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Clinical and MRI findings in patients with pediatric optic pathway glioma presenting with initial leptomeningeal dissemination

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AIMS: Although leptomeningeal dissemination (LMD) is a hallmark of malignant brain tumors, optic pathway glioma (OPG) of various grades can initially present with LMD, which is thenceforth interpreted as an aggressive tumor. In this study, we aimed to evaluate the clinical and imaging findings of pediatric OPG (POPG) patients who presented with initial LMD to ensure a prompt diagnosis and better outcomes.

MATERIALS AND METHODS: Between 2000 and 2022, 35 pediatric patients with pathologically proven OPG who presented with and without LMD at our institute were retrospectively reviewed. We compared the demographic and histopathology characteristics, magnetic resonance imaging features, and clinical outcomes of the initial LMD group and the non-LMD group.

RESULTS: Compared with those in the non-LMD group (n = 27), POPGs in the LMD group (n = 8) were more symmetrically midline-positioned (75% versus 22.2%, $P = .006$) and had more ill-defined tumor borders (25% versus 0%, $p = .007$), and patients were more likely to develop hydrocephalus (100% versus 63%, $P = .042$). There was no significant difference regarding the histopathology ($P = .686$) and outcome of tumor recurrence/progression ($P = .341$). However, the mortality rate was higher in the LMD group than in the non-LMD group (62.5% versus 18.5%, $P = .016$).

CONCLUSIONS: Features of a more symmetrical midline-positioned POPG with indistinct tumor borders and hydrocephalus are risk factors for initial LMD regardless of histopathology. Compared with those without initial LMD, patients with POPG with initial LMD had poorer outcomes, which may suggest the need for a more aggressive treatment protocol.

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Introduction

Optic pathway glioma (OPG) accounts for 2%–5% of pediatric brain tumors,[1] and it is the most common primary optic nerve and pathway tumor, constituting approximately 66% of such tumors.[2] The mean age at presentation is 8.8 years, and approximately 90% of patients are under 19 years of age.[2] Additionally, it is the most common central nervous system tumor in neurofibromatosis 1 (NF1) patients, with a prevalence ranging from approximately 20% to 40%.[1–3] Most OPGs are histologically low-grade gliomas, with 60%–70% of them being pilocytic astrocytomas (PAs),[4,5] while other types of tumors, such as pilomyxoid astrocytoma, have been reported.[2,3,6] The prognosis of OPG is generally favorable.[7,8] Nicolin *et al.* reported that the overall survival (OS) rates at 5 and 10 years were 97.6% and 94.6%, respectively, for those with OPG who needed therapy.[7] Similarly, a 5-year OS of 97.7% was reported by Kim *et al.*[8]

The presence of leptomeningeal dissemination (LMD) is rare in the context of low-grade gliomas and is particularly worrisome due to its heightened potential for diagnosing malignant brain tumors. The reported incidence of low-grade glioma with metastasis at initial diagnosis is approximately 2.6%–7%, and that of low-grade glioma with metastasis at follow-up is 5%–12%.[9–12] Regarding the prognosis of low-grade glioma patients with LMD, unfavorable results have been reported across studies. The 5-year progression-free survival (PFS) rate reported in the multicenter HIT-LGG 1996 study was only 6%,[13] and that for children with initial LMD following the administration of adjuvant therapy was 17%.[14] Chamdine *et al.* also reported a poor prognosis for patients with low-grade glioma with LMD, with OS rates of 81%, 63%, and 50.9% at 5, 10, and 15 years, respectively.[9]

Nevertheless, all of these studies are focused mainly on low-grade gliomas, but pediatric OPG (POPG) is neither specifically subjected nor evaluated. To date, there are only a few case reports of POPG with LMD in the literature.[10–12,14–16]

In light of molecular and genetic characteristics, NF1-associated OPGs involve constitutive activation of the RAS signaling pathway,[17] whereas sporadic OPGs are associated with BRAF mutations and overactivation of the RAK/MEK pathway,[17] with the most common genetic alteration being the BRAF-KIAA1549 fusion.[18] The clinical impact of the BRAF-KIAA1549 fusion remains controversial. Some studies indicate that clinical outcomes are independent of BRAF fusion status,[19–21] while others suggest that BRAF fusion improved 5-year PFS.[22] Moreover, Gessi *et al.* reported a comparable incidence of BRAF-KIAA1549 fusions and BRAF mutations between disseminated PA and typical PA.[23]

The differences in incidence, clinical findings, and outcomes between POPG patients with an initial LMD presentation and those without it have not yet been determined. The presence of initial LMD can make the diagnosis of POPG more challenging as POPG may resemble an aggressive suprasellar tumor such as a germ cell tumor (GCT)[24] or atypical teratoid/rhabdoid tumor.[25] This can lead to a misdiagnosis of POPG and result in different treatments. In this retrospective study, we aimed to investigate the clinical and magnetic resonance imaging (MRI) findings of POPG patients with LMD as its initial manifestation and compare them with those of POPG patients without LMD to ensure the early diagnosis of POPG and improve clinical treatment.

Materials and methods

Ethics statement

Our study received approval from the Institutional Review Board of our center and adhered to the principles of the Declaration of Helsinki. Written informed consent for performing an MRI and surgical intervention was obtained from each patient. Given the retrospective nature of the study, the need for informed consent was waived.

Patient selection

Between 2000 and 2022, 69 patients were diagnosed with OPG at our institution. We included patients who met the following criteria: (1) had a histopathologically proven diagnosis of OPG, (2) were pediatric patients less than 18 years of age, (3) had a complete pretreatment MRI of the brain, and (4) had a regular clinical follow-up that included brain MRI. The algorithm for patient selection is shown in Fig 1. A total of 35 patients who were diagnosed with POPG were enrolled in our study. The patients were categorized into two groups: the LMD group, comprising patients diagnosed with LMD at the initial time of diagnosis, and the non-LMD group. We collected data on the demographic characteristics, clinical symptoms, histopathology results, treatment, and outcomes of the patients. We also evaluated the extent of surgical resection according to surgical records and postoperative MRI and categorized the results as follows: biopsy (<10% resection), partial removal (10%–50%), subtotal removal (51%–90%) and near-total resection (> 90%).[8,26,27] Postsurgical treatment encompassed the whole clinical course, including the main chemotherapy used after surgery and during disease progression. In addition, early contrast-enhanced brain MRI was performed in the first month after surgery. To assess the tumor status, all patients underwent regular clinical and contrast-

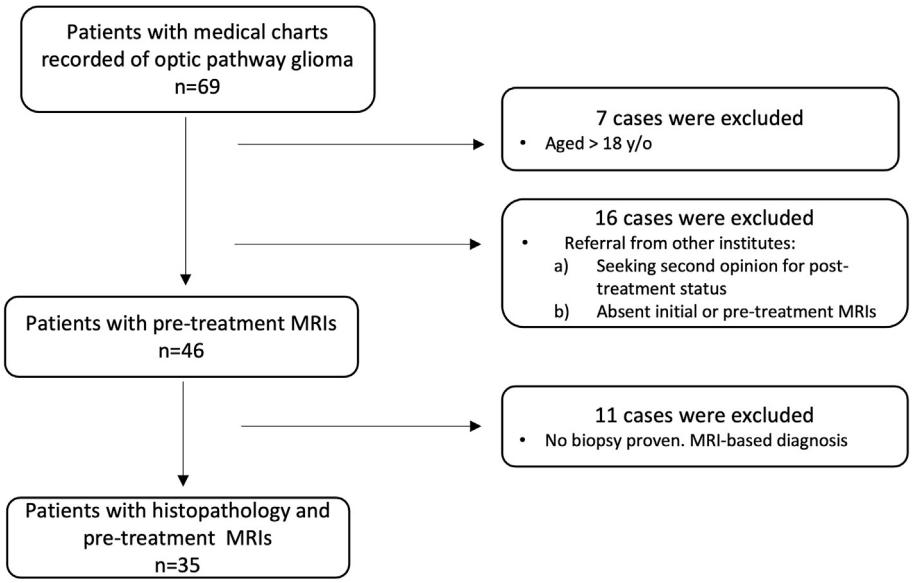

Figure 1 Flow diagram of the study of pediatric patients with optic pathway glioma (OPG).

enhanced brain MRI follow-ups at three-month intervals for the first two years following surgery and six-to twelve-month intervals thereafter. The tumor status (stability, regression, and progression) as well as the time from surgery to disease progression or recurrence, survival time, and interval between diagnosis and mortality was recorded.

MRI data acquisition

All patients underwent complete neuroaxis MRI, which included cranial and spinal imaging. The data were acquired by conventional MRI performed with a 1.5 T clinical MR scanner (Siemens Medical Solutions, Erlangen, Germany; GE Medical Systems, Milwaukee, WI, USA; or Philips Medical Systems, Shelton, CT). The MRI protocols used included axial, coronal T2-weighted imaging; axial T1-weighted imaging; a contrast-enhanced three-dimensional T1-weighted scan using a brain volume gradient echo sequence; axial, coronal, and sagittal spin–echo imaging; contrast-enhanced T1-weighted imaging; diffusion-weighted imaging with b values of 0 and 1000 s/mm^2, corresponding to an automatically calculated apparent diffusion coefficient (ADC) factor; and sagittal and axial contrast-enhanced T1-weighted imaging of the whole spine. The MRI findings were reviewed by two independent neuroradiologists to reach a consensus.

We evaluated the MRI manifestations of the tumor, including (1) the size (in the superior-inferior dimension) and (2) the location of the tumor and its extension, by adopting the Dodge classification because of its ease of use. Patients were categorized as follows: stage 1, involving only optic nerves; stage 2, involving the optic chiasm either with or without optic nerves; and stage 3, involving hypothalamic and/or adjacent structures.[28] To evaluate the cerebrospinal fluid (CSF) contact with the tumor surface, we further defined the site of greater than 50% of the solid part of primary tumors and categorized them into two groups: (a) those with the solid component located in the midline structure (Fig 2A) and (b) those whose solid components were asymmetrically positioned with one side predominant or off the midline (Fig 2B). (3) The morphology of the primary tumor included its shape tumor border and components. To determine the T2 signal intensity and tumoral enhancement on T1WI, we compared the solid part of the primary tumor with adjacent cerebral peduncles and cavernous sinus, respectively. (4) To determine the ADC values, the regions of interest (ROIs) were manually selected in the corresponding solid enhancing part to quantify the absolute ADC values (ADC_{min})[29] on a hospital picture archiving and communication system workstation. (5) The involvement of surrounding structures, such as the presence of perifocal edema, the presence of secondary arachnoid cysts, involvement of the anterior commissure, and encasement of the adjacent intracranial arteries were evaluated. (6) The presence of intracranial and spinal leptomeningeal seeding and hydrocephalus was also evaluated.

Statistical analysis

All the statistical analyses were performed with SPSS software, version 22 (IBM, Chicago, IL). The Shapiro–Wilk test was used to evaluate the normality of continuous data. Normally distributed data are presented as the mean ± standard deviation (SD), and Student's *t* test was used for comparisons. Non-normally distributed data are presented as the median (range) and the Mann–Whitney *U* test or Fisher's exact test was used for comparisons. Categorical data are summarized as counts (percentages) and the Pearson χ^2 test was applied. The Kaplan–Meier method was used to estimate the follow-up time in months, interval between surgery and disease recurrence/progression, and survival data, and the log-rank test was used to generate *P* values. Statistical significance was defined as a 2-tailed *P* value of less than 0.05 (in bold). Patients were excluded from the analysis of that particular variable if there were any missing data.

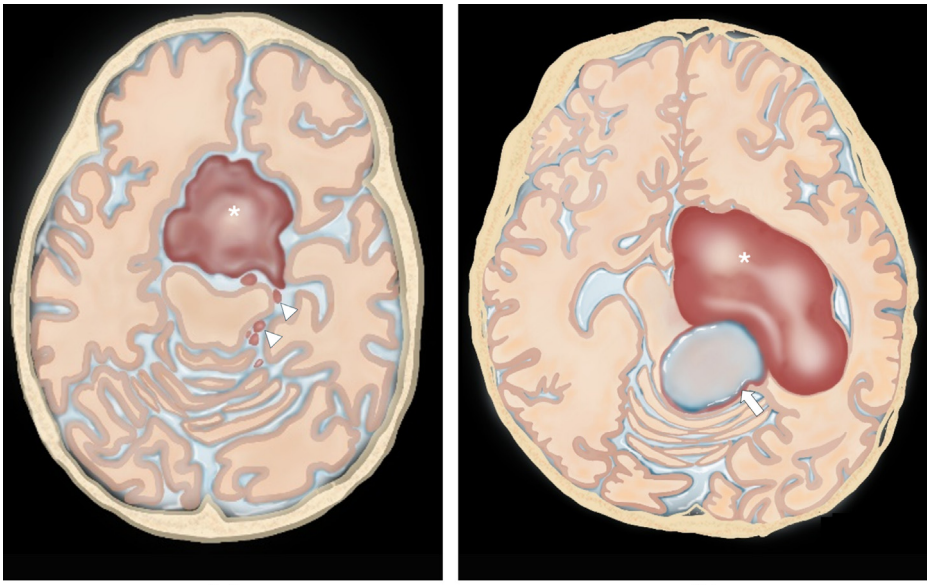

Figure 2 Based on the location of the solid component of the primary OPG, we categorized the patients into two groups. (a) Tumors with a solid component (asterisk) of more than 50% are located in the midline and (b) tumors with a solid component (asterisk) of more than 50% are asymmetrically positioned with one side predominant or off-midline. Leptomeningeal dissemination (arrowheads) and mixed solid and cystic changes in the tumor are noted (arrow) in Fig 2a and 2b, respectively. OPG: optic pathway glioma

Results

Demographic features and clinical outcomes

The demographic data and clinical characteristics of all the patients are reported in Table 1. The details regarding demographic and clinical treatment are displayed in Supplementary Table 1. A total of 35 patients with histopathologically proven POPG were enrolled in our study. There were 8 patients (22.9%) in the LMD group and 27 patients (77.1%) in the non-LMD group. The histopathological results of the LMD group revealed PA in 5 (62.5%) patients, WHO grade 2 astrocytoma in 2 (25%) patients, and WHO grade 3 anaplastic astrocytoma in 1 (12.5%) patient. In the non-LMD group, 21 patients were diagnosed with PA (77.8%), 4 patients with WHO grade 2 astrocytoma (14.8%), and 2 patients with WHO grade 3 anaplastic astrocytoma (7.4%). All low-grade astrocytomas were classified as non−NF1 or sporadic type. There was no significant difference in age, sex, clinical symptoms, histopathology, initial surgical treatment, clinical outcome of tumor progression/recurrence, tumor stability, or regression during follow-up, survival time, and interval between diagnosis and mortality between the LMD and non-LMD groups. However, the mortality rate was significantly higher in the LMD group than in the non-LMD group (62.5% [5/8] versus 18.5% [5/27], $P = .016$). The cause of mortality in the LMD group is due to disease progression.

MRI features

The MRI features of the LMD and non-LMD groups of patients are listed in Table 2. More than 50% of the solid component of the OPG tended to be significantly more symmetrically midline-positioned in the LMD group (Fig 3, Supplementary Fig 1) than in the non-LMD group (6/8 [75%] versus 6/27 [22.2%], $P = .006$) (Fig 4). Compared to those without LMD, patients with LMD had significantly more ill-defined tumor borders (2/8 [25%] versus 0 [0%], $P = .007$) (Fig 3A, Supplementary Fig 1B). Additionally, patients in the LMD group were significantly more likely to develop hydrocephalus (8/8 [100%] versus 17/27 [63%], $P = .042$). There were no significant differences in tumor size, shape, calculated ADC values, enhancement, or involvement of surrounding structures between the LMD and non-LMD groups.

Discussion

The manifestation of POPG is variable, and despite several published case series,[10–12,14–16] there is no clinical or neuroimaging method that can be used to distinguish the initial LMD of OPG from classical OPG without LMD. To date, the current study comprises the largest series of POPG with initial LMD in the literature. Our results demonstrated that POPG patients in the initial LMD group had more midline-positioned tumors, more ill-defined tumor borders regardless of histopathology, and a higher incidence of hydrocephalus than those without LMD. Furthermore, the LMD group experienced a significantly higher mortality rate.

LMD of low-grade astrocytoma is rare, particularly at the time of diagnosis. The contribution of low-grade astrocytoma in the development of LMD at initial diagnosis has been of particular concern in the context of POPG since the majority of these tumors are low-grade gliomas. Several risk

Table 1
Demographics and clinical characteristics of the 35 patients with POPG

	Non-LMD (n=27)	LMD (n=8)	Test statistic *P* vvalue
Demographics			
Age at diagnosis (years)	5 ± 3.7 (range 0.5–14)	7.5 ± 5.5 (range 0.3–13)	$P = .086$
Female sex	13 (44.8)	3 (37.5)	$P = .727$
Symptoms/Signs			$P = .114$
Blurred vision	11 (40.7)	3 (37.5)	
Nystagmus	4 (14.8)	4 (50)	
Headache	7 (25.9)	0 (0)	
Diencephalic syndrome	1 (3.8)	1 (12.5)	
Weakness	4 (14.8)	0 (0)	
Histopathology			$P = .686$
Pilocytic astrocytoma	21 (77.8)	5 (62.5)	
Astrocytoma	4 (14.8)	2 (25)	
Anaplastic astrocytoma	2 (7.4)	1 (12.5)	
Initial surgical treatment			$P = .433$
Biopsy	1 (3.8)	1 (12.5)	
Partial removal	11 (40.7)	5 (62.5)	
Subtotal removal	14 (51.7)	2 (25)	
Near-total removal	1 (3.8)	0	
Follow-up (months)	129.7 ± 51.3 (range 24.3–217.4)	87 ± 79 (range 13.9–248.7)	$P = .933$
Interval between surgery and first disease progression/ recurrence	24.6 ± 23.0 (range 2.23–83.23)	29.6 ± 36.9 (range 1.23–99)	$P = .876$
Outcome			$P = .341$
Tumor recurrence/ progression	17 (63)	7 (87.5)	
Tumor stable	5 (18.5)	1 (12.5)	
Tumor regression	5 (18.5)	0	
Survival			$\mathbf{P = .016}$
Alive	22 (81.5)	3 (37.5)	
Deceased	5 (18.5)	5 (62.5)	
Survival time (months)	158.7 ± 66.3 (range 25.2–260.8)	109.3 ± 85.3 (range 14.3–256.9)	$P = .135$
Interval between diagnosis and mortality (months)	73.0 ± 56.5 (range 25.2–158.7)	26.8 ± 117.6 (range 14.3–256.9)	$P = .394$

Abbreviations: POPG: pediatric optic pathway glioma, LMD: leptomeningeal dissemination.

factors have been documented in the literature, such as histopathology of the primary tumor, location of the primary tumor, younger age at diagnosis, surgical procedures, and/or shunting.[9,10,13,30–35] Among all the proposed risk factors, the location of the primary tumor is one of the most discussed features. Accumulative studies have shown that those who have optic chiasm and hypothalamic region involvement are at high risk for LMD due to proximity to the subarachnoid space and subtotal resection of the primary tumor.[9–12]

In addition to the tumor location, our findings of LMD at the initial diagnosis revealed that more than 50% of the solid component tends to be midline-positioned and symmetrically involved in the optic chiasm. We proposed two possible mechanisms for facilitating LMD.

Table 2
MRI features of 35 patients with POPG with or without LMD

	Non-LMD (n=27)	LMD (n=8)	Test statistic *P* value
MRI features			
Tumor size-mm	35.7 ± 9.2 (range 14–58)	36.8 ± 8.5 (range 23–51)	$P = .738$
Tumor shape			$P = .730$
Round/oval	1 (3.7)	0	
Lobulated	25 (92.6)	8 (100)	
Fusiform/tubular	1 (3.7)	0	
Symmetry			$\mathbf{P = .006}$
Symmetrical midline-positioned	6 (22.2)	6 (75)	
Asymmetry with one side dominant	21 (77.8)	2 (25)	
Tumor location/dodge classification			$P = .428$
Stage 1: optic nerve only	0	0	
Stage 2: optic chiasm ± optic nerve	2 (7.4)	0	
Stage 3: hypothalamic or adjacent	25 (92.6)	8 (100)	
Tumor border			$\mathbf{P = .007}$
Well-defined	27 (100)	6 (75)	
Ill-defined	0	2 (25)	
Tumor component			$P = .421$
Solid	22 (81.5)	8 (100)	
Cystic >50%	1 (3.7)	0	
Mixed	4 (14.8)	0	
Tumor T2 signal intensity			$P = .427$
Heterogenous T2 hyperintensity	20 (74)	7 (87.5)	
Homogenous T2 hyperintensity	7 (26)	1 (12.5)	
Tumor enhancement			$P = .247$
No-slight enhanced	4 (14.8)	0	
Well-enhanced	23 (85.2)	8 (100)	
ADC_{min}-$10^{-6}mm^2/s$[a]	1583.1 ± 328.61 (range 998.64–2167.63)	1738.95 ± 189.58 (range 1120.6–1873)	$P = .921$
Surrounding structures			$P = .869$
No perifocal edema	23 (85.2)	7 (87.5)	
Perifocal edema	4 (14.8)	1 (12.5)	
Anterior commissure			$P = .799$
No anterior commissure involvement	19 (70.4)	6 (75)	
Anterior commissure involvement	8 (29.6)	2 (25)	
Vascular Encasement			$P = .546$
No encasement	6 (22.2)	1 (12.5)	
Vascular encasement	21 (77.8)	7 (87.5)	
Secondary arachnoid cyst			$P = .687$
Absent	22 (81.5)	6 (75)	
Present	5 (18.5)	2 (25)	
Hydrocephalus			$\mathbf{P = .042}$
No hydrocephalus	10 (37)	0	
Hydrocephalus	17 (63)	8 (100)	

[a] Due to different MRI sequences performed at other institutions without an apparent diffusion coefficient (ADC) map at the time of diagnosis, ADC values were calculated only for 5 of 8 patients with LMD and 20 of 27 patients without LMD. Abbreviations: POPG: pediatric optic pathway glioma, LMD: leptomeningeal dissemination.

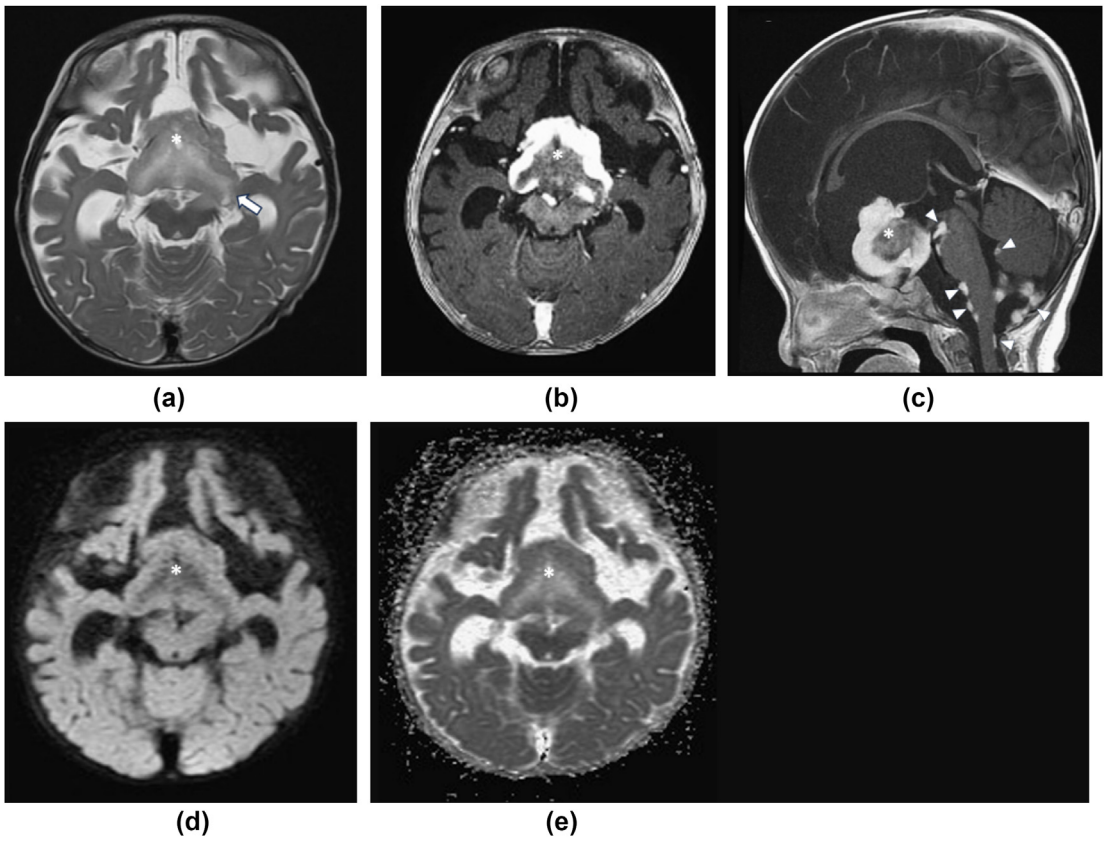

Figure 3 Example of a patient with pediatric optic pathway glioma (POPG) who presented with initial leptomeningeal dissemination (LMD). A 7-month-old male patient had nystagmus, and histopathology-confirmed astrocytoma. (a) On presurgical MRI, axial T2-weighted imaging showed a heterogenous T2 signal intensity indicating that POPG was symmetrically midline-positioned in the suprasellar cistern with an indistinct border (arrows) and hydrocephalus. (b) Axial contrast-enhanced T1-weighted imaging demonstrated vivid heterogeneous enhancement of the POPG (asterisk). (c) Sagittal postcontrast T1-weighted imaging showed POPG (asterisk) with multiple discrete enhancing nodules disseminated along the interpeduncular, prepontine, medullary cisterns, cisterna magna, fourth ventricle, and cervical spine (arrowheads). (d)–(e) The axial views on DWI and ADC values showed absent restricted diffusion of the POPG (asterisk). ADC: apparent diffusion coefficient; DWI: diffusion-weighted imaging; MRI: magnetic resonance imaging

(1) CSF drainage flow. The optic chiasm/hypothalamus is situated within the suprasellar cistern, which is filled with freely circulating CSF and consists of major intracranial arteries.[36] Several studies have reported that the motion of CSF fluid is coupled with the rhythmic pulsation of the intracranial vasculature.[36,37] Furthermore, a recent study by Taoka *et al.* suggested that there was greater CSF movement in the suprasellar cistern.[38] Given the anatomical location of the optic chiasm/hypothalamus situated in the suprasellar cistern, we speculated that tumors predominantly involving the midline structure may experience greater exposure to CSF flow pulsation than off-midline tumors as the CSF flow in these regions is more dynamic, which might ultimately increase the risk of LMD.
(2) CSF contact with the tumor surface. In our study, a more midline tumor had a greater suprasellar cistern tumor component, increasing the surface area of CSF contact. Conversely, tumors asymmetrically involving the visual pathway, with the solid component confined to the optic radiation or lateral geniculate body, had less CSF exposure. Our findings are paralleled with previous studies. For example, the close proximity of the tumor to the subarachnoid space was elucidated by Chamdine *et al.*,[9] whereas Pollack suggested that tumors near the basal cisterns have a propensity for CSF seeding.[11] Our result highlighted the impact of CSF flow and its contact surface with the tumor on initial LMD harboring, which is an aspect that the previous literature has not described despite the tumoral location.

Additionally, we found that there is no significant difference in histopathology and ADC values between the LMD and non-LMD groups. We propose the following explanations. (1) There were only 3 cases with high-grade tumors (anaplastic astrocytoma) compared with 32 cases of low-grade tumors. This uneven case distribution posed challenges for statistical analysis. (2) High-grade tumors may exhibit more rapid primary tumor growth and symptom onset compared with low-grade tumors, prompting patients and their families to seek early medical consultation. Consequently, these patients underwent clinical and imaging studies earlier, allowing for tumor diagnosis before LMD is detectable on MRI. (3) The characteristics or

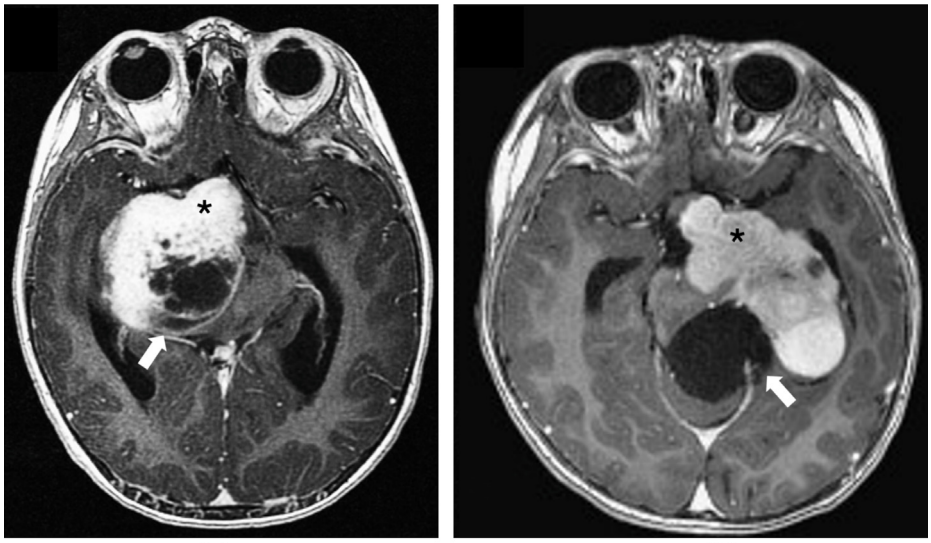

Figure 4 Two patients with pediatric optic pathway glioma (POPG) without initial leptomeningeal dissemination (LMD). (a) A 2-year-old boy with pilocytic astrocytoma. Axial post-contrast T1-weighted imaging revealed that more than 50% of the solid component of the tumor (asterisk) was asymmetrically positioned along the right visual pathway, with a well-defined tumor border, cystic changes (arrow), and heterogeneous enhancement. (b) A 2-year-old girl with pilocytic astrocytoma. Similarly, the POPG (asterisk) was asymmetrically positioned along the left visual pathway with a well-defined tumor border, cystic changes (arrow), and heterogeneous enhancement.

behaviors of OPG differ from other astrocytomas in brain parenchyma. Our study showed no significant differences in ADC values between the LMD and non-LMD groups. The ADC value correlates negatively with tumor cellularity, particularly in gliomas, implying a more aggressive or higher tumor grade.[39] Our results are similar to those of Jost *et al.*, who also failed to differentiate between clinically aggressive and stable OPGs regarding ADC values.[40] This could be due to the reduced cellularity and low tumor proliferative index[40] of OPGs, distinguishing them from other gliomas.[39] The lack of difference in ADC values indirectly supports the credibility of the two hypotheses we proposed regarding CSF drainage flow and CSF contact with the tumor surface.

Besides, the LMD group presented with more ill-defined tumor borders than the non-LMD group. There is neither supporting evidence of microscopic findings showing differences in features between patients with OPG or low-grade glioma with LMD and those without LMD[14,16] nor is there a difference in significant malignant transformation.[9,13,30,31] Intriguingly, it has been observed microscopically that even macroscopically well-circumscribed PAs can infiltrate into adjacent brain parenchyma,[41,42] particularly those originating from the optic nerve and optic chiasm, which often lack a distinct border between tumor and the normal tissue.[42] Moreover, microscopic leptomeningeal infiltration is found in the cerebellum and optic nerve tumors.[41] In addition, PAs located in the suprasellar/hypothalamic region are reportedly less circumscribed.[3]

Our findings demonstrated a higher incidence of hydrocephalus in the LMD group compared with the non-LMD group. In a previous study, obstructive hydrocephalus[12] was postulated to be due to the adhesion of tumor cells, either in the ventricles or subarachnoid spaces. Considering CSF drainage flow, we extrapolated that LMD may be associated with communicating hydrocephalus. A recent study found that CSF primarily drains through the basal lymphatic outflow and that basal meningeal lymphatic vessels are crucial for clearing CSF macromolecules.[43] Elevated CSF protein in OPG was reported due to exposure to the subarachnoid space, resulting in CSF malabsorption.[44,45] The location of OPG with increased CSF protein may impact the CSF basal lymphatic outflow, potentially resulting in communicating hydrocephalus and aggravating LMD.

According to the published literature, the reported incidence of LMD of low-grade astrocytoma ranged from 2.6% to 7%.[10–12,14,16] Table 3 lists the reported initial LMD cases from an english literature review of patients diagnosed with low-grade astrocytoma. Among these studies, D. Yecies *et al.* reported 5 patients with primarily metastatic juvenile PA, without disclosing its incidence rate.[15] Our incidence of initial LMD (20%) was comparable with that in the Perilongo *et al.* study[16] (25%) but higher than that in other published studies[10–12,14] as shown in Table 3. This is because we included only the tumors located along the optic pathway region, which were confirmed histopathologically. This contrasts with the majority of published studies in which low-grade astrocytoma was reviewed without separation of OPGs from low-grade gliomas, resulting in heterogeneity in the incidence rate.

In our study, we observed that the LMD group had a higher mortality rate. Despite disease progression, we suggested the following explanations. (1) The presence of hydrocephalus usually requires shunting treatment[8,27,46] and carries risks, such as high failure rate[46] or

Table 3
The english literature review of patients with low-grade astrocytoma with LMD at initial diagnosis

Authors	Year of publish	Initial LMD case/ Total series	Incidence of LMD	Primary Tumor Sites
IF Pollack *et al.*[11]	1994	2/76	2.6%	Superior vermian, suprasellar cistern
Mamelak AN *et al.*[10]	1994	2/33[a]	6.1%	Hypothalamus
A Gajjar *et al.*[12]	1995	8/150	5.3%	Hypothalamus, pons, spinal cord, left temporal lobe
G Perilongo *et al.*[16]	1997	3/12[a]	25%	Optic chiasm, hypothalamus
Hukin *et al.*[14]	2003	13/528	3%	Diencephalon, brainstem, spinal cord, cerebral, cerebrum
D Yecies *et al.*[15]	2018	5/?	-	Suprasellar, hypothalamus, tectum
ZA Hwang *et al.*		7/35[a]	20%	Optic chiasm, hypothalamus

[a] low-grade astrocytoma subjected to optic pathway, diencephalon. LMD: leptomeningeal dissemination

development of ascites owing to protein secretion by OPG.[8,44,45] (2) Currently, the mainstay chemotherapy for POPG is vincristine and carboplatin,[47] and no standardized treatment guidelines have established effective therapies for LMD. Alternative therapy is individually variable with vincristine/cisplatin/cyclophosphamide, monotherapy with vinblastine, irinotecan/bevacizumab, thioguanine/procarbazine/cisplatin/vincristine.[47] Adverse effects such as toxicity derived from this therapy might be inevitable. Our findings are comparable with those of a study evaluating sporadic OPG outcomes, which indicated a poor prognosis for children with LMD regardless of therapy.[48] (3) The indolent behavior of POPG might cause a delay in diagnosis from the onset of symptoms and possibly impact the inferior outcome.

Clinically, LMD usually manifests in malignant suprasellar tumors, such as germ cell tumors,[24] prompting pediatric patients to undergo additional medical assessments in endocrinology departments. This extended evaluation may lead to considerations for aggressive treatment of presumed malignant tumors, potentially delaying the timely diagnosis and management of the predominantly low-grade histology characteristic of OPGs. Therefore, our study aims to address these implications to improve early diagnosis of OPGs.

This study has several limitations. First, this was a single-center cohort study with a small number of patients. This is because we included only patients with tumors located in the suprasellar region and along the optic pathway region and that were histopathologically confirmed, whereas in clinical practice, proven tissue is usually not warranted. This is different but unique from the majority of published literature, which contains reviews of low-grade astrocytoma without limits regarding the primary tumor location. However, this is the first study and largest case series of POPG with an initial LMD given its rarity. Further prospective multicenter studies with larger sample sizes are warranted. Second, our study did not include only PA, with one astrocytoma and one anaplastic astrocytoma included, which may have challenged the analysis. Third, our study lacked molecular and genetic testing methods. However, Gessi *et al.* reported similar and stable genetic features between disseminated PA and typical PA.[23] Further studies investigating the genetic and molecular profiles subjected to POPG with LMD should be conducted. Fourth, some of the missing data, such as different pre-surgery MRI protocols from other institutes, lack an ADC map.

In conclusion, this study highlights the imaging features of POPG as being more symmetrically positioned in the midline with an ill-defined tumor border and hydrocephalus regardless of histopathology, which may increase the risk of LMD at the time of diagnosis. Early identification of these signatures could offer clinicians a framework for ensuring an accurate diagnosis, informing tailored therapy, and improving patient outcomes.

Patient consent statement

Written informed consent for performing an MRI and surgical intervention was obtained from each patient. Given the retrospective nature of the study, the need for informed consent was waived.

Ethical approval statement

This retrospective study was approved by the Institutional Review Board of Taipei Veterans General Hospital (IRB:2022-07-020BC).

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Author contributions

Zhen-An Hwang: Study concepts and design, literature research, statistical analysis, manuscript preparation, and manuscript editing. **Kai-Hsiang Chang:** Experimental studies/Data analysis, manuscript editing. **Yi-Yen Lee**: Clinical studies, manuscript editing. **Hsin-Hung Chen**: Clinical studies, manuscript editing. **Hsin-Wei Wu**: Manuscript editing. **Chia-Hung Wu**: Manuscript editing. **Jung-Hsuan Chen**: Manuscript editing. **Te-Ming Lin:** Manuscript editing. **Chih-Chun Wu**: Manuscript editing. **Feng-Chi Chang**: Guarantor of integrity of the entire study, study concepts and design, manuscript editing. All authors provided critical revisions related to intellectual content, approved the final version for publication, agreed to be accountable for all aspects of the work, and will appropriately investigate and resolve questions related to the accuracy and integrity of any part of the work. All the authors have read and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crad.2024.10.004.

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