Pineal cysts and other pineal region malignancies: determining factors predictive of hydrocephalus and malignancy

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OBJECTIVE Cystic lesions of the pineal gland are most often uncomplicated benign lesions with typical MRI characteristics. The authors aimed to study pineal lesion characteristics on MRI to better distinguish benign pineal cysts from other pineal region malignancies as well as to determine which characteristics were predictive of the latter malignancies. They also aimed to study risk factors predictive of hydrocephalus or malignancy in patients harboring these lesions.

METHODS The authors performed a retrospective review of a prospectively compiled database documenting the outcomes of patients with suspected pineal cysts on MRI who had presented in the period from 1998 to 2004. Inherent patient and lesion characteristics were assessed in a univariate logistic regression analysis to predict the following dependent variables: development of hydrocephalus, biopsy-confirmed malignancy, and intervention. Possible inherent patient and lesion characteristics included age, sex, T1 and T2 MRI signal pattern, contrast enhancement pattern, presence of cyst, presence of blood, complexity of lesion, presence of calcification, and duration of follow-up. Inherent patient and lesion characteristics that were predictive in the univariate analysis ($p < 0.15$) were included in the multivariable logistic regression analysis.

RESULTS Of the 79 patients with benign-appearing pineal cysts, 26 (33%) were male and 53 (67%) were female, with a median age of 38 years (range 9–86 years). The median cyst radius was 5 mm (range 1–20 mm). Two patients (2.5%) had evidence of calcifications, 7 (9%) had multicystic lesions, and 25 (32%) had some evidence of contrast enhancement.

The median follow-up interval was 3 years (range 0.5–13 years). Seven patients (9%) had an increase in the size of their lesion over time. Eight patients (10%) had a hemorrhage, and 11 patients (14%) developed hydrocephalus. Nine (11%) received ventriculoperitoneal shunts for the development of hydrocephalus, and 12 patients (16%) were found to have malignancies following biopsy or resection. In the multivariate analysis, contrast enhancement on MRI (OR 1.6, 95% CI 2.86–74.74, $p = 0.013$) and hemorrhage (OR 26.9, 95% CI 3.4–212.7, $p = 0.022$) were predictive of hydrocephalus. Increasing lesion size and hydrocephalus were near perfect predictors of malignancy and thus were removed from multivariate analysis. In addition, contrast enhancement on MRI (OR 8.8, 95% CI 2.0–38.6, $p = 0.004$) and hemorrhage (OR 6.8, 95% CI 1.1–40.5, $p = 0.036$) were predictive of malignancy.

CONCLUSIONS Although cystic abnormalities of the pineal gland are often benign lesions, they are frequently monitored over time, as other pineal region pathologies may appear similarly on MRI. Patients with growing lesions, contrast enhancement, and hemorrhage on MRI are more likely to develop hydrocephalus and have malignant pathology on histological examination and should therefore be followed up with serial MRI with a lower threshold for neurosurgical intervention.

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KEY WORDS pineal cyst; hemorrhage; adult; aqueductal stenosis; hydrocephalus

ABBREVIATIONS EVD = external ventricular drainage.

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PINEAL cysts are commonly occurring lesions, with a reported incidence in roughly 1%–4% of individuals undergoing standard MRI studies.^{1,6,10,14,16,19,20,25,42} Autopsy series have shown the rate to be even greater, with occurrence in 25%–40% of subjects.^{4,11,18,34,37} Their incidence is typically higher in women, with lesions most frequently occurring in the 2nd decade of life and subsequently decreasing in frequency with age.³⁹ These cysts are traditionally benign and are normal variants of the pineal gland composed of cystic structures surrounded by parenchyma.⁷

Patients with pineal cysts are typically asymptomatic; however, they can also present with a broad array of symptoms, with headache being the most frequent.^{7,8,36} Interestingly, these headaches were once thought to be caused by increased intracranial pressure, but new research suggests that a hormonal imbalance involving melatonin may be to blame.^{8,12,24,27,35,36,40,45} Other commonly encountered symptoms include seizures, vertigo, blurred vision, hemiparesis, and emesis.^{4,14,26,43,46}

The radiological appearance of pineal cysts varies based on the imaging modality used. Magnetic resonance imaging with gadolinium contrast enhancement is the preferred radiological method, allowing for greater evaluation of lesion size, vascularity, composition, and anatomical relationships.^{7,32,47} Despite all of the advances in high-resolution MRI, however, there is no current definitive method by which we can distinguish benign pineal cysts from pineal region malignancies such as pineocytomas, pineoblastomas, germinomas, or mature teratomas, particularly when any of these pathologies can often include cystic components visible on imaging.¹¹ Therefore, we assessed the imaging characteristics of pineal cystic lesions with the goal of differentiating between asymptomatic benign pineal cysts and pineal malignancies. We additionally aimed to identify any characteristics of these cysts that would predict the development of hydrocephalus.

Methods

We performed a retrospective review of patients reported to have pineal cysts on MRI of the brain at the University of Virginia between 1998 and 2004. These patients had all been referred to the neurosurgery service as outpatients and were followed up over time with serial MRI. For each patient we subsequently collected and documented the appropriate demographics and clinical details, including age, sex, duration of follow-up, indications for initial imaging, histology of malignancy if present, and clinical outcome.

Additionally, we collected and documented the imaging characteristics for each patient, including lesion diameter, T1 or T2 imaging pattern (hyperintensity, hypointensity, or isointensity), postcontrast enhancement pattern, presence of calcifications, any multiplicity of cysts, whether hemorrhage was present (as evidenced by hyperdensity on head CT or hyperintensity on brain MRI), and whether there was any increase in the size of the lesion over time. Finally, we identified subsets of patients who had presented with hydrocephalus and underwent procedural intervention (including external ventricular drainage [EVD],

shunt placement, or resection), as well as patients who underwent resection and/or biopsy and had a histological diagnosis of pineal malignancy.

We reviewed our findings to identify any apparent difference in imaging characteristics between benign cysts and malignancies and between symptomatic and asymptomatic benign cysts. For purposes of analysis, cysts were considered “simple” if their imaging characteristics did not contain any of the following: a multicystic component, a hemorrhagic component, calcification, or postcontrast enhancement.

Statistical Analysis

Data are presented as the mean and range for continuous variables and as the frequency for categorical variables. Calculations of normality were performed using the ladder of powers. Statistical analyses of categorical variables were performed using the chi-square and Fisher’s exact tests, as appropriate. Statistics of means were performed using an unpaired Student t-test both with and without equal variance (Levene’s test), as necessary, and Wilcoxon rank-sum tests when variables were not normally distributed. Analysis of variance followed by Bonferroni post hoc testing was used to assess means between 3 or more groups. Odds ratios and 95% confidence intervals were calculated using univariate logistic regression analysis. Inherent patient and lesion characteristics were assessed as independent variables to predict the following dependent variables: biopsy-confirmed malignancy, development of hydrocephalus, and intervention (EVD, shunt, resection).

Possible inherent patient and lesion characteristics included age, sex, T1 and T2 MRI signal pattern, contrast enhancement pattern, presence of cyst, presence of blood, complexity of lesion, presence of calcification, and duration of follow up.

Inherent patient and lesion characteristics predicting biopsy-confirmed malignancy with a univariate $p < 0.15$ were included in a multivariable logistic regression analysis to assess the most robust predictors of having a biopsy-proven malignancy. Inherent lesion characteristics predicting the development of hydrocephalus with a univariate $p < 0.15$ were included in a multivariable logistic regression analysis to assess the most robust predictors of the development of hydrocephalus. Inherent lesion characteristics predicting the necessity of a procedure (EVD, shunt, resection) with a univariate $p < 0.15$ were included in a multivariable logistic regression analysis to assess the most robust predictors of the need for an intervention. A p value ≤ 0.05 was considered statistically significant.

Results

Of the 79 patients with benign-appearing pineal cysts, 26 (33%) were male and 53 (67%) were female, with a median age of 38 years (range 9–86 years; Table 1). The median cyst radius was 5 mm (range 1–20 mm). Two patients (2.5%) had evidence of calcifications, 7 (9%) had multicystic lesions, and 25 (32%) had some evidence of contrast enhancement. Twelve patients (15%) had cysts displaying a peripheral enhancement pattern, whereas 13 (16%) had another type of contrast enhancement.

TABLE 1. Summary of patient characteristics

Characteristic	Value
No. of patients	79
Median age at diagnosis in yrs (range)	38 (9–86)
Sex	
Male	26 (33%)
Female	53 (67%)
Calcifications	2 (2.5%)
Multicystic	7 (9%)
Contrast enhancement	25 (32%)
Enhancement pattern	
Peripheral	12 (15%)
Nonperipheral	13 (16%)
Median FU in yrs (range)	3 (0.5–13)
Interval increase in lesion size	7 (9%)
Hemorrhage	8 (10%)
Hydrocephalus	11 (14%)
No. of patients undergoing procedure	11 (14%)
Type of procedure	
EVD	3 (4%)
VPS	9 (11%)
Resection	6 (8%)
Malignancy	12 (16%)

FU = follow-up; VPS = ventriculoperitoneal shunting.

The median follow-up interval was 3 years (range 0.5–13 years). Seven patients (9%) had an increase in the size of their lesion over time. Eight patients (10%) had a hemorrhage, and 11 patients (14%) developed hydrocephalus. Nine (11%) received ventriculoperitoneal shunts, and 12 patients (16%) were found to have malignant histology following biopsy or resection. In a multivariate analysis, contrast enhancement on MRI (OR 1.6, $p = 0.013$) and hemorrhage (OR 26.9, 95% CI 3.4–212.7, $p = 0.022$) were predictive of hydrocephalus (Table 2). Increasing lesion size and hydrocephalus were near perfect predictors of pineal region malignancy and thus were removed from multivariate analysis. In addition, contrast enhancement on MRI (OR 8.8, 95% CI 2.0–38.6, $p = 0.004$) and hemorrhage (OR 6.8, 95% CI 1.1–40.5, $p = 0.036$) were predictive of a pineal malignancy (Table 3).

Discussion

As the use of MRI has become more frequent, the number of incidentally discovered pineal cysts has greatly increased.^{1,6,10,14,16,19,20,25,42} Despite the advances made with respect to high-resolution MRI, however, there is no clearly defined means of distinguishing these cysts from other pineal region malignancies.¹¹ It is generally accepted that typical benign pineal cysts are small (< 1 cm in diameter) and have a round to oval appearance with smooth boundaries and a cyst wall with a maximum thickness of 2 mm on radiological studies.^{9,15} In our patient population, we found a median cyst radius of 5 mm (range 1–20 mm). The average radius of pineal lesions ultimately diagnosed as pineal malignancy was 12.3 mm, whereas the average radius of simple cysts was 5.4 mm and the average radius of lesions requiring a procedure (EVD, shunt, resection) was 9.7 mm. This need for intervention is most likely due to the increasing degree of compression of the rostral third ventricle with an enlarging lesion, causing hydrocephalus or general mass effect, with the subsequent production of neurological symptoms. We also found that smaller lesions are more frequently benign pineal cysts.

The etiology of pineal cysts is still under debate; however, several postulates have been presented in an attempt to explain their origin. The first theory is that pineal cysts could be the congenital remnant of the embryological diverticulum that develops from the third ventricle and forms the pineal gland.^{18,20,25} The second theory is that these cysts could be an embryogenic remnant of the cavum pineale.⁹ Additional theories suggest that they may be the result of the degeneration of pinealocytes^{13,22} or a byproduct of ischemic necrosis.²³ The most current theories, however, suggest formation via hemorrhage^{1,13,15,22,28} or a hormonal cause.⁸ As stated previously, the incidence of pineal cysts is typically higher in women, with lesions most frequently occurring in the 2nd decade of life and subsequently decreasing in occurrence with age.³⁹ Many authors have acknowledged a female predominance specifically consisting of a subgroup in the reproductive age range (age 15–49 years). Our study confirmed this predominance, which may support a hormonal cause for pineal cyst formation; however, further in-depth analysis is necessary.

On a similar note, hormonal imbalance may also be responsible for the headache that many pineal cyst patients present with. As noted previously, patients with

TABLE 2. Statistical analysis: factors predictive of hydrocephalus

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p Value	OR	95% CI	p Value
Age	1.00	0.9–1.0	0.913	—	—	—
Sex	1.2	0.3–4.5	0.793	—	—	—
FU	1.0	1.0–1.1	0.393	—	—	—
Hemorrhage	37.2	6.3–249.5	<0.001	26.9	3.4–212.7	0.022
Multicystic	6.0	1.3–31.8	0.035	—	—	—
Contrast enhancement	14.6	2.9–74.8	0.01	1.60	2.86–74.74	0.013
T1/T2 pattern*	6.1	2.2–17.1	—	—	—	—

* T1/T2 MRI signaling pattern.

TABLE 3. Statistical analysis: factors predictive of pineal malignancy

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p Value	OR	95% CI	p Value
Age	1.0	0.9–1.0	0.343	—	—	—
Sex	2.3	0.7–8.2	0.189	—	—	—
FU	1.00	0.9–1.0	0.904	—	—	—
Hemorrhage	14.29	2.8–73.0	0.001	6.8	1.1–40.5	0.036
Multicystic	6.67	1.2–38.2	0.033	—	—	—
Contrast enhancement	12.75	3.0–54.4	0.001	8.8	2.0–38.6	0.004
T1/T2 pattern	7.50	2.35–23.88	0.001	—	—	—

pineal cysts are typically asymptomatic; however, headache is the most common presenting symptom among a broad list of possible symptoms.^{7,8,36} The cause of these headaches was initially thought to be increased intracranial pressure caused by hydrocephalus due to superior compression of the third ventricle by larger lesions. Larger lesions can cause compression of adjacent structures, including rostral compression of the third ventricle, leading to hydrocephalus.⁷ Unfortunately, given the location of the pineal gland, even smaller lesions can cause symptoms.⁸ Direct compression of the midbrain can result in motor and sensory disturbances.²² Other commonly encountered symptoms include seizures, vertigo, blurred vision, hemiparesis, and emesis.^{4,14,26,43,46} Pineal apoplexy (caused by hemorrhage), Parinaud's phenomenon (caused by compression of the superior colliculus), parkinsonian symptoms, choroid plexus papilloma formation, aseptic meningitis (due to cyst rupture), pseudo-precocious puberty (due to immaturity of the hypothalamic-gonadal axis), and diabetes insipidus are less frequent yet reported symptoms.^{21,26,30,31,37,38,41} There is also thought to be a hormonal and melatonin imbalance in most of these patients with headaches. In our patient population, we found that headache was one of the most common indications for undergoing MRI, with a total of 16 patients (20%) presenting with this symptom. Moreover, of the 16 patients with headaches, 9 (56%) of them were reproductive-age females, suggesting that there may indeed be a hormonal cause behind these headaches.

Pineal lesions usually lack nodularity or heterogeneous enhancement and are stable over time.³ Their radiological appearance varies based on the imaging modality used. Magnetic resonance imaging with gadolinium contrast enhancement is the preferred radiological method, allowing for greater evaluation of lesion size, vascularity, composition, and anatomical relationships.^{7,32,47} Occasionally, however, CT may be used, particularly for the initial scan before the diagnosis of a pineal cyst is made. These cysts can be either hypodense or undetectable on CT as the fluid may be similar in density to CSF.^{8,12,13,44} Hyperdensity may indicate hemorrhage or calcification.^{28,33} On MRI, pineal cysts appear hypointense to white matter and either isointense or diffusely hyperintense to CSF on T1-weighted sequences. This appearance on MRI is variable based on the protein content of the cystic fluid, prior hemorrhage, or stagnation of the fluid.⁸ With the addition of contrast, there is typically thin rim enhancement given the lack of

a blood-brain barrier.⁸ On T2-weighted imaging, there is usually a homogeneous appearance that is isointense or slightly hyperintense relative to the CSF, which is thought to be mainly secondary to stagnation of the cystic fluid.⁸ Proton density and FLAIR sequences appear isointense or slightly hyperintense and slightly hyperintense in comparison to CSF, respectively.⁸

We found that patients with a complex pattern on MRI, as well as those with postcontrast lesion enhancement, were much more likely to have malignant lesions; 13 (52%) of 25 patients with a complex imaging structure on MRI ultimately had a lesion diagnosed as a malignancy. Pineal cysts can also have rim enhancement after contrast administration. The type of enhancement varied in our study, and a large percentage (70%) of lesions with nonperipheral enhancement were ultimately diagnosed as malignancies.

In a multivariate analysis, we found the most accurate predictor of malignancy to be cyst enhancement on MRI (OR 8.8, 95% CI 2.0–38.6, $p = 0.004$) and hemorrhage (OR 6.8, 95% CI 1.1–40.5, $p = 0.036$). Increasing lesion size and hydrocephalus were near perfect predictors of malignancy and thus were removed from multivariate analysis.

Similarly, we found on multivariate analysis that contrast enhancement of cysts on MRI (OR 1.6, $p = 0.013$) and hemorrhage (OR 26.9, 95% CI 3.4–212.7, $p = 0.002$) were predictive of hydrocephalus. A complex imaging pattern was a near-perfect predictor and thus was removed from the multivariate analysis.

We believe that this information will provide possible insight into determining which patients with pineal cysts should be monitored over time. There is still much contradiction in the literature about the most appropriate therapeutic approach to pineal cysts as the natural history remains unclear, particularly with regard to asymptomatic pineal cysts. The management of asymptomatic cysts ranges from the absence of any follow-up to possible surgical intervention; however, the most common practice is to refrain from surgical intervention in an asymptomatic patient. Additionally, while some clinicians do not support routine imaging in adults with known pineal cysts, others recommend annual follow-up with clinical examination and imaging.^{2,17} Routine clinical examination coupled with routine imaging is highly recommended in any child with a pineal cyst.^{1,26,29,33,48} In symptomatic patients, particularly those with hydrocephalus, treatment can be divided

into shunt placement, cyst excision, endoscopic or stereotactic aspiration, and endoscopic third ventriculostomy.^{5,17}

As stated, there has been no uniform management of patients with pineal cysts found on MRI, and the question of which patients to follow up over time has remained largely unanswered. Given our findings, we recommend that all patients with pineal region lesions that enlarge over time, have contrast enhancement, or have hemorrhage on MRI should undergo routine follow-up, as their lesions have a much greater likelihood of ultimately being diagnosed as a malignancy. Further investigation is needed to determine whether the rest of these patients without the above characteristics necessitate follow-up over time.

This study is not without limitations. The small sample size and retrospective nature are inherent weaknesses to the overall design of the study. Additionally, the population studied (patients referred to the outpatient neurosurgery clinic) skews the sample such that there are a greater number of pineal region malignancies that were eventually diagnosed within this group. Furthermore, as this study focuses on patients referred to the neurosurgery outpatient clinic between 1998 and 2004, imaging and other records are no longer available. Nonetheless, these study limitations do not detract from the main purpose of the paper, which was to distinguish imaging and lesion characteristics that would be predictive of hydrocephalus and tumor and offer a means by which benign pineal cysts and pineal region tumors could be distinguished from one another on MRI.

Conclusions

Benign pineal cysts are a common occurrence and can be difficult to distinguish from other pathologies of the pineal region. Furthermore, no specific management guidelines exist regarding follow-up of these lesions and whether patients need to be monitored over time. Although a majority of patients will not have pineal malignancies, those who present with growing lesions, contrast enhancement, and hemorrhage are more likely to develop hydrocephalus and to have malignant pathology on histological examination and should therefore be followed up with serial MRI with a lower threshold for neurosurgical intervention.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Sherman, Starke. Acquisition of data: Sherman, Starke. Analysis and interpretation of data: Starke, Cappuzzo. Drafting the article: Starke, Cappuzzo, Erickson. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sherman. Statistical analysis: Starke. Study supervision: Sherman.

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