complications (Fig. 3). The pathological examination revealed pineal cyst surrounded by a piloid-like glial layer. Six months after surgery, the patient is still headache-free.

Conclusions

The higher prevalence and increasing rate to develop neurological signs in children harboring PC, compared with adults, make them more prone to undergo surgery. In our opinion, an operation should be considered when the child is symptomatic or shows the signs of radiological progression. Asymptomatic children, on the other hand, should undergo a close observation up to the adult age.

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