

Ophthalmological Evaluation in Children Presenting With a Primary Brain Tumor

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Background: Children with a brain tumor are prone to develop visual impairment, which to date is often underestimated and unrecognized. Our aim was to assess the prevalence of ophthalmological evaluation and abnormal ophthalmological findings, and investigate whether demographic and tumor-related characteristics are associated with abnormal ophthalmological findings in children presenting with a primary brain tumor.

Methods: Medical records of all 90 children diagnosed with a primary brain tumor between June 2018 and May 2019 and treated at the Princess Máxima Center for Pediatric Oncology, a tertiary referral center in the Netherlands, were retrospectively reviewed. Univariate regression analysis was used to investigate associations between demographic, tumor-related and clinical characteristics, and abnormal ophthalmological findings.

Results: Sixty children (34 male [56.7%]; median [range] age, 9.3 [0–16.9] years) underwent ophthalmological evaluation within 6 weeks before or after diagnosis, 11 children

(5 male [45.5%]; median [range] age, 5.7 [0.1–17.2] years) were seen more than 6 weeks before or after diagnosis, and 19 children (7 male [36.8%]; median [range] age, 7.2 [1.9–16.6] years) did not receive ophthalmological evaluation within at least 6 months from diagnosis. A total of 19 children (21.1%) presented with visual symptoms as first sign leading to the diagnosis of a brain tumor. Children who presented with visual symptoms (odds ratio [OR], 22.52; 95% confidence interval [CI], 4.90–103.60) and/or hydrocephalus (OR, 3.60; 95% CI, 1.38–9.36) at diagnosis were more often seen for ophthalmological evaluation. The most common abnormal ophthalmological findings were eye movement disorders (66.0%), papilledema (44.1%), and visual field defects (58.1%). Eye movement disorders occurred more frequently in patients with an infratentorial tumor (OR, 4.71; 95% CI, 1.03–21.65). The risk of papilledema was associated with older age (OR, 1.19; 95% CI, 1.05–1.34), hydrocephalus (OR, 9.63; 95% CI, 2.68–34.61), and infratentorial (OR, 9.11; 95% CI, 1.77–46.78) and supratentorial (OR, 13.13; 95% CI, 1.92–89.52) tumors.

Conclusions: In this study, most children with a primary brain tumor underwent ophthalmological evaluation around diagnosis, 21% of the children were not evaluated. The high prevalence of abnormal ophthalmological findings stresses the importance of early standardized ophthalmological evaluation to detect visual impairment and provide timely treatment to potentially prevent permanent visual loss.

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Brain tumors are the most frequent solid tumors in children with an annual incidence of 40.1 cases per 1 million children (1). Although survival rates vary depending on tumor type and location, the overall 5-year survival rate for pediatric brain tumors has improved up to 65%

because of advances in diagnostics, treatment, and surveillance (2–4). As a result of this improved survival rate, insight in the late sequelae of pediatric brain tumors and their treatment has become more relevant (5).

Visual impairment (VI) is one of the most common, persistent, and serious late sequelae. Previous research has shown that 45%–67% of pediatric brain tumor survivors have VI (6,7). Often VI has lifelong implications for both the children and their caregivers. It can affect the child's psychomotor development, education, self-perception, and societal participation (8,9). All of these can lead to a decreased quality of life in childhood brain tumor survivors (10,11).

Brain tumors can cause VI in various ways. First, the tumor can cause direct compression or infiltration of the optic nerves, optic chiasm, optic tracts, lateral geniculate nuclei, optic radiations, and primary visual cortex leading to decreased visual acuity (VA) and visual field (VF) defects. Second, a brain tumor can cause cranial nerve palsies and strabismus by affecting the efferent visual pathway (8,12,13). Third, obstruction of the cerebrospinal fluid circulation or mass effect of the tumor can lead to increased intracranial pressure (ICP) and subsequent papilledema. Severe or prolonged papilledema can lead to optic nerve atrophy and irreversible VI (8,14). Finally, treatment of the brain tumor with neurosurgery, chemotherapy, and/or radiotherapy can lead to visual loss with decreased VA, VF defects, eye movement disorders, radiation induced optic neuropathy, radiation necrosis of the visual pathway, cataract, retinopathy, and/or dry eye disease (7,8,15–17).

Children with an optic pathway glioma (OPG), a suprasellar tumor or a tumor in the posterior fossa region often present with visual symptoms (18–20). However, previous studies found that a substantial amount of visual abnormalities, such as VF defects, remain unrecognized in children with a brain tumor (21,22). Unrecognized visual abnormalities may partly be the result of the large ability of (young) children to adapt and compensate and the inability to complain of visual loss and describe visual complaints clearly (8). This emphasizes the importance of adequate ophthalmological evaluation with age-appropriate tests in children with a brain tumor at diagnosis.

Currently, there are no international guidelines for ophthalmological evaluation at diagnosis in children with a primary brain tumor (23). Lack of these systematic risk-based guidelines results in insufficient or late referral from or to an ophthalmologist and underestimation of VI (21). Early monitoring of visual function and detection of VI is important to provide treatment to potentially preserve the visual function. In addition, in children with severe, irreversible VI, timely referral for visual rehabilitation may reduce the adverse effects of VI on cognitive development and quality of life (24).

For these reasons, the primary objectives of our retrospective cohort study were to assess the prevalence of

ophthalmological evaluation and to analyze the prevalence and type of abnormal ophthalmological findings in children presenting with a primary brain tumor. The second objective of this study was to identify demographic and tumor-related characteristics that are associated with ophthalmological evaluation and abnormal ophthalmological findings.

METHODS

Patients and Study Design

The study protocol was approved by the Biobank and Data Access Committee of the Princess Máxima Center for Pediatric Oncology on October 17, 2019. A waiver of informed consent was granted by the committee given the retrospective design of the study and minimal risk to patient care. All study procedures were in accordance with institutional guidelines and adhered to the principles of the 1964 Declaration of Helsinki and its further amendments. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were used in the reporting of this study (25).

We included all patients who were diagnosed with a primary brain tumor between June 2018 and May 2019; age <18 years at diagnosis; and who were treated at the Princess Máxima Center for Pediatric Oncology, a tertiary pediatric oncology reference center in Utrecht, the Netherlands. Patients diagnosed with a central nervous system tumor in the spinal region, focal cortical dysplasia, arachnoid/dermoid cyst, cavernous hemangioma, hamartoma, hematoma, white matter abnormalities, or brain infection were excluded.

Data Collection and Definitions

Data were retrospectively collected by reviewing medical records. Demographic and tumor characteristics, clinical manifestations (general symptoms: headache/neck pain, vomiting/nausea, motor impairment, fatigue, seizure, different behavior, facial palsy, dizziness, loss of consciousness, paresthesia; and visual symptoms: decreased vision, diplopia, wobbling eyes, ocular misalignment, VF defects), and the presence of neurofibromatosis type I (NF1) and/or hydrocephalus at diagnosis were recorded. Because of the retrospective nature, we did not use a standardized ophthalmological evaluation protocol for this study. Therefore general and visual symptoms were recorded if mentioned by the patient and/or their parents/caregivers and documented in the patient file. In patients who underwent an ophthalmological evaluation, ophthalmological data were collected from patient charts.

Ophthalmological evaluation was performed at the ophthalmology department at the University Medical Center Utrecht, the Netherlands, or at the ophthalmology

department of the referring center. From each ophthalmologic evaluation, the following data were collected when available: date of examination, orthoptic examination, pupillary responses, VA, slit-lamp biomicroscopy, fundus examination, cycloplegic refraction, and VFs.

Best-corrected visual acuity (BCVA) was measured in decimals by the most appropriate testing method per age (e.g., Kay Pictures, E-charts, Snellen or numeral charts) and converted to the logarithm of the minimum angle of resolution (logMAR). To gain insight in the presence and severity of VI, BCVA of the best eye was graded according to the definitions of VI and blindness of the World Health Organization (WHO): mild or no VI (BCVA ≤ 0.5 logMAR), moderate VI (BCVA $> 0.5 - \leq 1.0$ logMAR), severe VI (BCVA $> 1.0 - \leq 1.3$ logMAR), and blindness (BCVA > 1.3 logMAR). Patients without quantitative BCVA examination were categorized as unspecified VA (26).

Results of fundus examination were recorded to evaluate the presence/absence of papilledema and optic nerve head pallor. VF examination was performed in cooperative children using age appropriate testing methods. The Donders' confrontational method and the Behavioral Visual Field screening test were most often performed in children aged 0–5 years (27), whereas the semiautomatic-static Peritest, Goldmann kinetic perimetry, and the Humphrey Visual Field Analyzer were performed in older children (aged 6–18 years) (28–30). Results of VF examination were categorized as normal VF, homonymous hemianopia, bitemporal hemianopia, concentric defect, central scotoma, VF defect plus the specific location, and blind spot enlargement.

Statistical Analysis

Categorical data are presented as frequencies with percentage, continuous data are presented as mean \pm SD, or as median with ranges, depending on the distribution of the

data. To test for the predictive value of demographic, tumor-related, and clinical characteristics on eye movement disorders, VI, papilledema, and VF defects, univariable logistic regression was used. In addition, a linear mixed-model regression analysis was used to test for the above-mentioned regression characteristics on BCVA, taking into account the correlation between eyes within 1 patient. A *P* value of < 0.05 was considered statistically significant. We analyzed the collected data using Statistical Package for the Social Sciences version 25.0.0.2 (SPSS Inc, Chicago, IL).

RESULTS

One hundred twenty-two patients with an intracranial lesion were assessed for eligibility in this study (Fig. 1). Patients with no primary brain neoplasm ($N = 32$ [26.2%]) were excluded, leaving 90 patients eligible for inclusion in our study.

Baseline Patient and Tumor-Related Characteristics

In total, 90 patients with a newly diagnosed primary brain tumor were included (46 men [51.1%]; median age [range], 9.2 [0–17.2]). Of these 90 patients, 60 patients (66.7%) were seen for ophthalmological evaluation within 6 weeks before or after diagnosis (Table 1). Thirty-two of these 60 patients (53.3%) were seen before start of treatment. Overall, hydrocephalus was seen in 42 patients (46.7%), of whom 34 patients (37.8%) were seen for ophthalmological evaluation within 6 weeks before or after diagnosis. The most common tumor type was low-grade glioma (LGG) ($N = 35$ [38.9%]), followed by medulloblastoma ($N = 15$ [16.7%]), high-grade glioma ($N = 9$ [10.0%]), and germ cell tumor ($N = 7$ [7.8%]). Brain tumor histology was not available in 10 patients, with a radiological suspicion of

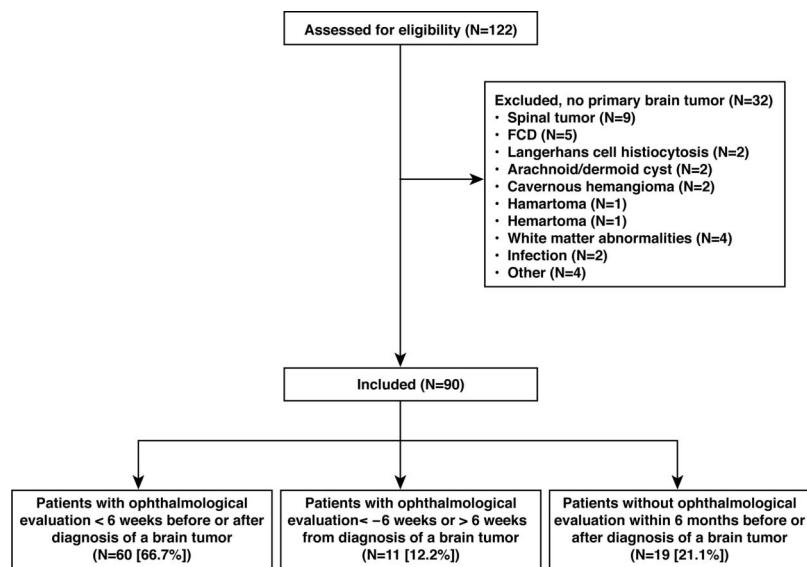


FIG. 1. Patient flow demonstrating the patient selection and grouping process.

OPG (N = 5 [5.6%]) and nonoptic pathway LGG (N = 5 [5.6%]) in these patients. Three of 5 patients with radiologically presumed OPG (3.3%) were diagnosed with NF1. All 5 patients with radiological suspicion of nonoptic pathway LGG, localized in the cerebral hemisphere (N = 3 [60.0%]) and infratentorial region (N = 2 [40.0%]), were not seen for ophthalmological evaluation. Brain tumors were mainly located in the infratentorial region (N = 46 [51.1%]), followed by the supratentorial region (N = 24 [26.7%]) and suprasellar region (N = 20 [22.2%]). Regarding the symptoms at presentation in general, children most often presented with headache and/or neck pain (60.0%), vomiting and/or nausea (57.8%), and motor skill impairment (42.2%). Visual symptoms at diagnosis were present in 39 patients (43.3%), of whom 19 patients (21.1%) primarily presented with visual symptoms leading to the diagnosis of a brain tumor. Ten patients (11.1%) eventually diagnosed with a brain tumor were first seen by the ophthalmologist because of visual symptoms. In these 10 patients, diplopia (36.8%), decreased vision (31.6%), ocular misalignment (26.3%), wobbling eyes (15.8%), and anisocoria (5.3%) were the presenting visual symptoms. Overall, the most common visual symptoms were diplopia (22.2%) and decreased vision (21.1%).

Ophthalmological Findings

Ophthalmological evaluation identified any abnormal ophthalmological findings in 47 of 60 patients (78%) evaluated within 6 weeks before or after diagnosis (Table 2). Strabismus was diagnosed in 21 of 47 patients (44.7%) tested, gaze deficits in 20 of 47 patients (42.6%) tested, and nystagmus in 17 of 47 (36.20%) patients tested.

Monocular BCVA measurement was performed in 44 patients (73.3%), of whom 26 patients (59.1%) were tested before neurosurgical intervention. The median BCVA in logMAR was 0.0 (range -0.18 to 0.82) in the best eye and 0.10 (-0.18 to 2.52) in the worst eye. According to definitions of VI and blindness from the WHO, 3 patients (5.9%) were moderately visually impaired and 2 patients (3.9%) were blind.

Fundoscopy was performed in 59 of 60 patients (98.3%). Papilledema was found in 19 of 40 patients (47.5%) seen before neurosurgical intervention and in 7 of 19 patients (36.8%) in whom fundoscopy was performed after neurosurgical intervention. Optic disc pallor was seen in 7 patients (11.9%). No new funduscopic findings were present after neurosurgical intervention in patients who were seen before and after neurosurgical intervention.

VF examination was completed in 31 of 60 patients (51.7%). VF examination was performed before neurosurgical intervention in 15 patients (48.4%) and after neurosurgical intervention in 16 patients (51.6%). In particular, VF was tested in 5/15 patients (33.3%) younger than 5 years, in 12/20 patients (60.0%) aged 5–10 years, in

12/18 patients (66.7%) aged 10–15 years, and in 2/7 patients (28.6%) older than 15 years of age. Among the tested patients, VF defects were found in 18 of 31 patients (58.1%). In patients in whom VF examination was performed before and after neurosurgical intervention (N = 5 [16.1%]), 2 patients showed improvement of their VF after intervention, no patients showed progression of VF defects.

Twenty-three of 60 patients (38.3%) initially presented without visual symptoms. However, abnormal ophthalmological findings were identified during ophthalmological evaluation in 13 of these 23 patients (50.0%). In particular, eye movement disorders (N = 7 [30.4%]), decreased VA (N = 3 [13.0%]), papilledema (N = 4 [17.4%]), optic disc pallor (N = 2 [8.7%]), and VF defects (N = 4 [17.4%]) were found.

Predictive Factors for Ophthalmological Evaluation at Diagnosis

Children with visual symptoms at diagnosis (odds ratio [OR], 22.52; 95% confidence interval [CI], 4.90–103.60) and hydrocephalus (OR, 3.60; 95% CI, 1.38–9.36) were more often seen for ophthalmological evaluation within 6 weeks before or after diagnosis (Table 3). Location of the brain tumor was not statistically associated with the performance of ophthalmological evaluation.

Risk Factors for Abnormal Ophthalmological Findings at Diagnosis

Children with an infratentorial tumor had a higher risk of developing eye movement disorders (OR, 4.71; 95% CI, 1.03–21.65) (Table 4). In addition, older children (OR, 1.19; 95% CI, 1.05–1.34), children with hydrocephalus at diagnosis (OR, 9.63; 95% CI, 2.68–34.61), and children with an infratentorial (OR, 9.11; 95% CI, 1.77–46.78) and supratentorial tumor (OR, 13.13; 95% CI, 1.92–89.52) had a statistically significant higher risk of developing papilledema. BCVA scores, VI, and VF defects were not statistically associated with age, hydrocephalus at diagnosis, and/or tumor location. Regression analysis to investigate whether patients with a specific tumor location (e.g., optic pathway) had a higher risk of abnormal ophthalmological findings was not possible because of small group sizes.

DISCUSSION

In this study, we show that the prevalence of abnormal ophthalmological findings in children presenting with a primary brain tumor is high, which underlines the importance of early standardized assessment of the visual function. Overall, 67% of the children in our cohort were seen for ophthalmological evaluation at diagnosis and abnormal ophthalmological findings were found in 78% of these children. More importantly, we identified abnormal ophthalmological findings in half of the children who initially

TABLE 1. Patient demographics and clinical characteristics at diagnosis of a brain tumor (n = 90)

Covariate	Patients With Eye Examination Within 6 wk Before or After Diagnosis (n = 60 [66.7])	Patients With Eye Examination < -6 wk or >6 wk From Diagnosis (n = 11 [12.2])	Patients Without Eye Examination (n = 19 [21.1])
Gender			
Male	34 (56.7)	5 (45.5)	7 (36.8)
Female	26 (43.3)	6 (54.6)	12 (63.2)
Age at brain tumor diagnosis, yr			
Median (range)	9.3 (0–16.9)	5.7 (0.1–17.2)	7.2 (1.9–16.6)
0–5	15 (25.0)	4 (36.4)	4 (21.1)
>5–10	20 (33.3)	4 (36.4)	7 (36.8)
>10–15	18 (30.0)	1 (9.1)	4 (21.1)
>15	7 (11.7)	2 (18.2)	4 (21.1)
Hydrocephalus at diagnosis	34 (56.7)	3 (27.3)	5 (26.3)
Neurofibromatosis type 1	2 (3.3)	1 (9.1)	0
General symptoms			
Headache/neck pain	37 (61.7)	7 (63.6)	10 (52.6)
Vomiting/nausea	37 (61.7)	4 (36.4)	11 (57.9)
Motor impairment	30 (50.0)	3 (27.3)	5 (26.3)
Fatigue	18 (30.0)	2 (18.2)	6 (31.6)
Seizure	3 (5.0)	4 (36.4)	7 (36.8)
Different behaviour	7 (11.7)	3 (27.3)	1 (5.3)
Facial palsy	6 (10.0)	1 (9.1)	1 (5.3)
Dizziness	4 (6.7)	0	3 (15.8)
Loss of consciousness	3 (5.0)	1 (9.1)	2 (10.5)
Paresthesia	1 (1.7)	0	1 (5.3)
Visual symptoms			
Decreased vision	18 (30.0)	1 (9.1)	0
Diplopia	20 (33.3)	0	0
Wobbling eyes	4 (6.7)	0	0
Ocular misalignment	8 (13.3)	0	0
Visual field loss	5 (8.3)	1 (9.1)	0
Histology			
Low-grade glioma	22 (36.7)	5 (45.5)	8 (42.1)
High-grade glioma	7 (11.7)	1 (9.1)	1 (5.3)
Medulloblastoma	13 (21.7)	0	2 (10.5)
Ependymoma	2 (3.3)	3 (27.3)	1 (5.3)
Germ cell tumor	7 (11.7)	0	0
Craniopharyngioma	3 (5.0)	1 (9.1)	0
ATRT	0	0	1 (5.3)
Other	2 (3.3)*	0	1 (5.3)†
Without histology	4 (6.7)‡	1 (9.1)§	5 (26.3)
Tumor location¶			
Infratentorial region	32 (53.3)	4 (36.4)	10 (52.6)
Supratentorial region	11 (18.3)	4 (36.4)	9 (47.4)
Suprasellar region	17 (28.3)	3 (27.3)	0

Data are presented as n (%) unless otherwise noted.

*Pineoblastoma (1), schwannoma (1).

†Meningioma (1).

‡Radiological suspicion of OPG (4).

§Radiological suspicion of OPG (1).

||Radiological suspicion of nonoptic pathway low grade glioma (5).

¶Infratentorial region: posterior cranial fossa, medulla oblongata, and pons. Supratentorial region: cerebral hemisphere, lateral ventricle, and pineal region. Suprasellar region: diencephalon, hypothalamus, optic chiasm, optic pathway, and thalamus.

ATRT, atypical teratoid rhabdoid tumor; OPG, optic pathway glioma.

presented without visual symptoms at diagnosis. VI adversely affects physical, psychological, and social well-being of children and adolescents (10,31). Knowing that early visual rehabilitation services may be effective in

improving functioning, participation, and quality of life in children with VI (24), ophthalmological evaluation at diagnosis should be recommended in all children with a primary brain tumor.

TABLE 2. Ophthalmological evaluation in children with eye examination within 6 weeks before or after diagnosis of a brain tumor (n = 60)

	Number*	n (%)
Inspection	47	
Lagophthalmos		3 (6.4)
Ptosis		3 (6.4)
Proptosis		1 (2.1)
Orthoptic examination	47	
Strabismus		21 (44.7)
Gaze deficits		20 (42.6)
Nystagmus		17 (36.2)
Pupillary function	41	
Anisocoria		2 (4.9)
No pupillary light response		1 (1.9)
Delayed pupillary light response		2 (4.9)
RAPD		3 (7.3)
Visual acuity		
BCVA (in logMAR)	44	
Best eye		0.00 [−0.18 to 0.82]
Worst eye		0.10 [−0.18 to 2.52]
Category†	51	
Normal vision or mild VI		42 (82.4)
Moderate VI		3 (5.9)
Severe VI		0
Blindness		2 (3.9)
Undetermined/unspecified		4 (7.8)‡
Slit-lamp biomicroscopy	47	
Keratitis		2 (4.3)
Fundoscopy	59	
Papilledema		26 (44.1)
Optic disc pallor		7 (11.9)
Visual field examination	31	
Homonymous hemianopia		4 (12.9)
Bitemporal hemianopia		1 (3.2)
Concentric defect		3 (9.7)
Central scotoma		1 (3.2)
Inferior defect		3 (9.7)
Temporal/nasal defect		2 (6.5)
Blind spot enlargement		6 (19.4)

Data are presented as n (%) or median [range].

*In case of missing data, the number of patients with available data is presented.

†Visual acuity is categorized according to definitions of visual impairment and blindness of the World Health Organization.

‡All 4 patients had good fixation without protest when other eye was covered.

BCVA, best-corrected visual acuity; logMAR, logarithm of minimal angle of resolution; VF, visual field; VI, visual impairment; RAPD, relative afferent pupillary defect.

Previous studies have analyzed the prevalence of abnormal ophthalmological findings in children with a primary brain tumor. However, most of these studies included only children with a certain type of brain tumor (20,32–35), or children examined regarding a specific type of abnormal ophthalmological finding (22,35,36). Moreover, some studies did not primarily assess the visual function at the time of diagnosis of a brain tumor (7,21,22,36), which makes it challenging to meaningfully compare the prevalence of abnormal ophthalmological findings of the present study with previously published studies.

Children with certain tumor characteristics have an increased risk of developing abnormal ophthalmological

findings. In our cohort, children with hydrocephalus and an infratentorial or supratentorial brain tumor were at increased risk of papilledema. Furthermore, children with an infratentorial brain tumor were at risk for the development of eye movement disorders. Previous authors, who especially described patients with medulloblastoma and posterior fossa ependymoma, suggested prolonged increased ICP and more aggressive cerebellar surgery with involvement of the cranial nerves, as possible explanatory factors for papilledema and eye movement disorders in these children (20). In addition, older children in our cohort were at increased risk of papilledema. This finding may be

TABLE 3. Predictive factors for ophthalmological evaluation in children presenting with a primary brain tumor

	Seen for Ophthalmological Evaluation Within 6 wk Before or After Diagnosis (n = 60)	Not Seen for Ophthalmological Evaluation Within 6 wk Before or After Diagnosis (n = 30)	OR (95% CI)
Age at diagnosis, yr	9.3 [0.0–16.9]	7.0 [0.1–17.2]	1.02 (0.93–1.11)
Hydrocephalus at diagnosis			
No	26 (43.3)	22 (73.3)	Ref
Yes	34 (56.7)	8 (26.7)	3.60 (1.38–9.36)*
Tumor location			
Infratentorial	32 (53.3)	14 (46.7)	Ref
Supratentorial	11 (18.3)	13 (43.3)	0.37 (0.13–1.03)
Suprasellar	17 (28.3)	3 (10.0)	2.48 (0.62–9.84)
Visual symptoms at presentation†			
No	23 (38.3)	28 (93.3)	Ref
Yes	37 (61.2)	2 (6.7)	22.52 (4.90–103.60) *

Data are presented as n (%) or median [range] with OR (95% CI).

*Statistical significant OR.

†Decreased vision, diplopia, wobbling eyes, ocular misalignment, and visual field loss.
CI, confidence interval; OR, odds ratio.

attributable to the presence of incompletely ossified cranial sutures in young children. Because the cranial sutures have not yet closed, the cranial vault can expand in response to increased ICP (37,38). Authors of previous studies already mentioned that clinicians should be aware that increased ICP could exist without the presence of papilledema. This absence of papillary changes was also the case in 15% of our patients with hydrocephalus (37,39).

Our cohort consisted of children visiting a tertiary, national, pediatric oncology referral center in the Netherlands. Given that most pediatric neuro-oncological care in the Netherlands is centralized in this center, this could explain the relatively high prevalence of ophthalmological evaluation around diagnosis (67%) compared with a previous study showing an ophthalmological referral rate of 48% (21). Other explanations may be the regular attendance of an ophthalmologist at the biweekly multidisciplinary tumor board meetings and the relatively high prevalence of visual symptoms at diagnosis (43%) in comparison with previous published studies who reported a median of 21% with a range of 10%–31% (21,40–43).

Not only was the prevalence of visual symptoms in our cohort high, also 11% of the children were firstly seen for ophthalmological evaluation because of visual symptoms. Awareness among clinicians of these visual symptoms and their possible relation with a brain tumor is of major importance for timely diagnosis.

Although the ophthalmological evaluation rate in our cohort is reasonably high, performing a complete and reliable ophthalmological evaluation including orthoptic examination, VA measurement, funduscopy, and VF

examination, proved to be a challenge. In particular, VF examination was performed timely in 52% of the children in our study. Missing VF data can be caused by the physical condition of the child, too young age or inadequate planning logistics. However, these reasons are hard to identify retrospectively.

Even when the examination consists of age-appropriate tests, results of VA measurement and VF examination remain partially subjective. Adequate ophthalmological testing in children with a brain tumor is challenging because of limitations in cooperation and concentration due to their young age and/or illness (44,45). Consistent and reliable ophthalmological evaluation is of major importance for detection of VI and providing treatment to preserve the visual function or, if necessary, timely referral for visual advice and rehabilitation. Several studies have suggested the use of optical coherence tomography (OCT) as a reliable objective ophthalmological testing method for young and noncooperative children with OPG or cranio-pharyngioma (46–48). OCT is a noninvasive imaging modality that provides cross-sectional images of the optic nerve and retinal structures (49). Our currently ongoing CCISS study investigates ophthalmological outcomes at diagnosis and in follow-up to define the value of OCT in children with any type of brain tumor (50).

Some limitations need to be addressed. As with any retrospective cohort study, the reliability of patient history data is dependent on the completeness of original documentation in the patient file. A standardized screening protocol for ophthalmological evaluation in brain tumor patients was not yet available in our center. Different VA

TABLE 4. Risk factors associated with abnormal ophthalmological findings in patients with eye examination within 6 weeks before or after diagnosis of a primary brain tumor

	Eye Movement Disorders (n = 31/47)		BCVA in logMAR (n = 44)		Visual Impairment* (n = 5/51)	
	OR (95% CI)†		B (95% CI)‡		OR (95% CI)	
Age at diagnosis, yr§	9.69 [0.32–16.69]	1.05 (0.93–1.19)	9.59 [0.49–13.85]	−0.02 (−0.03 to 0.00)	4.26 [0.32–16.69]	0.96 (0.83–1.11)
Hydrocephalus at diagnosis						
No	12 (38.7)	Ref	20 (45.5)	Ref	2 (40.0)	Ref
Yes	19 (61.2)	1.23 (0.36–4.19)	24 (54.5)	0.05 (−0.07 to 0.18)	3 (60.0)	1.26 (0.19–8.27)
Tumor location						
Infratentorial	22 (71.0)	4.71 (1.03–21.65)	25 (56.8)	Ref	1 (20.0)	0.15 (0.01–1.57)
Supratentorial	5 (16.1)	2.50 (0.37–16.89)	8 (18.2)	0.00 (−0.16 to 0.17)	1 (20.0)	0.57 (0.05–6.61)
Suprasellar	4 (12.9)	Ref	11 (25.0)	0.07 (−0.08 to 0.22)	3 (60.0)	Ref
	Papilledema (n = 26/59)		Visual Field Defects (n = 18/31)			
	OR (95% CI)		OR (95% CI)			
Age at diagnosis, yr§	0.79 [0.62–1.00]	1.19 (1.05–1.34)	10.88 [0.32–15.76]		1.04 (0.89–1.21)	
Hydrocephalus at diagnosis						
No	4 (15.4)	Ref	8 (44.4)		Ref	
Yes	22 (84.6)	9.63 (2.68–34.61)	10 (55.6)		2.81 (0.63–12.61)	
Tumor location						
Infratentorial	17 (65.4)	9.11 (1.77–46.78)	6 (33.3)		Ref	
Supratentorial	7 (26.9)	13.13 (1.92–89.52)	2 (11.1)		0.56 (0.07–4.76)	
Suprasellar	2 (8.7)	Ref	10 (55.6)		1.68 (0.34–8.26)	

Data are presented as n (%) with OR (95% CI) or as n (%) with B (95% CI) unless otherwise noted.

*BCVA of the best eye was graded according to definitions of visual impairment and blindness of the World Health Organization.

†Patients with strabismus and/or gaze deficits and/or nystagmus were included in this analysis.

‡For the linear mixed model regression analysis, BCVA measurements of 88 eyes from 44 patients were included.

§Data presented as median [range].

||Statistical significant OR.

B, beta regression coefficient; BCVA, best corrected visual acuity; CI, confidence interval; OR, odds ratio.

and VF testing methods were performed, which makes grouping and comparison of results sometimes difficult. In addition, in a few patients, data regarding ophthalmological evaluation were not completely available because these patients were seen by an ophthalmologist at their referring center. Although ophthalmological information from the referring center was requested, data were not always provided. Finally, only 67% of the patients in our cohort were seen for ophthalmological evaluation within the predetermined period of 6 weeks before or after diagnosis of a brain tumor. Thus, when interpreting the conclusions in this study regarding the prevalence of abnormal ophthalmological findings in children with a primary brain tumor, one must keep in mind possible confounding and referral bias.

Large, prospective studies with standardized ophthalmological evaluation and long-term follow-up in children with a brain tumor are necessary to investigate other potential associations between patient, tumor and treatment-related characteristics and VI and provide better prognostic information to patients and their families. Insights in a complete unselected cohort will provide better insight in which subgroup of children with a brain tumor may have previously unrecognized VI and provide true risk estimates. In conclusion, this retrospective study demonstrates abnormal ophthalmological findings in 78% of the tested children presenting with a primary brain tumor. These findings highlight the importance of early, standardized ophthalmological evaluation. Timely diagnosis of VI is important to assist in treatment decisions and provide timely treatment to potentially prevent or stabilize visual loss and improve quality of life.

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