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Magnetic resonance imaging findings in Parinaud's syndrome: comparing pineal mass findings to other etiologies

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ABSTRACT

Purpose: In a recent study, it was found that, although intrinsic midbrain signal abnormality (IMSA) on MRI is associated with Parinaud's syndrome (PS) in patients with pineal gland masses (PM), it had no predictive value with respect to resolution of PS. We sought to compare the PM and non-pineal etiologies (NPE) of PS by reviewing imaging features of PS and whether or not they are predictive of resolution of symptoms.

Methods: We reviewed electronic medical records from 1980 to 2017 and identified 71 patients with PS from any etiology who had MR imaging: 26 with PM and 45 with NPE. We subdivided the 45 NPE patients into those with intrinsic midbrain lesions (IMBL) ($n = 23$) and those with extrinsic midbrain lesions (EMBL) ($n = 22$). PS resolution and hydrocephalus data were collected. Imaging studies were reviewed for the presence of IMSA and hydrocephalus.

Results: PS patients with EMBL were less likely to have IMSA than those with PM or IMBL ($p \leq 0.001$). PS resolution occurred more commonly with PM than IMBL and NPE ($p = 0.03$, $p = 0.01$). For all NPE patients, resolution of PS occurred with equal frequency in patients with and without IMSA ($p = 1.00$). Hydrocephalus occurred more frequently in patients with PM and EMBL than IMBL ($p = 0.01$, $p = 0.03$).

Conclusions: IMSA is present more often in patients with PS from PM or IMBL than in patients with EMBL. EMBL, including PM, have an increased likelihood for PS resolution. There is no predictive value of IMSA with respect to resolution of PS in NPE as well as PM.

1. Introduction

The classic etiology of Parinaud's syndrome (PS) has been thought to be a pineal gland lesion; however, small case series have suggested that lesions of the pineal gland may be a less common cause of PS than intrinsic brainstem pathologies such as infarction and hemorrhage, or extrinsic, non-pineal etiologies, such as primary hydrocephalus [1–4]. Etiologies of PS also vary with age: neoplastic etiologies occur with increased frequency in children and young adults, whereas vascular etiologies are more common in middle-aged and elderly patients [1,3]. In this large retrospective study encompassing both children and adults, we sought to determine the prevalence of PS from pineal gland masses (PM) and non-pineal etiologies (NPE). Moreover, a recent publication by Vuppala et al. showed a significant association between intrinsic midbrain signal abnormality (IMSA) and PS in patients with PM, although its presence held no predictive value for PS resolution in these patients [5]. Based on this finding, we sought to compare the PM and NPE of PS by reviewing imaging features of PS and whether or not they are predictive of resolution of symptoms. Imaging features included location of the mass, presence of IMSA, and presence of hydrocephalus.

Abbreviations: PS, Parinaud's syndrome; IMSA, intrinsic midbrain signal abnormality; NPE, non-pineal etiology; PM, pineal mass; EMBL, extrinsic midbrain lesions of non-pineal etiology; IMBL, intrinsic midbrain lesions of non-pineal etiology

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2. Methods

2.1. Study population and data collection

This study was a retrospective chart review that was approved by our institutional review board and was HIPAA compliant. We searched our institution's electronic medical record (Epic) to identify all patients with PS from 1980 to 2017. Keywords for the search included "Parinaud's syndrome", "upgaze palsy", "convergence-retraction nystagmus", "light-near dissociation", "double vision", "diplopia", "pineal", and "dorsal midbrain." We also used the teaching file of one of the authors, which consisted of patients diagnosed with PS to identify additional cases with a confirmed clinical diagnosis.

We also performed a search of the Radiology Information System at our institution for the years 2007–2017 to identify pineal region masses via a keyword search for the terms "Parinaud's syndrome", "pineal tumor", "pinealoma", "pineoblastoma", "pineocytoma", "germinoma", "yolk sac tumor", "choriocarcinoma", "papillary pineal tumor", and "pineal parenchymal tumors", and "pineal parenchymal tumor of intermediate differentiation." We included in this study additional patients with PM and PS found in this search; however, we excluded patients with benign pineal cysts because pineal cysts are common, incidental findings that rarely become symptomatic [6]. In addition, we excluded patients for whom no MRIs were available for review.

We reviewed all medical charts to obtain data regarding demographics, clinical findings, diagnosis, and imaging findings at the time the patients were diagnosed with PS. Clinical findings of PS included one or more of the following: upgaze palsy, convergence-retraction nystagmus, and pupillary light-near dissociation [7,8]. The final diagnosis was based on either a pathologic diagnosis or a chart review. We defined resolution of PS as documented improvement in PS symptoms within one year of clinical symptom onset, as there are no prior definitions to define resolution of PS in the literature.

2.2. Data and statistical analysis

To determine the most common etiology of PS, we divided patients from the NPE group into nine major categories. For comparisons regarding presence of IMSA, presence of hydrocephalus, and resolution of PS, we first divided patients into PM and NPE. We further separated the NPE patients into anatomical groups according to the relation of the causative lesions to the midbrain: those with extrinsic midbrain lesions (EMBL) and those with intrinsic midbrain lesions (IMBL). We determined statistical significance using Fisher's exact test given small sample sizes when making comparisons across the various groups. *t*-test was used for analyzing statistical significance between the PM and NPE groups' average age at diagnosis. We defined statistical significance as a p-value < 0.05.

2.3. Imaging review

All images and imaging reports were reviewed by a neuroradiologist with > 30 years of experience who documented the degree of midbrain compression, the presence of IMSA, and the presence of hydrocephalus. We then cross-referenced the imaging findings documented by the neuroradiologist with those from the imaging reports in the medical chart performed by independent reviewers. Thus, each imaging study had two independent reviews.

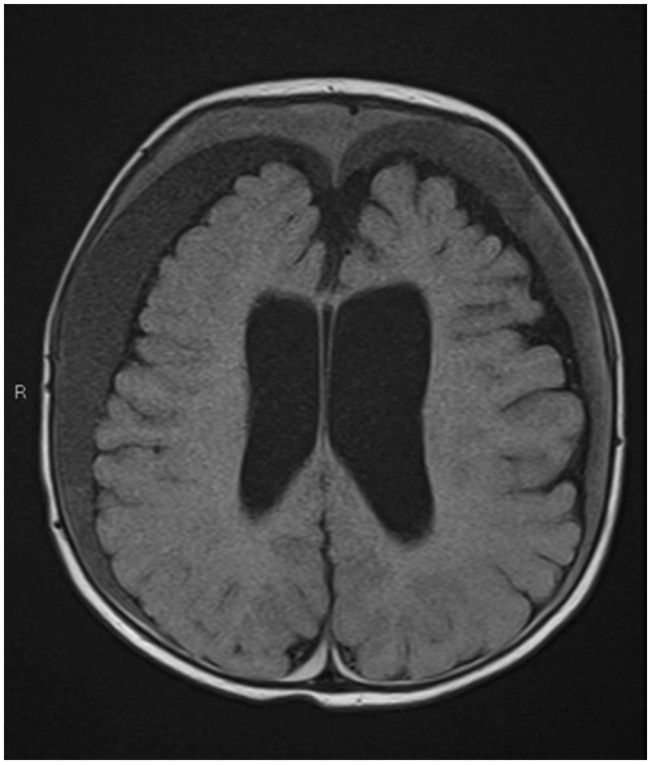

Fig. 1. Vascular lesion categorized as EMBL. Flair scan in a 3 month old shows bilateral subdural hematomas of different signal intensities and different ages suspected of being due to non-accidental trauma.

3. Results

3.1. Demographics

We identified 71 patients with PS, 45 (63.4%) with NPE and 26 (26.6%) with PM (Fig. 1). Forty-five of these patients were male (28 NPE and 17 PM) and 26 were female (17 NPE and 9 PM). In regard to race, 31 NPE and 21 PM identified themselves as Caucasian, five NPE and one PM as African-American, and seven NPE and four PM as "other" (including Asian, African and Hispanic). Two NPE were considered "unknown" as there was no indication of race in their chart. In the NPE group, the mean age at diagnosis was 33.2 years, with the lowest age being at birth and the highest age being 80 years old. The mean age in the PM group was 28.2 years, with the lowest age being 1 year old and the oldest being 69 years old. No statistically significant differences in group demographics were identified between the NPE and PM groups for gender ($p = 1.00$), race (Caucasian, $p = 0.40$; African-American, $p = 0.40$; "other", $p = 1.00$), or mean age at diagnosis ($p = 0.35$). In regard to the PM, the pineal mass was present at the time of imaging in 20 of the 26 patients [5]. The average pineal mass size was 2.2 cm (range: 0.6–3.4 cm, standard deviation = 0.55 cm) [5].

3.2. Etiologies

To determine the most common etiology of PS, the 45 NPE patients were categorized into nine major groups: vascular ($n = 15$), space-occupying lesion ($n = 13$), primary hydrocephalus ($n = 6$), autoimmune/

Table 1
Description of Non-Pineal Etiologies (NPE) group.

Vascular (*N* = 15)	EMBL (7): Ruptured PICA aneurysm; intraventricular hemorrhage; skull-based AV fistula; thalamic arteriovenous (AV) malformation; thalamic hemorrhage; subdural hematoma IMBL (8): Bilateral AV malformation of mesencephalon; brainstem hematoma; ischemic midbrain stroke; midbrain hemorrhage; vertebrobasilar arterial dissection with ischemic stroke; brainstem AV malformation
Space-occupying lesion (N = 13)	Ventricular mass or cyst EMBL (1): Loculated ventricular cysts IMBL (2): Fourth ventricle cleft cyst; intraventricular germinoma Brainstem Mass EMBL (0) IMBL (6): Brainstem glioma; midbrain germinoma; midbrain glioma (associated with Neurofibromatosis 1); pilocytic astrocytoma Posterior fossa/cerebellar mass EMBL (2): Atypical teratoid rhabdoid tumor; bilateral retrocerebellar cyst IMBL (0) Sellar/Suprasellar EMBL (2): Pituitary germinoma; suprasellar pilocytic astrocytoma IMBL (0)
Primary hydrocephalus (N = 6)	EMBL (6): Acquired hydrocephalus, congenital hydrocephalus; congenital ventriculomegaly; normal pressure hydrocephalus IMBL (0)
Inflammatory/autoimmune process (N = 4)	EMBL (0) IMBL (4): Multiple sclerosis lesion in thalamus; CNS vasculitis with midbrain involvement; sarcoidosis with midbrain involvement; Langerhans cell histiocytosis
Neoplastic (N = 2)	EMBL (1): Acute lymphocytic leukemia IMBL (1): Metastatic lung cancer
Trauma (N = 1)	EMBL (0) IMBL (1): Traumatic brain injury
Infection (N = 1)	EMBL (1): Meningitis IMBL (0)
Congenital anomaly (N = 1)	EMBL (1): Chiari malformation IMBL (0)
Iatrogenic (N = 1)	EMBL (0) IMBL (1): After placement of leads for EEG monitoring
Unknown (N = 1)	EMBL (1) IMBL (0)

inflammatory process (n = 4), metastasis/malignancy (n = 2), trauma (n = 1), infection (n = 1), congenital anomaly (n = 1), iatrogenic (n = 1), and a category of "unknown diagnoses" (i.e., the diagnosis could not be ascertained from the medical record (n = 1)). Examples of diagnoses in each category specific to our study population with available imaging are seen in Table 1.

In addition to the above categorization, the NPE lesions causing PS were separated into intrinsic midbrain lesions (IMBL) and extrinsic to the midbrain lesions (EMBL).

3.3. Overall prevalence of IMSA in patients with PS from NPE versus PM

Among the 45 patients with NPE, 22 (48.9%) were noted to have IMSA on imaging. Among the 26 patients with PM, 22 (84.6%) had IMSA (Table 2). Statistical analysis of these data revealed a statistically significant increased prevalence of IMSA in PM patients with PS compared with NPE patients with PS (p = 0.005) (Table 3).

3.4. Prevalence of IMSA in patients with PS from EMBL, IMBL, and PM

In addition to comparing the prevalence of IMSA in PS patients with PM with PS patients with NPE, we compared the prevalence of IMSA in the two subgroups of NPE—IMBL and EMBL—with each other and with patients with PS from PM (Tables 2 and 3). We found, as expected, that patients with IMBL had a significantly greater prevalence of IMSA than patients with EMBL ($p \leq 0.0001$). Specifically, of the 23 IMBL patients, 18 (78.3%) showed IMSA. In contrast, of the 22 EMBL patients, four (18.2%) showed IMSA. Patients with PS from PM had a significantly greater prevalence of IMSA on MRI than patients with EMBL ($p \leq 0.0001$), but there was no statistically significant difference in the prevalence of IMSA in PS patients with PM versus IMBL (p = 0.72).

Table 2
Prevalence of IMSA in PS patients with PM, NPE, and NPE subgroups.

Etiology	Number with IMSA/total N with available imaging
PM	22/26 (84.6%)
NPE total	22/45 (48.9%)
IMBL	18/23 (78.3%)
EMBL	4/22 (18.2%)

Table 3
Statistical analysis of prevalence of IMSA in PS patients with PM, NPE, and NPE subgroups.

Groups being compared	P-value
PM vs. NPE	P = 0.005*
IMBL vs EMBL	P ≤ 0.0001*
EMBL vs PM	P ≤ 0.0001*
IMBL vs PM	P = 0.72

Note: All p-values calculated using Fisher's exact test.
* Indicates a statistically significant finding.

Table 4A
Comparison of resolution of PS in NPE versus PM groups.

Etiology	Number with resolution/N with data on resolution
PM	12/24 (50.0%)
NPE total	9/38 (23.7%)
EMBL	5/19 (26.3%)
IMBL	4/19 (21.1%)

Table 4B
Comparison of resolution of PS in EMBL versus IMBL groups.

Groups being Compared	P-value
PM vs. NPE	P = 0.01*
IMBL vs EMBL	P = 0.72
PM vs EMBL	P = 0.07
PM vs IMBL	P = 0.03*

Note: All p-values calculated using Fisher's exact test.
* Indicates a statistically significant finding.

3.5. Resolution of PS with respect to lesion location

To determine if resolution was more common in patients with NPE than in patients with PM, we calculated the number of patients who had resolution of their PS in the NPE group compared with the PM group overall (Table 4A). Of 45 patients with NPE, resolution data were available for 38 (84.4%), of whom nine (23.7%) had resolution of their PS. In comparison, resolution data were available for 24 (92.3%) of the 26 patients with PM, and 12/24 (50.0%) had resolution of their PS. In regard to comparison based on anatomical location, five (26.3%) of the 19 patients in the EMBL group for whom data were available experienced resolution of PS compared with four (21.1%) of the 19 patients in the IMBL group.

We compared the PM and NPE groups, as well as the midbrain anatomy-based subgroups, with respect to any statistically significant increases or decreases in the relative frequencies of resolution (Table 4B). We found that, in general, following treatment, PM patients were more likely to experience resolution of PS than patients with NPE ($p = 0.01$) and also than patients with IMBL ($p = 0.03$), but no more than patients with EMBL ($p = 0.07$). There was no significant difference in frequency of resolution of PS in patients with IMBL vs EMBL ($p = 0.72$).

3.6. IMSA and resolution of PS

We also were interested in whether or not the presence of IMSA was associated with an increased or decreased frequency of resolution of PS in patients with NPE overall or in the IMBL and EMBL NPE subgroups. We therefore compared the resolution of PS in patients with IMSA and those without IMSA in these groups (Table 4C). None of the comparisons held statistical significance, in that the frequency of resolution in PS patients with IMSA on imaging was similar to the frequency of resolution in PS patients without IMSA on imaging across all subgroups and when comparing the PM and NPE etiologies overall ($p = 1.00$ for all subgroups, $p = 0.61$ overall) (Table 4C).

3.7. Role of hydrocephalus

To investigate the prevalence of hydrocephalus among different etiologies of PS, we determined the percentage of patients that had hydrocephalus within each subgroup of etiologies (Table 5). Among 45 patients with NPE of PS, data regarding hydrocephalus were available for 43 (95.6%), of whom 26 (60.5%) were found to have had hydrocephalus at some point during their illness, whereas 17 (39.5%) had not. Information in the medical chart regarding hydrocephalus was available for all 26 patients with PM and PS, of whom 21 (80.7%) had hydrocephalus at some point in their disease course. Hydrocephalus occurred with equal frequency in both the NPE and PM groups with PS ($p = 0.11$) (Table 5).

Table 5
Comparing presence of hydrocephalus in NPE versus PM groups.

Etiology	Number with hydrocephalus/N with data regarding hydrocephalus
PM	21/26 (80.7%)
NPE total	26/43 (60.5%)
EMBL	17/22 (77.3%)
IMBL	9/21 (42.9%)

Table 6
Comparing hydrocephalus in EMBL versus IMBL groups.

Groups being compared	P-value
PM vs. NPE	P = 0.11
EMBL vs IMBL	P = 0.03*
PM vs EMBL	P = 1.00
PM vs IMBL	P = 0.01*

Note: All p-values calculated using Fisher's exact test.
* Indicates a statistically significant finding.

When grouped by anatomical relationship to the midbrain, 17 (77.3%) of 22 patients with EMBL had hydrocephalus at some point in their disease course, compared with nine (42.9%) of 21 patients in the IMBL group ($p = 0.03$). Thus, there is a significantly higher prevalence of the presence of hydrocephalus in PS patients with EMBL than IMBL, as well as in patients with PM versus patients with IMBL ($p = 0.01$) (Table 6). Hydrocephalus occurred with equal frequency in the PM group compared with the EMBL group ($p = 1.00$).

4. Discussion

In a 25-year retrospective review, Shields et al. found that in 40 adult cases of PS, primary midbrain lesions including vascular causes and non-pineal neoplasms comprised 65% of the cases, whereas pineal etiologies were responsible for 30% [1]. Of the primary midbrain lesions, midbrain hemorrhage was responsible for 30% and midbrain infarction for 20%. A larger retrospective review by Keane, published in 1990, found that hydrocephalus secondary to cysticercosis and meningitis was the leading etiology of PS (39%), followed by strokes in the midbrain or thalamus (26%), brainstem tumors (13%), and pineal tumors (9%); however, these data were skewed because Keane's practice was located in southern California where central nervous system (CNS) cysticercosis was common at the time [7]. Most recently, a review of 26 patients by Pollak et al. found that the leading etiology of PS in their patient population was intrinsic brainstem tumor (38%), followed by pineal tumor (31%), vascular lesion (19%), and hydrocephalus without a mass lesion (8%) [9]. Our study, encompassing all etiologies of PS over a 37-year period, yielded 26 patients with PS from PM and 45 patients with PS from NPE, thus confirming the work of others that NPE are indeed a more common cause of PS than PM. The NPE of PS in our

Table 4C
Resolution of PS in patients with IMSA versus patients without IMSA.

Etiology	Number with IMSA and resolution/total N with IMSA and data regarding resolution	Number without IMSA and resolution/total N without IMSA and data regarding resolution	P-value
PM	12/20 (60.0%)	2/4 (50.0%)	1.00
NPE total	4/18 (22.2%)	5/20 (25.0%)	1.00
EMBL	1/3 (33.3%)	4/16 (25.0%)	1.00
IMBL	3/15 (20.0%)	1/4 (25.0%)	1.00
PM + NPE	16/38 (42.1%)	7/24 (29.2%)	0.61

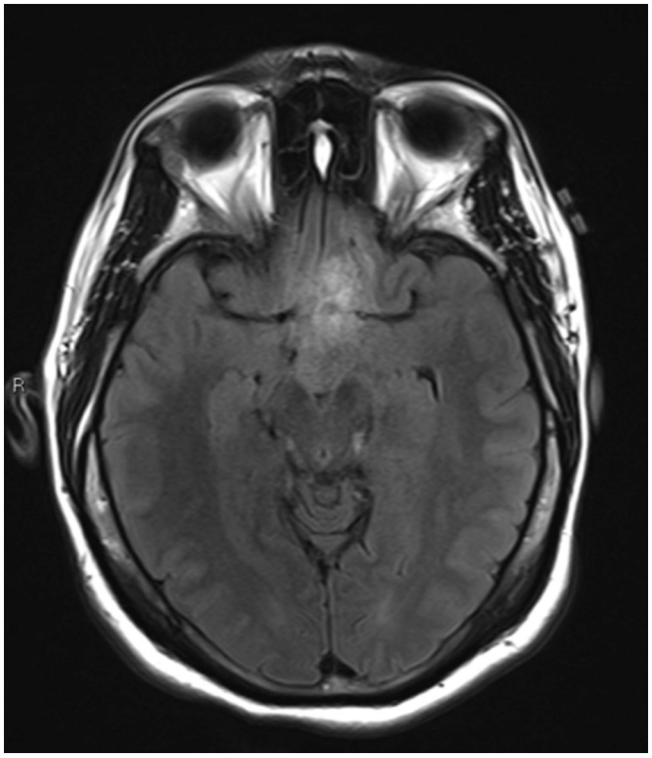

Fig. 2. Space-occupying lesion categorized as EMBL. Infiltrative pilocytic astrocytoma extends from the suprasellar cistern posteriorly to the interpeduncular cistern and abuts on the midbrain.

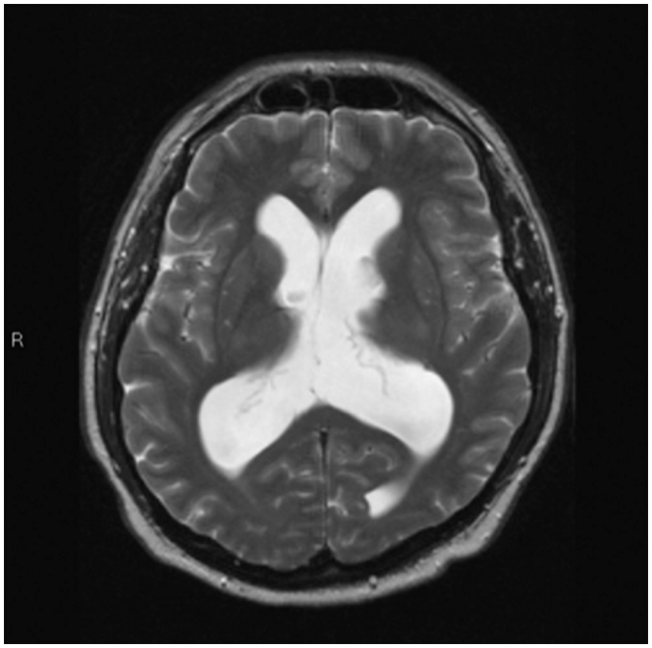

Fig. 3. Primary hydrocephalus categorized as EMBL. T2W MRI scan demonstrates ventricular enlargement in a 53 year old with adult normal pressure hydrocephalus, gait and cognitive deficits, and Parinaud's syndrome.

study include a diverse group of vascular lesions, space-occupying lesions, primary hydrocephalus, autoimmune/inflammatory diseases, trauma, malignancy, infection, congenital anomalies and iatrogenic damage. Examples of vascular lesions, space-occupying lesions, and primary hydrocephalus can be seen in Figs. 1-5. As in the series of Shields et al. [1], we found that vascular etiologies occurred most frequently in the NPE group, with 15 of 45 (33.3%) of patients presenting with a vascular lesion. To our knowledge, based on a review of the PubMed database, our study is the largest retrospective study looking at all etiologies of PS.

In regard to the importance of MRI findings of IMSA, a recent study of pineal gland lesions in patients with PS by Vuppala et al. found a statistically significant difference in the presence of IMSA in PS patients with a PM, compared with PM patients who did not develop PS [5]. That study concluded that the presence of IMSA suggests that PS is likely to be present or develop. In this study, we sought to determine whether or not a similar percentage of patients with PS had IMSA in the setting of NPE. After comparing the incidence of IMSA in all patients with PS and PM versus NPE, and within NPE, EMBL versus IMBL, we found that IMSA was significantly less likely to occur in patients with PS from NPE compared with patients with PS from PM ($p = 0.005$), and that patients with PS from both PM and IMBL had significantly higher rates of IMSA compared with patients with PS from EMBL ($p \leq 0.0001$ for both). The high incidence of IMSA with IMBL is not surprising, as most IMBLs would be expected to cause IMSA, with the exception of some degenerative diseases (e.g., progressive supranuclear palsy, Joubert syndrome). However, the finding of increased prevalence of IMSA in patients with PS from PM, even when compared with other EMBL, suggests that PM do indeed behave differently from other EMBL and are more likely to cause IMSA in the setting of PS. We are not able to comment on an association between IMSA and the occurrence of PS in patients with NPE as we do not have controls for patients with EMBL and IMBL who do not have PS to see if IMSA can be used to predict PS as previously shown in patients with PS from PM.

We also sought to determine if IMSA had any predictive value for resolution of PS. On the whole, the data revealed that PM have a greater likelihood for resolution of PS than IMBL. For each group, there was no difference in the frequency of resolution for the patients with IMSA versus without. Based on these findings, we conclude that IMSA has no predictive value for resolution of PS in patients with NPE. Together with the previous finding in patients with PS from PM, it also can be concluded that the MRI finding of IMSA in patients with PS is not a useful clinical tool for predicting the long-term outcome of PS, regardless of what lesion caused it. We hypothesize that the lack of predictive value of IMSA with respect to PS resolution in IMBL could be due to different long-term outcomes depending on the specific midbrain nuclei that are impacted, as well as the possibility that the resolution of symptoms may, in some cases, predate the finding of IMSA on MRI. Moreover, it is known from literature on gliomas that the presence of edema does not necessarily affect function; thus, it is possible that in the case of PS that the presence of IMSA does not necessarily affect resolution. Nevertheless, the results of this study indicate that physicians may inform their patients with PS from a PM that there is an increased likelihood of resolution of PS with appropriate therapy.

Based on our review of the Pubmed database, the utility of IMSA in predicting resolution has not been evaluated before. Although there was one study that used imaging to analyze the presence of abnormal midbrain signaling in patients with PS, that study looked at the correlation of the degree of brainstem involvement and hydrocephalus compared with the number of neuro-ophthalmological findings for 26 patients with PS [9]. Of note, no correlation was found.

There have been varying conclusions in the literature regarding the resolution of PS relative to treatment, with some studies reporting that ocular symptoms of PS resolved quickly post treatment [7], and others showing the long-term persistence of ocular symptoms in pediatric patients [2]. A study focusing on PM and PS showed that resolution rates were dependent on the treatment type, with patients undergoing tumor resection experiencing higher rates of persistent PS symptoms [10]. In another recent review of 26 patients with PS, 8% of patients experienced complete resolution of PS, whereas 67% experienced no change despite treatment, and 25% experienced worsening [9]. In our study, we did not follow each individual ocular symptom of PS (upgaze

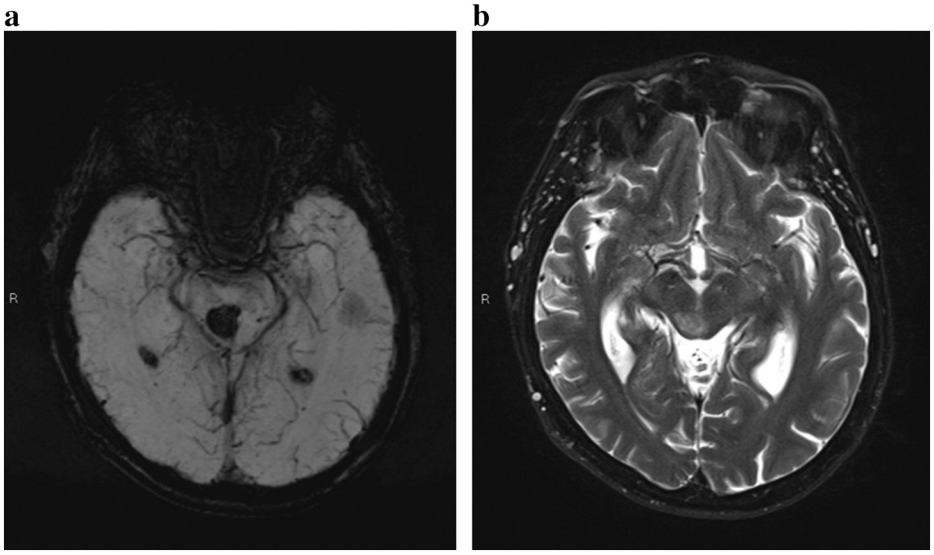

Fig. 4. Vascular lesion categorized as IMBL.
a and b: Susceptibility weighted image (a) and T2WI (b) confirm the right midbrain hemorrhage and intrinsic midbrain signal intensity abnormality in this patient with a bleeding cavernoma.

palsy, convergence retraction nystagmus, or light-near dissociation) that may have improved or persisted over time, nor did we compare the types of treatment each patient received. Previous clinical reviews have noted that resection (pinealomas) or chemoradiotherapy (germinomas) for pineal masses can result in resolution of some or all of the ocular manifestations of PS [10,11]. It is possible that these interventions in our PM group could have accounted for the overall higher rate of resolution of PS in this group relative to the NPE group. Due to the retrospective nature of this study, it is not possible to account for the effects of these treatments on the rates of resolution in any of the PS patients.

Finally, hydrocephalus historically has been thought to be important in the development of PS. Hankinson et al. found that patients with moderate brainstem involvement and hydrocephalus had a significantly higher incidence of ocular findings compared with patients who had the same level of brainstem involvement but no hydrocephalus [10]. Conversely, it has been reported that hydrocephalus occurred with equal and high frequency in all patients with PM regardless of whether or not PS was present [5]. When comparing NPE with PM in our cohort, both groups had a high incidence of hydrocephalus, and there was no statistically significant difference between the two groups ($p = 0.11$). However, there was a statistically significant difference among the subgroups of NPE, in that there was a higher incidence of hydrocephalus in patients with PS from EMBL than those with PS from IMBL ($p = 0.03$), as well as those with PM than those with IMBL ($p = 0.01$). Thus, our data indicate that hydrocephalus occurs with increased frequency in patients with PS from EMBL of any etiology when compared with IMBL. In regard to the prevalence of PS resolution between patients with and without hydrocephalus, it was found that hydrocephalus has no impact on the resolution of PS [5].

Similar to the findings from Keane [7], in which he found that 17 (65.4%) of 26 patients with PS had hydrocephalus, we also found a high incidence of hydrocephalus overall in our PS patient population (80.7% of PM and 60.5% of NPE). In addition, just as only two (7.7%) of the patients in the Keane paper had primary hydrocephalus, the minority of our cases (6 of 45 = 13.3%) had primary hydrocephalus. This finding is

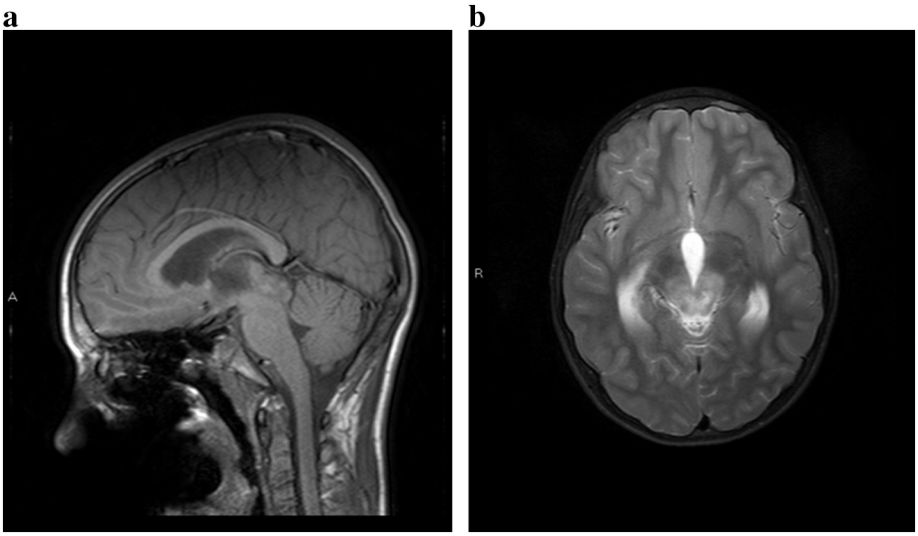

Fig. 5. Space-occupying astrocytic neoplasm categorized as IMBL.
a and b: Sagittal T1WI (a) and axial T2WI (b) show an intrinsic midbrain neoplasm infiltrating bilaterally and causing Parinaud's syndrome.

important in that, unlike the population evaluated by Keane that was skewed by a predominance of patients with CNS cysticercosis, ours was not.

4.1. Strengths and limitations

A major strength of our paper is the large number of patients with PS and the large number of etiologies of the PS. There also are no prior studies that have studied the anatomic relation to the midbrain of the lesions that produce hydrocephalus or that are associated with resolution of PS. One limitation is the retrospective nature of the study, which limited the number of available images and information for data points being compared, thereby limiting the overall sample size. A second limitation due to the retrospective nature of the study is the potential loss of follow-up of patients, which could have limited the availability of data for PS resolution. The study also encompasses a wide range of dates of imaging examinations (1980–2017), which could be a potential limitation given any heterogeneity in the quality of imaging and differences in imaging protocol impacting the ability to detect subtle midbrain signal abnormalities. However, this is unlikely as the assessment of signal intensity in the midbrain is based on standard T2-weighted imaging, for which there have been very few modifications over the years. Similarly, identification of a pineal mass is done primarily with sagittal standard T1-weighted (T1W) images; spin echo T1W scans have also not changed significantly over time. Still, by focusing on specific imaging findings such as IMSA, and by making new comparisons of pineal and nonpineal etiologies, we hope this paper will both aid in future efforts to better understand PS and its imaging associations, as well as assist clinicians in using imaging findings to guide clinical discussions with patients with PS.

5. Conclusions

As a group, PS is more commonly caused by NPE ($n = 45$) than PM ($n = 26$). Among NPE that cause PS, vascular pathologies are most common, including brainstem ischemic strokes, aneurysms, hemorrhagic strokes, arteriovenous malformations, fistulas, and arterial dissections. Although patients with PS from PM and from IMBL have a significantly higher incidence of IMSA compared with patients with PS from EMBL, we are not able to comment on the association of IMSA and the prevalence of PS in the EMBL and IMBL groups as we did not have a control subset.

In regard to resolution of PS, we find that patients who present with PS from a PM have significantly higher rates of resolution than patients with PS from NPE overall ($p = 0.01$). We ultimately conclude that IMSA does not have predictive value for the resolution of PS. Given sample size considerations, larger prospective studies are needed to confirm this.

As far as hydrocephalus is concerned, we find no statistical difference in the high incidence of hydrocephalus in patients with PS from PM versus NPE. However, hydrocephalus is more frequently present in patients with EMBL and PM than in patients with IMBL ($p = 0.03$ and $p = 0.01$).

Declarations of Competing Interest

Dr. Yousem reports royalties from Elsevier, personal fees from Medicolegal consultant, speaker fees from ACR, other from Analytical Informatics, outside the submitted work. The other authors declare that they have no conflict of interest.

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