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Ophthalmological Findings in Youths With a Newly Diagnosed Brain Tumor

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IMPORTANCE Visual impairment is an irreversible adverse effect in individuals who experienced a childhood brain tumor. Ophthalmological evaluation at diagnosis enables early detection of vision loss, decision-making about treatment, and when applicable, the timely use of visual interventions. However, awareness of visual impairment in clinical practice is suboptimal, and adherence to ophthalmological evaluation needs to be improved.

OBJECTIVE To assess the prevalence and types of abnormal ophthalmological findings in youths with a newly diagnosed brain tumor.

DESIGN, SETTING, AND PARTICIPANTS In this nationwide, prospective cohort study, youths aged 0 to 18 years with a newly diagnosed brain tumor between May 15, 2019, and August 11, 2021, were consecutively enrolled in 4 hospitals in the Netherlands, including the dedicated tertiary referral center for pediatric oncology care.

EXPOSURES A standardized and comprehensive ophthalmological examination, including orthoptic evaluation, visual acuity testing, visual field examination, and ophthalmoscopy, was performed within 4 weeks from brain tumor diagnosis.

MAIN OUTCOMES AND MEASURES The main outcomes were prevalence and types of visual symptoms and abnormal ophthalmological findings at brain tumor diagnosis.

RESULTS Of 170 youths included in the study (96 [56.5%] male; median age, 8.3 years [range, 0.2-17.8 years]), 82 (48.2%) had infratentorial tumors; 53 (31.2%), supratentorial midline tumors; and 35 (20.6%), cerebral hemisphere tumors. A total of 161 patients (94.7%) underwent orthoptic evaluation (67 [41.6%] preoperatively; 94 [58.4%] postoperatively); 152 (89.4%), visual acuity testing (63 [41.4%] preoperatively; 89 [58.6%] postoperatively); 121 (71.2%), visual field examination (49 [40.4%] preoperatively; 72 [59.6%] postoperatively); and 164 (96.5%), ophthalmoscopy (82 [50.0%] preoperatively; 82 [50.0%] postoperatively). Overall, 101 youths (59.4%) presented with visual symptoms at diagnosis. Abnormal findings were found in 134 patients (78.8%) during ophthalmological examination. The most common abnormal findings were papilledema in 86 of 164 patients (52.4%) who underwent ophthalmoscopy, gaze deficits in 54 of 161 (33.5%) who underwent orthoptic evaluation, visual field defects in 32 of 114 (28.1%) with reliable visual field examination, nystagmus in 40 (24.8%) and strabismus in 32 (19.9%) of 161 who underwent orthoptic evaluation, and decreased visual acuity in 13 of 152 (8.6%) with reliable visual acuity testing. Forty-five of 69 youths (65.2%) without visual symptoms at diagnosis had ophthalmological abnormalities on examination.

CONCLUSIONS AND RELEVANCE The results of this study suggest that there is a high prevalence of abnormal ophthalmological findings in youths at brain tumor diagnosis regardless of the presence of visual symptoms. These findings support the need of standardized ophthalmological examination and the awareness of ophthalmologists and referring oncologists, neurologists, and neurosurgeons for ophthalmological abnormalities in this patient group.

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In the past decades, advances in the diagnosis and treatment of childhood brain tumors have been associated with considerably improved survival, with a current 5-year survival rate reaching 75% in developed countries.[1,2] Improved survival rates emphasize the importance of the adverse effects associated with the tumor and its treatment. Visual impairment is a well-known adverse effect, mainly caused by damage to the optic pathway, increased intracranial pressure, cranial nerve palsies, and various therapies, that has been reported by approximately 45% to 67% of individuals who experienced a childhood brain tumor.[3-8]

Visual impairment poses a substantial burden on the health, quality of life, and participation in daily life of individuals who experienced a childhood brain tumor because of its association with sensorial development and physical, psychological, and social well-being.[9,10] Therefore, ophthalmological surveillance is important to enable early detection of vision loss, decision-making about treatment, and when applicable, timely referral to a visual rehabilitation center. Timely referral for visual rehabilitation is important to achieve optimal visual performance and safe mobility and for enabling children with a brain tumor and visual impairment to adjust successfully to their vision loss.[11] However, despite the high prevalence of visual impairment in children with a brain tumor, ophthalmological evaluation is not standard of care and only 48% to 67% are referred for ophthalmological evaluation.[12,13]

Previous studies have focused particularly on subgroups of brain tumors (ie, optic pathway gliomas, craniopharyngiomas, and pineal region tumors) that are known to cause visual impairment.[14-18] Other studies have included children with all types of brain tumors but were primarily retrospective in nature, making them more prone to selection bias.[12,13,19,20] Prospective studies including larger numbers of patients with all types of brain tumors that investigate the visual function with standardized ophthalmological evaluation are lacking. Thus, we conducted a prospective, nationwide study of a cohort of consecutive youths with a newly diagnosed brain tumor in the Netherlands to assess the prevalence and types of abnormal ophthalmological findings.

Key Points

Question What are the prevalence and types of visual symptoms and abnormal ophthalmological findings in youths at brain tumor diagnosis?

Findings In this cohort study of 170 Dutch youths aged 0 to 18 years with a newly diagnosed brain tumor, abnormal ophthalmological findings were found in 78.8%, and 65.2% without visual symptoms at diagnosis had ophthalmological abnormalities on examination.

Meaning These findings suggest that standardized ophthalmological examination in youths with a newly diagnosed brain tumor should be considered to enable early detection of vision loss, decision-making about treatment, and when applicable, timely referral for visual rehabilitation.

Methods

Study Design and Patients

This cohort study was performed as part of a larger prospective, longitudinal, multicenter, cohort study investigating visual impairment in youths newly diagnosed with a brain tumor in the Netherlands.[21] The study was approved by the Medical Ethical Committee Utrecht as part of that study and adhered to the principles of the Declaration of Helsinki.[22] Written informed consent was obtained from parents or legal guardian(s) of youths younger than 16 years and from adolescents aged 12 to 18 years. Participants received no stipend or incentives to participate. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Consecutive youths aged 0 to 18 years with a newly diagnosed brain tumor between May 15, 2019, and August 11, 2021, were eligible for inclusion in this study. The complete national neuro-oncology tumor board patient lists were screened biweekly to identify all eligible patients. Selection, invitation, and inclusion of youths and the ophthalmological examination took place at the Princess Máxima Center for Pediatric Oncology Utrecht, University Medical Center Utrecht, Amsterdam University Medical Center, and Erasmus Medical Center Rotterdam. For some youths, the ophthalmological examination took place at the University Medical Center Groningen before proton therapy. Most youths were included at the Princess Máxima Center for Pediatric Oncology, the national tertiary referral center for pediatric oncology care.

Data Collection

Clinical and Oncological Data

Clinicopathological data including age at brain tumor diagnosis; sex (defined based on self-report); medical history; tumor histologic features; type and duration of prediagnostic generalized, focal, and visual symptoms; and the type of treatment modality applied or planned at diagnosis were collected from electronic health records and were then entered anonymized into electronic case report forms (Castor EDC). Prediagnostic symptoms were collected by the treating neurologist, oncologist, and/or ophthalmologist. Histopathological data were obtained from the original pathology reports with tumor staging according to the World Health Organization classification.[23]

Radiological Data

Diagnostic magnetic resonance images of the brain and, in some patients, the spinal cord were performed at diagnosis. Two medical researchers (M.A.N., M.D.B.) who were trained by a qualified neuroradiologist (T.v.S.) and blinded for patient details assessed the images independently using a prespecified format. Discrepancies between the reviewers were discussed with an experienced neuroradiologist (T.v.S.). The following radiological variables were recorded: tumor location, presence and degree of hydrocephalus, presence and location of metastasis, mass effect of the tumor on the optic pathway, involvement of the optic pathway, hypothalamic involvement, and cerebral features of neurofibromatosis type I. Based on the location, brain tumors were classified into 3

groups: supratentorial cerebral hemisphere tumors, supratentorial midline tumors, and infratentorial tumors. The presence and degree of hydrocephalus followed the classification of Traunwieser et al[24] and was restricted to 3 grades: minor, moderate, and severe. The relationship between the tumor and the optic pathway was classified as follows: no relationship between the tumor and optic pathway, mass effect of the tumor on the optic pathway, and tumor growth into the optic pathway. For tumors compressing the optic pathway, the relationship with the optic chiasm was further classified as no relationship between tumor and optic chiasm, extension of the tumor to the optic chiasm, and displacement of the optic chiasm by the tumor. Optic pathway gliomas were classified according to the modified Dodge classification. The most posterior tumor location was assigned to optic pathway gliomas involving multiple regions.[25]

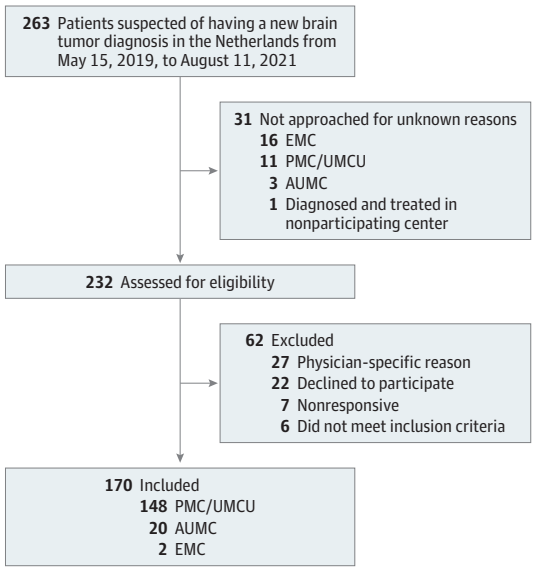
Ophthalmological Data

Children underwent a comprehensive ophthalmological examination within 4 weeks from brain tumor diagnosis, including orthoptic evaluation, best-corrected visual acuity (BCVA), pupillary responses, slitlamp examination, ophthalmoscopy, and visual field examination. Orthoptic evaluation included inspection and observation of the patient, light reflex and cover tests, ocular motility and convergence, stereopsis, and refraction. The BCVA was evaluated monocularly using age-appropriate testing methods. Binocular VA testing was performed for youths for whom monocular VA testing failed. The BCVA measurements were converted into logMAR values and categorized according to the definitions of visual impairment and blindness based on the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*: mild or no visual impairment (BCVA ≤0.5 logMAR [Snellen fraction (SF) ≥20/70]), moderate visual impairment (BCVA >0.5 to 1.0 logMAR [SF <20/70 to ≥20/200]), severe visual impairment (BCVA >1.0 to 1.3 logMAR [SF <20/200 to ≥20/400]), and blindness (BCVA >1.3 logMAR [SF <20/400]). Visual acuity values corresponding to counting fingers, hand motion, light perception, and no light perception were converted to 2.0 logMAR (SF 20/2000), 2.4 logMAR (SF 20/5024), 2.7 logMAR (light perception), and 3.0 logMAR (no light perception), respectively.[26]

Pupillary responses and the presence of a relative afferent pupillary defect were evaluated with the swinging flashlight test. Slitlamp examination evaluated the anterior segment of the eye. Ophthalmoscopy was performed to assess the presence and severity of optic disc edema (Modified Frisén Scale) and optic nerve atrophy.[27]

Visual field examination was performed using age-adapted testing with the Behavioral Visual Field Screening test,[28] the semiautomatic-static Peritest,[29] Goldmann kinetic perimetry,[30] or the Humphrey Visual Field Analyzer (Carl Zeiss Meditec) (Swedish Interactive Threshold Algorithm Fast 24-2).[31] Two experienced ophthalmology graders (M.A.N., G.L.P.) who were blinded for patient details assessed available visual fields for the presence of visual field defects according to previously described definitions.[21,28,32] Discrepancies were resolved by discussion between the graders. The reliability of visual field examination was assessed qualitatively using the Examiner-Based Assessment of Reliability scoring system[33] and quantitatively by test-specific cutoff values.[21] Unreliable visual fields were excluded from further analysis.

Figure. Patient Flowchart



Patients were aged 0 to 18 years. AUMC indicates Amsterdam University Medical Center; EMC, Erasmus Medical Center; PMC, Princess Máxima Center for Pediatric Oncology; UMCU, University Medical Center Utrecht.

Statistical Analysis

Data were exported from the electronic case report forms to SPSS for Windows, version 26.0.0.1 (SPSS Inc) for statistical analyses. Data analysis was performed using descriptive statistics. Continuous variables were presented by median and range, and categorical data were summarized by frequency and percentage. The prevalence of visual symptoms and abnormal ophthalmological findings at diagnosis were calculated as a measure of frequency. Subgroup outcomes were described according to tumor location and timing of ophthalmological evaluation (before or after neurosurgery).

Results

Patients

The participant flowchart is given in the **Figure**. From May 15, 2019, to August 11, 2021, 263 patients aged 0 to 18 years in the Netherlands were suspected of having a new brain tumor; 93 patients (35.4%) were excluded because they were not assessed for eligibility by the local investigator (30 [32.3%]), a physician-specific reason (ie, unstable clinical condition or unfavorable prognosis) (27 [29.0%]), the patient and/or parents or legal guardian(s) declined participation (22 [23.7%]) or did not respond (7 [7.5%]), the patient did not meet our inclusion criteria (6 [6.5%]), or the patient was not approached at a nonparticipating center (1 [1.1%]). Finally, 170 patients (median age,

8.3 years [range, 0.2-17.8 years]; 96 [56.6%] male) were included in this study.

Clinicopathological and radiological characteristics at diagnosis are summarized in **Table 1**. The most common tumor type was low-grade glioma (76 [44.7%]), followed by high-grade glioma (20 [11.8%]), medulloblastoma (12 [7.1%]), and craniopharyngioma (11 [6.5%]). The tumor location was in the cerebral hemispheres in 35 patients (20.6%), supratentorial midline in 53 (31.2%), and infratentorial in 82 (48.2%). Application of the modified Dodge classification in 21 optic pathway gliomas showed involvement of the optic nerve only (1 [4.8%]), optic nerve and chiasmatic junction (3 [14.3%]), chiasm only (2 [9.5%]), optic nerves and chiasm (3 [14.3%]), chiasm and optic tracts (2 [9.5%]), and the optic nerves, chiasm, and optic tracts (10 [47.6%]).

The optic pathways were compressed by the tumor in 30 of 67 patients (44.8%) with a non-optic pathway supratentorial tumor (14 cerebral hemisphere tumors [46.7%]; 16 supratentorial midline tumors [53.3%]). Hydrocephalus was present in 113 patients (66.5%) (48 of 88 supratentorial tumors [54.5%]; 65 of 82 infratentorial tumors [79.3%]). With regard to the treatment modality applied and/or planned at diagnosis, 153 patients (90.0%) underwent at least 1 neurosurgical procedure, chemotherapy was planned for 61 (35.9%), irradiation was planned for 53 (32.9%), and a wait-and-see approach was chosen for 12 (7.1%).

Clinical Presentation

Median time from symptoms to brain tumor diagnosis was 61 days (range, 0-1826 days) (**Table 2**). Overall, 101 youths (59.4%) presented with visual symptoms at diagnosis; 93 patients (54.7%) presented with a combination of generalized, focal neurological and visual symptoms, 66 (38.8%) with generalized and focal neurological symptoms only, and 8 (4.7%) with visual symptoms only; 3 patients (1.8%) were asymptomatic. Visual symptoms at diagnosis were most often diplopia (42 [24.7%]), decreased vision (42 [24.7%]), eye movement disorders (32 [18.8%]), and visual field loss (23 [13.5%]). In addition, visual symptoms were the first presenting complaint in 34 patients (20.0%), and 30 patients (17.6%) were first seen by an ophthalmologist, after which the diagnosis of a brain tumor was established.

Ophthalmological Findings

Ophthalmological examination at diagnosis revealed abnormal findings in 134 of 170 patients (78.8%). **Table 3** lists rates of the various ophthalmological findings according to (1) tumor location and (2) whether the ophthalmological examination was performed before or after neurosurgical intervention. Orthoptic evaluation was available for 161 of 170 patients (94.7%; 67 [41.6%] preoperative; 94 [58.4%] postoperative). Of these 161 patients, 14 (8.8%) presented with torticollis, 6 (3.7%) with ptosis, and 4 (2.5%) with proptosis. Strabismus was reported in 32 of 161 patients (19.9%) (3 of 30 with cerebral hemisphere tumors [10.0%], 11 of 50 with supratentorial midline tumors [22.0%], and 18 of 81 with infratentorial tumors [22.2%]), of whom 1 (3.1%) had preexistent strabismus and consequent amblyopia. Of 161 patients, gaze deficits were pre-

Table 1. Clinicopathological and Radiological Characteristics

Characteristic	Patients (N = 170)[a]
Age at diagnosis, y	
Median (range)	8.3 (0.2-17.8)
0-5	60 (35.3)
>5 to 10	39 (22.9)
>10 to 15	49 (28.8)
>15	22 (12.9)
Sex	
Female	74 (43.5)
Male	96 (56.5)
Neurofibromatosis type I[b]	12 (7.1)
Tumor histologic features	
Low-grade glioma	76 (44.7)
High-grade glioma	20 (11.8)
Medulloblastoma	12 (7.1)
Craniopharyngioma	11 (6.5)
Ependymoma	9 (5.3)
Germ cell tumor	9 (5.3)
ATRT	5 (2.9)
Plexus tumor	3 (1.8)
Other[c]	7 (4.1)
No histologic findings[d]	18 (10.6)
Tumor location	
Supratentorial	
All	88 (51.8)
Cerebral hemispheres	35 (20.6)
Midline	53 (31.2)
Thalamus	8 (4.7)
Pituitary gland	14 (8.2)
Optic pathways and/or optic chiasm	21 (12.4)
Pineal gland[e]	10 (5.9)
Infratentorial	
All	82 (48.2)
Cerebellum or fourth ventricle	69 (40.6)
Brainstem or medulla oblongata	10 (5.9)
Tectum	3 (1.8)
Hydrocephalus at diagnosis[f]	
None	52 (30.6)
Minor	21 (12.4)
Moderate	67 (39.4)
Severe	25 (14.7)
No information	5 (2.9)
Relationship with optic pathways	
Any	51 (30.0)
Mass effect of the tumor on optic pathways	30 (17.6)
No relationship with optic chiasm	9 (5.3)
Extension to the optic chiasm	3 (1.8)
Displacement of the optic chiasm	18 (10.6)
Optic pathway involvement by OPGs	21 (12.4)

(continued)

Table 1. Clinicopathological and Radiological Characteristics (continued)

Characteristic	Patients (N = 170)[a]
Modified Dodge classification[g]	
Single optic nerve	1 (0.6)
Bilateral optic nerve	0
Cisternal segment optic nerve	3 (1.8)
Central chiasmatic	1 (0.6)
Asymmetric chiasmatic	4 (2.4)
Optic tracts	7 (4.1)
Asymmetric tracts	5 (2.9)
Diffuse posterior tracts	0
Asymmetric posterior tracts	0
Hypothalamic involvement	23 (13.5)
Metastases at diagnosis	15 (8.8)
Treatment modality applied and/or planned at diagnosis	
Wait and see	12 (7.1)
Neurosurgery only	87 (51.2)
Chemotherapy only	4 (2.4)
RT only	0
Neurosurgery and chemotherapy	16 (9.4)
Neurosurgery and RT	10 (5.9)
Chemotherapy and RT	1 (0.6)
Neurosurgery, chemotherapy, and RT	40 (23.5)

Abbreviations: ATRT, atypical teratoid rhabdoid tumor; OPGs, optic pathway gliomas; RT, radiotherapy.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Diagnosis of neurofibromatosis type I was based on genetic testing (n = 11) or the presence of characteristic clinical features (n = 1).

[c] Meningioma (n = 2), pineoblastoma (n = 2), dysembryoplastic neuroepithelial tumor (n = 1), embryonal tumor with multilayered rosettes (n = 1), and hemangioblastoma (n = 1).

[d] Radiological suspicion of optic pathway glioma (n = 9), non–optic pathway low-grade glioma (n = 3), optic pathway glioma and non–optic pathway low-grade glioma (n = 1), and serum or cerebrospinal fluid suspicion of germ cell tumor (n = 5).

[e] Two patients with bifocal germinoma localized in the pineal gland and pituitary gland were classified as having pineal region tumor.

[f] Hydrocephalus was described according to the classification of Traunwieser et al.[24]

[g] Optic pathway gliomas were classified according to the modified Dodge classification of Taylor et al.[25] The most posterior tumor location was assigned to OPGs involving multiple regions.

sent in 54 (33.5%) and nystagmus in 40 (24.8%). The most common gaze deficits included cranial nerve palsies in 25 patients (15.5%; sixth nerve in 19 [76.0%], fourth nerve in 4 [16.0%], and third nerve in 2 [8.0%]), saccades in 5 (3.1%), bilateral gaze palsy in 5 (3.1%), and unilateral gaze palsy in 2 (1.2%).

Quantitative VA was available for 152 of 170 patients (89.4%; 63 [41.4%] preoperative; 89 [58.6%] postoperative). Monocular VA was reported for 133 patients (78.2%) (median age, 10.1 years [range, 2.1-17.8 years]) and binocular VA for 19 patients (11.2%) (median age, 2.3 years [range, 0.2-11.5 years]) in whom monocular VA failed. The median BCVA was 0.0 logMAR (range, −0.2 to 2.0 logMAR) in the best eye and 0.0 logMAR (range, −0.1 to 3.0) in the worst eye. The median BCVA in SF was 20/20 (range, 20/12.5 to 20/2000) in the best eye and 20/20 (range, 20/16 to no light perception) in the worst eye. A total of 13 patients (8.6%) were binocularly visually impaired, of whom 6 (3.5%) were moderately visually impaired (1 of 27 with cerebral hemisphere tumors [3.7%], 1 of 49 with supratentorial midline tumors [2.0%], and 4 of 76 with infratentorial tumors [5.3%]), 4 (2.4%) were severely visually impaired (3 of 49 with supratentorial midline tumors [6.1%], 1 of 76 with infratentorial tumors [1.3%]), and 3 (1.8%) were legally blind (1 of 27 with cerebral hemisphere tumors [3.7%], 1 of 49 with supratentorial midline tumors [2.0%], and 1 of 76 with infratentorial tumors [1.3%]). Of the 13 visually impaired or blind patients, 10 (76.9%) had hydrocephalus and 1 (7.7%) had a known, preexisting retinal dystrophy. Quantitative VA measurement was missing for 18 of 170 patients (10.6%), because only fix-and-follow testing was possible (7 [4.1%]), VA examination was not performed or unreliable at diagnosis (7 [4.1%]), or the patient had a poor clinical condition (4 [2.4%]).

Ophthalmoscopy was performed for 164 of 170 patients (96.5%; 82 [50.0%] preoperative; 82 [50.0%] postoperative). Papilledema was diagnosed in 161 of 328 eyes (49.1%) of 86 of 164 patients (52.4%) (40 of 60 eyes [66.7%] of patients with cerebral hemisphere tumor, 38 of 106 eyes [35.8%] of patients with supratentorial midline tumor, and 83 of 162 eyes [51.2%] of patients with infratentorial tumor). Of 86 patients with papilledema, 76 (88.4%) had a hydrocephalus. Papilledema was classified as moderate to severe (Modified Frisén Scale ≥ grade 3) in 80 of 328 eyes (24.4%). Optic disc pallor was seen in 21 of 328 eyes (6.4%) of 13 of 164 patients (7.9%) (2 of 60 eyes [3.3%] of patients with cerebral hemisphere tumor, 19 of 106 eyes [17.9%] of patients with supratentorial midline tumor).

Visual field examination was performed in 121 of 170 patients (71.2%; 49 [40.4%] preoperative; 72 [59.6%] postoperative) (median age, 10.4 years [range, 0.5-17.8 years]). The visual fields of 29 eyes (12.0%) were excluded from further analysis owing to unreliable results, leaving 213 reliable visual fields for 114 patients (67.1%). Visual field defects were found in 50 of 213 eyes (23.5%) of 32 of 114 patients (28.1%) (14 of 44 eyes [31.8%] of patients with cerebral hemisphere tumor, 27 of 80 eyes [33.8%] of patients with supratentorial midline tumor, and 9 of 89 eyes [10.1%] of patients with infratentorial tumor). The most common visual field defects in youths examined with the Humphrey Visual Field Analyzer, the Peritest, or Goldmann kinetic perimetry were hemianopia (19 of 144 eyes [13.2%]), an enlarged blind spot (10 of 144 eyes [6.9%]), and an arcuate scotoma (5 of 144 eyes [3.5%]). Among youths who underwent the Behavioral Visual Field Screening test, symmetric (concentric) defects were found in 10 of 69 eyes (14.5%). Bilateral visual field defects were present in 9 of 114 patients (7.9%), all with a supratentorial midline tumor (homonymous hemianopia, 5 [4.4%]; bitemporal hemianopia, 4 [3.5%]). Of 32 patients with a visual field defect, hydrocephalus was present in 22 (68.8%). Visual field examination was lacking in 49 of 170 patients (28.8%) owing to logistical reasons (22 [44.9%]), poor clinical condition (15 [30.6%]), visual field examination failure (7 [14.3%]), or missed at diagnosis (5 [10.2%]).

Table 2. Prediagnostic Symptoms Among Youths With a Brain Tumor According to Tumor Location

Symptom	Patients			
		Supratentorial tumors		
	All	Cerebral hemispheres	Midline	Infratentorial tumors
No. (%)	170 (100)	35 (20.6)	53 (31.2)	82 (48.2)
Prediagnostic symptomatic interval, median (range), d[a]				
All WHO grades	61 (0-1826)	45.5 (1-1461)	91 (0-1826)	61 (1-1461)
WHO grade I	84 (0-1826)	52 (1-1461)	152 (0-1826)	62 (1-1461)
WHO grade II	32 (1-271)	76.5 (1-271)	NA	NA
WHO grade III	31 (14-365)	61 (22-365)	NA	30 (14-152)
WHO grade IV	42 (1-365)	26 (5-152)	51.5 (4-365)	61 (1-274)
Generalized and focal neurological symptoms and signs, No. (%)				
Headache	111 (65.3)	23 (65.7)	26 (49.1)	62 (75.6)
Nausea and/or vomiting	107 (62.9)	23 (65.7)	23 (43.4)	61 (74.4)
Abnormal gait and/or coordination	56 (32.9)	2 (5.7)	7 (13.2)	47 (57.3)
Lethargy	54 (31.7)	8 (22.9)	16 (30.2)	30 (36.6)
Weight loss	41 (24.1)	7 (20.0)	7 (13.2)	27 (32.9)
Behavioral change or school difficulties	37 (21.8)	12 (34.3)	9 (17.0)	16 (19.5)
Auditory symptoms or vertigo	31 (18.2)	5 (14.3)	6 (11.3)	20 (24.4)
Seizures	15 (8.8)	10 (28.6)	4 (7.5)	1 (1.2)
Stiff neck	13 (7.6)	5 (14.3)	1 (1.9)	7 (8.5)
Stomachache	12 (7.1)	4 (11.4)	2 (3.8)	6 (7.3)
Short stature	11 (6.5)	0	10 (18.9)	1 (1.2)
Voice abnormalities	10 (5.9)	0	2 (3.8)	8 (9.8)
Photophobia	9 (5.3)	2 (5.7)	3 (5.7)	4 (4.9)
Altered level of consciousness	8 (4.7)	4 (11.4)	0	4 (4.9)
Focal motor weakness	7 (4.1)	1 (2.9)	2 (3.8)	4 (4.9)
Cranial nerve palsies	6 (3.5)	0	2 (3.8)	4 (4.9)
Memory problems	6 (3.5)	2 (5.7)	3 (5.7)	1 (1.2)
Head tilt	5 (2.9)	0	0	5 (6.1)
Developmental delay	4 (2.4)	0	1 (1.9)	3 (3.7)
Increasing head circumference	3 (1.8)	2 (5.7)	0	1 (1.2)
Other general symptoms and signs[b]	14 (8.2)	5 (14.3)	4 (7.5)	5 (6.1)
No general symptoms or signs	11 (6.5)	0	10 (18.9)	1 (1.2)
Visual symptoms and signs, No. (%)				
Diplopia	42 (24.7)	6 (17.1)	9 (17.0)	27 (32.9)
Decreased vision	42 (24.7)	9 (25.7)	19 (35.8)	14 (17.1)
Eye movement disorders[c]	32 (18.8)	6 (17.1)	11 (20.8)	15 (18.3)
Visual field loss	23 (13.5)	6 (17.1)	9 (17.0)	8 (9.8)
Drooping eyelid	8 (4.7)	0	4 (7.5)	4 (4.9)
Wobbling eyes	6 (3.5)	0	5 (9.4)	1 (1.2)
Exophthalmos	3 (1.8)	0	3 (5.7)	0
Other visual symptoms and signs[d]	11 (6.5)	3 (8.6)	4 (7.5)	4 (4.9)
No visual symptoms or signs	69 (40.6)	15 (42.9)	20 (37.7)	34 (41.5)

Abbreviations: NA, not applicable; WHO, World Health Organization.

[a] Data missing for 4 patients. Tumor staging according to the classification of the WHO.[23]

[b] Central apnea (n = 2), dry mouth (n = 2), paresthesia (n = 2), weight gain (n = 2), epistaxis (n = 1), hemidystonia (n = 1), hemiplegia (n = 1), hypotony (n = 1), opisthotonus (n = 1), precocious puberty (n = 1), sleep problems (n = 1), and vasovagal reaction (n = 1).

[c] Strabismus and/or gaze deficits.

[d] Anisocoria (n = 3), disturbed color perception (n = 2), disturbed depth perception (n = 2), dilated pupils (n = 1), painful eyes (n = 3), and red eyes (n = 1).

Among the 69 patients without visual symptoms at diagnosis (40.6%), abnormal ophthalmological findings at diagnosis were identified during ophthalmological examination for 45 (65.2%) (8 of 15 with cerebral hemisphere tumors [53.3%], 11 of 20 with supratentorial midline tumors [55.0%], 26 of 34 with infratentorial tumors [76.5%], and 34 of 45 [75.6%] with hydrocephalus). In particular, optic disc abnormalities (32 [71.1%]), gaze deficits (12 [26.7%]), visual field defects (11 [24.4%]), nystagmus (10 [22.2%]), abnormal pupillary responses (5 [11.1%]), decreased VA (4 [8.9%]), and strabismus (4 [8.9%]) were found. With regard to ophthalmic interventions at brain tumor diagnosis, 8 youths (4.7%) received occlusion therapy because of diplopia, 5 (2.9%) received eye drops, and 4 (2.4%) were referred to a visual rehabilitation center.

Table 3. Ophthalmological Findings Among Youths With a Newly Diagnosed Brain Tumor Based on Tumor Location and Timing of Ophthalmological Examination

Findings	Patients (N = 170)	Eyes							
		Total (N = 340)	Supratentorial tumors				Infratentorial tumors (n = 164)	
			Cerebral hemispheres (n = 70)		Midline (n = 106)			
			Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
Orthoptic evaluations, No. (%)								
Total evaluations	161 (94.7)	322 (94.7)	24 (34.3)	36 (51.4)	64 (60.4)	36 (34.0)	46 (28.0)	116 (70.7)
Torticollis	14 (8.7)	NA	NA	NA	NA	NA	NA	NA
Ptosis[a]	6 (3.7)	8 (2.5)	0	0	3 (9.4)	2 (5.6)	0	3 (2.6)
Proptosis	4 (2.5)	5 (1.6)	0	0	5 (7.8)	0	0	0
Strabismus	32 (19.9)	33 (10.2)	2 (8.3)	1 (2.8)	6 (9.4)	5 (13.9)	4 (8.7)	15 (12.9)
Gaze deficits	54 (33.5)	67 (20.8)	3 (12.5)	5 (13.9)	7 (10.9)	9 (25.0)	8 (17.4)	35 (30.2)
Nystagmus	40 (24.8)	75 (23.3)	2 (8.3)	2 (5.6)	10 (15.6)	13 (36.1)	8 (17.4)	40 (34.5)
Missing data	9 (5.3)	18 (5.6)	10 (14.3)[b]		6 (5.7)[b]		2 (1.2)[b]	
Visual acuity								
Total examinations, No. (%)	152 (89.4)	304 (89.4)	20 (28.6)	34 (48.6)	58 (54.7)	40 (37.7)	48 (29.3)	104 (63.4)
Monocular BCVA								
No. (%)	133 (87.5)	266 (87.5)	20 (100)	28 (82.4)	52 (89.7)	30 (75.0)	46 (95.8)	90 (86.5)
Median (range), logMAR	NA	NA	0.0 (−0.1 to 0.2)	0.0 (−0.1 to 1.7)	0.0 (−0.2 to 3.0)	0.1 (−0.1 to 3.0)	0.0 (−0.2 to 0.3)	0.0 (−0.1 to 1.7)
Median (range), Snellen fraction	NA	NA	20/200 (20/16 to 20/32)	20/200 (20/16 to 20/1000)	20/20 (20/12.5 to LP−)	20/25 (20/16 to LP−)	20/20 (20/12.5 to 20/40)	20.20 (20/16 to 20/1000)
Best eye								
Median (range), logMAR	NA	NA	0.0 (−0.1 to 0.1)	0.0 (−0.1 to 0.4)	0.0 (−0.2 to 1.1)	0.1 (−0.1 to 2.0)	0.0 (−0.2 to 0.2)	0.0 (−0.1 to 1.0)
Median (range), Snellen fraction	NA	NA	20/200 (20/16 to 20/25)	20/20 (20/16 to 20/50)	20/20 (20/12.5 to 20/250)	20/25 (20/16 to 20/2000)	20/20 (20/12.5 to 20/32)	20/20 (20/16 to 20/200)
Worst eye								
Median (range), logMAR	NA	NA	0.0 (−0.1 to 0.2)	0.0 (−0.1 to 1.7)	0.1 (−0.1 to 3.0)	0.2 (−0.1 to 3.0)	0.0 (−0.1 to 0.3)	0.1 (−0.1 to 1.7)
Median (range), Snellen fraction	NA	NA	20/200 (20/16 to 20/32)	20/20 (20/16 to 20/1000)	20/25 (20/16 to LP−)	20/32 (20/16 to LP−)	20/20 (20/16 to 20/40)	20/25 (20/16 to 20/1000)
Binocular BCVA								
No. (%)	19 (12.5)	38 (12.5)	0	6 (17.6)	6 (10.3)	10 (25.0)	2 (4.2)	14 (13.5)
Median (range), logMAR	NA	NA	NA	0.6 (0.1 to 1.5)	0.4 (0.0 to 0.5)	0.4 (0.0 to 1.1)	0.7	0.2 (−0.1 to 1.4)
Median (range), Snellen fraction	NA	NA	NA	20/80 (20/25 to 20/630)	20/50 (20/20 to 20/63)	20/50 (20/20 to 20/250)	20/100	20/32 (20/16 to 20/500)
Missing data, No. (%)[c]	18 (10.6)	36 (10.6)	16 (22.9)[b]		8 (7.5)[b]		12 (7.3)[b]	
Pupillary response, No. (%)								
Total evaluations	150 (88.2)	300 (88.2)	20 (28.6)	36 (51.4)	60 (56.6)	36 (34.0)	42 (25.6)	106 (64.6)
Anisocoria	13 (8.7)	26 (8.7)	4 (20.0)	0	4 (6.7)	10 (27.8)	2 (4.8)	6 (5.7)
No pupillary light response	5 (3.3)	6 (2.0)	0	0	3 (5.0)	3 (8.3)	0	0

(continued)

Table 3. Ophthalmological Findings Among Youths With a Newly Diagnosed Brain Tumor Based on Tumor Location and Timing of Ophthalmological Examination (continued)

		Eyes						
			Supratentorial tumors					
			Cerebral hemispheres (n = 70)		Midline (n = 106)		Infratentorial tumors (n = 164)	
Findings	Patients (N = 170)	Total (N = 340)	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
Delayed pupillary light response	6 (4.0)	8 (2.7)	0	3 (8.3)	0	5 (13.9)	0	0
RAPD	13 (7.6)	13 (4.3)	0	2 (5.6)	6 (10.0)	3 (8.3)	0	2 (1.9)
Missing data	20 (11.8)	40 (13.3)	14 (20.0)[b]		10 (9.4)[b]		16 (9.8)[b]	
Slitlamp examination, No. (%)								
Total examinations	118 (69.4)	236 (69.4)	22 (31.4)	28 (40.0)	48 (45.3)	24 (22.6)	30 (18.3)	84 (51.2)
Lisch nodules[d]	3 (2.5)	6 (2.5)	0	0	4 (8.3)	0	0	2 (2.4)
Punctate keratitis	3 (2.5)	4 (1.7)	0	2 (7.1)	0	0	0	2 (2.4)
Corneal erosion	1 (0.8)	1 (0.4)	0	0	0	0	0	1 (1.2)
Conjunctival hyperemia	1 (0.8)	1 (0.4)	0	0	0	0	0	1 (1.2)
Lagophthalmos	1 (0.8)	1 (0.4)	0	0	0	0	0	1 (1.2)
Missing data	52 (30.6)	114 (33.5)	20 (28.6)[b]		34 (32.1)[b]		50 (30.5)[b]	
Ophthalmoscopy, No. (%)								
Total examinations	164 (96.5)	328 (96.5)	24 (34.3)	36 (51.4)	72 (67.9)	34 (32.1)	68 (41.5)	94 (57.3)
Papilledema[e]								
All	86 (52.4)	161 (49.1)	16 (66.7)	24 (66.7)	18 (25.0)	20 (58.8)	41 (60.3)	42 (44.7)
Grade 0	78 (47.6)	167 (50.9)	8 (33.3)	12 (33.3)	54 (75.0)	14 (41.2)	27 (39.7)	52 (55.3)
Grade 1	24 (14.6)	36 (11.0)	2 (8.3)	4 (11.1)	2 (2.8)	4 (11.8)	12 (17.6)	12 (12.8)
Grade 2	24 (14.6)	42 (12.8)	6 (25.0)	8 (22.2)	5 (6.9)	8 (23.5)	9 (13.2)	6 (6.4)
Grade 3	21 (12.8)	38 (11.6)	4 (16.7)	0	4 (5.6)	2 (5.9)	16 (23.5)	12 (12.8)
Grade 4	14 (8.5)	26 (7.9)	3 (12.5)	7 (19.4)	4 (5.6)	2 (5.9)	2 (2.9)	8 (8.5)
Grade 5	9 (5.5)	16 (4.9)	1 (4.2)	5 (13.9)	2 (2.8)	4 (11.8)	0	4 (4.3)
Not applicable	2 (1.2)	3 (0.9)	0	0	1 (1.4)	0	2 (2.9)	0
Pale optic disc	13 (7.9)	21 (6.4)	0	2 (5.6)	16 (22.2)	3 (8.8)	0	0
Missing data	6 (3.5)	12 (3.5)	10 (14.3)[b]		0[b]		2 (1.2)[b]	
Visual field examination, No. (%)								
Total examinations	114 (67.1)	213 (62.6)	19 (27.1)	25 (35.7)	50 (47.2)	30 (28.3)	17 (10.4)	72 (43.9)
HFA SITA 24-2 FAST	42 (36.8)	71 (33.3)	11 (57.9)	11(44.0)	9 (18.0)	7 (23.3)	7 (41.2)	26 (36.1)
Semiautomatic-static Peritest	35 (30.7)	69 (32.4)	6 (31.6)	6 (24.0)	18 (36.0)	17 (56.7)	6 (35.3)	16 (22.2)

(continued)

Table 3. Ophthalmological Findings Among Youths With a Newly Diagnosed Brain Tumor Based on Tumor Location and Timing of Ophthalmological Examination (continued)

Findings	Patients (N = 170)	Eyes							
			Supratentorial tumors						
			Cerebral hemispheres (n = 70)		Midline (n = 106)		Infratentorial tumors (n = 164)		
		Total (N = 340)	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative	
Goldmann kinetic perimetry	2 (1.8)	4 (1.9)	0	0	2 (4.0)	0	0	2 (2.8)	
Scotoma[f]	23 (20.2)	38 (17.8)	5 (26.3)	6 (24.0)	7 (14.0)	12 (40.0)	3 (17.6)	5 (6.9)	
Enlarged blind spot	6 (5.3)	10 (4.7)	0	2 (8.0)	0	0	3 (17.6)	5 (6.9)	
Altitudinal	1 (0.9)	2 (0.9)	0	0	0	2 (6.7)	0	0	
Arcuate	4 (3.5)	5 (2.3)	0	0	1 (2.0)	4 (13.3)	0	0	
Quadrantanopia	2 (1.8)	2 (0.9)	1 (5.3)	1 (4.0)	0	0	0	0	
Hemianopia	10 (8.8)	19 (8.9)	4 (21.1)	3 (12.0)	6 (12.0)	6 (20.0)	0	0	
Bilateral visual field defects	9 (7.9)	18 (8.5)	4 (21.1)	2 (8.0)	6 (12.0)	6 (20.0)	0	0	
Homonymous	5 (4.4)	10 (4.7)	4 (21.1)	2 (8.0)	4 (8.0)	0	0	0	
Bitemporal	4 (3.5)	8 (3.8)	0	0	2 (4.0)	6 (20.0)	0	0	
Blind	2 (1.8)	3 (1.4)	0	2 (8.0)	1 (2.0)	0	0	0	
BEFIE Screening test									
All	35 (30.7)	69 (32.4)	2 (10.5)	8 (32.0)	21 (42.0)	6 (20.0)	4 (23.5)	28 (38.9)	
Symmetric (concentric) defect[g]	7 (6.1)	10 (4.7)	0	2 (8.0)	7 (14.0)	0	0	1 (1.4)	
Mild-moderate	3 (2.6)	4 (1.9)	0	2 (8.0)	1 (2.0)	0	0	1 (1.4)	
Severe	4 (3.5)	6 (2.8)	0	0	6 (12.0)	0	0	0	
Asymmetric or homonymous defect[g]	2 (1.8)	2 (0.9)	0	1 (4.0)	1 (2.0)	0	0	0	
Incomplete quadrantanopia	0	0	0	0	0	0	0	0	
Complete quadrantanopia	0	0	0	0	0	0	0	0	
Incomplete hemianopia	0	0	0	0	0	0	0	0	
Complete hemianopia	2 (1.8)	2 (0.9)	0	1 (4.0)	1 (2.0)	0	0	0	
Blind	1 (0.9)	1 (0.5)	0	0	1 (2.0)	0	0	0	
Missing data[h]	56 (32.9)	127 (37.4)	26 (62.9)[b]		26 (24.5)[b]		75 (45.7)[b]		

Abbreviation: BCVA, best-corrected visual acuity; BEFIE, Behavioral Visual Field; HFA, Humphrey Visual Field Analyzer; LP−, no light perception; NA, not applicable; RAPD, relative afferent pupillary defect.

[a] Ptosis was caused by tumor location and/or cranial nerve palsies (eg, third nerve palsy), not by postoperative surgical swelling.

[b] Combined preoperative and postoperative data are shown.

[c] Missing quantitative visual acuity data (n = 18): only fix-and-follow testing was possible (n = 7), no ophthalmological examination at diagnosis (n = 5), poor clinical condition of patient (n = 4), and VA measurement failed (n = 2).

[d] All 3 patients with Lisch nodules received a diagnosis of neurofibromatosis type 1.

[e] The severity of papilledema was described according to the Modified Frisén Scale (grade 0, normal optic disc; grade 5, severe degree of edema).[27] The total number of patients with papilledema (n = 86) differed from the total number of patients with grade 1 to 5 papilledema (n = 92) because, for example, some patients presented with for grade 1 papilledema in one eye and grade 2 papilledema in their other eye.

[f] Visual field defects were categorized according to definitions described by Biousse et al.[32]

[g] Visual field defects were categorized according to definitions described by Koenraads et al.[28]

[h] Missing visual fields (n = 56): logistic reason (n = 22), poor clinical condition of patient (n = 15), measurement failed owing to lack of cooperation (n = 7), unreliable visual fields (ie, false-positive errors, false-negative errors, or fixation losses ≥20%) (n = 7), and no ophthalmological examination at diagnosis (n = 5).

Discussion

This prospective, nationwide cohort study of Dutch youths with a newly diagnosed brain tumor found a high prevalence of abnormal ophthalmological findings (78.8%) at brain tumor diagnosis. Because of the use of a standardized ophthalmological screening protocol and the unselected inclusion of youths with all types of brain tumors, the association of the brain tumor with the visual function at diagnosis expand on results of previous studies.[12,13,19,20,34]

The most prevalent ophthalmological abnormalities in youths at brain tumor diagnosis were papilledema (52.4%), gaze deficits (33.5%), visual field defects (28.1%), nystagmus (24.8%), strabismus (19.9%), and decreased VA (8.6%). These findings are in line with previous studies, although the exact prevalence numbers of the specific ophthalmological diagnoses slightly differ. In particular, the percentage of papilledema was higher (74%)[34] and lower (11%-44%)[12,13,19,35-37] in previous studies, whereas the percentage of visual field defects was comparable (27%)[13] or higher (50%-58%)[12,34] in previous studies, and the percentage of decreased VA (50%-54%)[13,20] and strabismus (45%-60%)[12,13,19,20] was higher in previous studies. An explanation for these differences in prevalence numbers may be referral and selection bias in previous retrospective studies, as also suggested by some of the authors[12,13,19,20]; these biases are feasible given the incomplete ophthalmological evaluation in a substantial proportion of the included children in those studies. One study[20] only reported ophthalmological findings for children who initially presented to the ophthalmologist, which may explain the higher prevalence of abnormal ophthalmological findings in that study. Also, by using stringent definitions for decreased VA and visual field defects in our study, results may deviate from numbers of previous studies, in which definitions were not always provided.

We identified ophthalmological abnormalities in 65.2% of youths who initially presented without visual symptoms, of whom 24.4% had visual field defects and 9.8% had visual impairment in both eyes. These findings emphasizes the importance of standardized ophthalmological evaluation at brain tumor diagnosis regardless of tumor location because timely detection of vision loss and subsequent early referral for visual rehabilitation therapy may be associated with improvement in regaining mobility, activities of daily living, and quality of life among youths with visual impairment.[38]

Despite the prospective nature of this study and standardized ophthalmological screening, it remained challenging to perform a complete and reliable ophthalmological examination in youths recently diagnosed with a brain tumor. Visual acuity measurement and visual field examination could not be performed or were not reliable, respectively, in 10.8% and 32.9% of patients in the cohort, mostly owing to a poor clinical condition of the patient (eg, cerebellar mutism) or logistical reasons. Future studies should weigh the potential benefits of ophthalmological examination shortly after brain tumor diagnosis against the patient burden of intensive ophthalmological testing. Postponing intensive ophthalmological tests until a few weeks after diagnosis may improve test reliability.

Strengths and Limitations

A strength of this study is the large number of included youths with a newly diagnosed brain tumor from an unselected cohort in combination with standardized and extensive ophthalmological evaluation. The ophthalmological follow-up data and patient-reported outcomes will be analyzed after the completion of the study and will provide further insight into the longitudinal association between clinicopathological characteristics and visual impairment and the impact of visual impairment in the daily life of individuals who experienced a childhood brain tumor.

This study also has limitations. Some eligible patients were not approached for study participation for unknown reasons. This highlights the importance of optimal motivation and communication between the participating study sites and coordinating investigators during a multicenter study. In addition, some eligible patients were not invited for study participation based on physician-specific reasons. Selection bias may have played a role since physicians may be less likely to approach a patient with an unfavorable prognosis for study participation owing to potential study burden. Nonetheless, physicians were committed to approach as many consecutive patients as possible, resulting in a cohort representing all brain tumor types. Also, there was variability in the timing of ophthalmological examination (ie, before and after surgery). Most youths with a cerebral hemisphere or infratentorial tumor were examined for the first time after surgery; thus, whether some ophthalmological findings were associated with the tumor or with the neurosurgical intervention was unclear. This variability in timing was unavoidable owing to a poor clinical condition of some youths before surgery. In addition, we were not able to collect data on the ethnicity of the youths owing to privacy regulations. This may affect the translatability of our findings given the relatively homogenous population in the Netherlands. However, we do not expect specific variation in ophthalmological findings between ethnicities.

Conclusions

This prospective, nationwide cohort study found a high prevalence of abnormal ophthalmological findings among Dutch youths with a newly diagnosed brain tumor, even when no visual symptoms were present. These findings emphasize the importance of ophthalmologists, neurosurgeons, neurologists, and oncologists having knowledge about ophthalmological abnormalities in this patient group and the potential need of standardized ophthalmological examination regardless of visual symptoms.

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REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al. SEER cancer statistics review, 1975-2018. National Cancer Institute. 2021. Accessed January 13, 2022.https://seer.cancer.gov/csr/1975_2018/

2. Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2013-2017. *Neuro Oncol*. 2020;22(12)(suppl 2):iv1-iv96. doi:10.1093/neuonc/noaa200

3. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2009;101(13):946-958. doi:10.1093/jnci/djp148

4. Pillai S, Metrie M, Dunham C, Sargent M, Hukin J, Steinbok P. Intracranial tumors in infants: long-term functional outcome, survival, and its predictors. *Childs Nerv Syst*. 2012;28(4):547-555. doi:10.1007/s00381-012-1707-y

5. Saha A, Salley CG, Saigal P, et al. Late effects in survivors of childhood CNS tumors treated on Head Start I and II protocols. *Pediatr Blood Cancer*. 2014;61(9):1644-1652. doi:10.1002/pbc.25064

6. Peragallo JH. Visual function in children with primary brain tumors. *Curr Opin Neurol*. 2019;32(1):75-81. doi:10.1097/WCO.0000000000000644

7. Peeler CE. A review of visual and oculomotor outcomes in children with posterior fossa tumors. *Semin Pediatr Neurol*. 2017;24(2):100-103. doi:10.1016/j.spen.2017.04.007

8. Echevarría ME, Weinstein JL. Ocular consequences and late effects of brain tumor treatments. In: *Late Effects of Treatment for Brain Tumors*. Springer Science Business Media; 2009:183-194, . doi:10.1007/b109924_12

9. de Blank PM, Fisher MJ, Lu L, et al. Impact of vision loss among survivors of childhood central nervous system astroglial tumors. *Cancer*. 2016;122(5):730-739. doi:10.1002/cncr.29705

10. Avery RA, Hardy KK. Vision specific quality of life in children with optic pathway gliomas. *J Neurooncol*. 2014;116(2):341-347. doi:10.1007/s11060-013-1300-6

11. American Academy of Ophthalmology. Decreased vision in infants and pediatric vision rehabilitation. In: *Pediatric Ophthalmology and Strabismus*. American Academy of Ophthalmology; 2019:187-188.

12. Nuijts MA, Stegeman I, Porro GL, et al. Ophthalmological evaluation in children presenting with a primary brain tumor. *J Neuro-Ophthalmology*. 2021;(1):1-10.

13. Liu Y, Abongwa C, Ashwal S, Deming DD, Winter TW. Referral for ophthalmology evaluation and visual sequelae in children with primary brain tumors. *JAMA Netw Open*. 2019;2(8):e198273. doi:10.1001/jamanetworkopen.2019.8273

14. Wan MJ, Zapotocky M, Bouffet E, Bartels U, Kulkarni AV, Drake JM. Long-term visual outcomes of craniopharyngioma in children. *J Neurooncol*. 2018;137(3):645-651. doi:10.1007/s11060-018-2762-3

15. Wijnen M, van den Heuvel-Eibrink MM, Janssen JAMJL, et al. Very long-term sequelae of craniopharyngioma. *Eur J Endocrinol*. 2017;176(6):755-767. doi:10.1530/EJE-17-0044

16. Frappaz D, Pedone C, Thiesse P, et al. Visual complaints in intracranial germinomas. *Pediatr Blood Cancer*. 2017;64(10):e26543. doi:10.1002/pbc.26543

17. Azizi AA, Walker DA, Liu JF, et al; SIOPE NF1 OPG Nottingham, UK, Workshop 2014. NF1 optic pathway glioma: analyzing risk factors for visual outcome and indications to treat. *Neuro Oncol*. 2021;23(1):100-111. doi:10.1093/neuonc/noaa153

18. Falzon K, Drimtzias E, Picton S, Simmons I. Visual outcomes after chemotherapy for optic pathway glioma in children with and without neurofibromatosis type 1: results of the International Society of Paediatric Oncology (SIOP) Low-Grade Glioma 2004 trial UK cohort. *Br J Ophthalmol*. 2018;102(10):1367-1371. doi:10.1136/bjophthalmol-2017-311305

19. Mole G, Edminson R, Higham A, Hopper C, Hildebrand D. The management of childhood intracranial tumours and the role of the ophthalmologist. *Neuroophthalmology*. 2019;43(6):375-381. doi:10.1080/01658107.2019.1597130

20. Alswaina N, Elkhamary SM, Shammari MA, Khan AO. Ophthalmic features of outpatient children diagnosed with intracranial space-occupying lesions by ophthalmologists. *Middle East Afr J Ophthalmol*. 2015;22(3):327-330. doi:10.4103/0974-9233.159739

21. Nuijts MA, Degeling MH, Stegeman I, Schouten-van Meeteren AYN, Imhof SM. Visual impairment in children with a brain tumor: a prospective nationwide multicenter study using standard visual testing and optical coherence tomography (CCISS study). *BMC Ophthalmol*. 2019;19(1):220. doi:10.1186/s12886-019-1225-8

22. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

23. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131(6):803-820. doi:10.1007/s00401-016-1545-1

24. Traunwieser T, Kandels D, Pauls F, et al. Long-term cognitive deficits in pediatric low-grade glioma (LGG) survivors reflect pretreatment conditions-report from the German LGG studies. *Neurooncol Adv*. 2020;2(1):vdaa094. doi:10.1093/noajnl/vdaa094

25. Taylor T, Jaspan T, Milano G, et al; PLAN Study Group. Radiological classification of optic pathway gliomas: experience of a modified functional classification system. *Br J Radiol*. 2008;81(970):761-766. doi:10.1259/bjr/65246351

26. Moussa G, Bassilious K, Mathews N. A novel excel sheet conversion tool from Snellen fraction to logMAR including 'counting fingers', 'hand movement', 'light perception' and 'no light perception' and focused review of literature of low visual acuity reference values. *Acta Ophthalmol*. 2021;99(6):e963-e965. doi:10.1111/aos.14659

27. Scott CJ, Kardon RH, Lee AG, Frisén L, Wall M. Diagnosis and grading of papilledema in patients

with raised intracranial pressure using optical coherence tomography vs clinical expert assessment using a clinical staging scale. *Arch Ophthalmol*. 2010;128(6):705-711. doi:10.1001/archophthalmol.2010.94

28. Koenraads Y, Braun KPJ, van der Linden DCP, Imhof SM, Porro GL. Perimetry in young and neurologically impaired children: the Behavioral Visual Field (BEFIE) Screening Test revisited. *JAMA Ophthalmol*. 2015;133(3):319-325. doi:10.1001/jamaophthalmol.2014.5257

29. Greve EL, Dannheim F, Bakker D. The Peritest, a new automatic and semi-automatic perimeter. *Int Ophthalmol*. 1982;5(3):201-214. doi:10.1007/BF00149155

30. Quinn GE, Fea AM, Minguini N. Visual fields in 4- to 10-year-old children using Goldmann and double-arc perimeters. *J Pediatr Ophthalmol Strabismus*. 1991;28(6):314-319. doi:10.3928/0191-3913-19911101-07

31. Donahue SP, Porter A. SITA visual field testing in children. *J AAPOS*. 2001;5(2):114-117. doi:10.1067/mpa.2001.113840

32. Biousse V, Newman N. *Optic Neuropathies*. 2nd ed. Neuro-Ophthalmology Illustrated; 2015.

33. Patel DE, Viswanathan AC, Garway-Heath D, et al; OPTIC Study Group. Study of Optimal Perimetric Testing In Children (OPTIC): development and feasibility of the Kinetic Perimetry Reliability Measure (KPRM). *Br J Ophthalmol*. 2017;101(2):94-96. doi:10.1136/bjophthalmol-2016-309402

34. Carbajal UM. Ocular findings in brain tumors in children. *AMA Arch Ophthalmol*. 1959;61(4):599-607. doi:10.1001/archopht.1959.00940090601015

35. Lanphear J, Sarnaik S. Presenting symptoms of pediatric brain tumors diagnosed in the emergency department. *Pediatr Emerg Care*. 2014;30(2):77-80. doi:10.1097/PEC.0000000000000074

36. Stocco C, Pilotto C, Passone E, et al. Presentation and symptom interval in children with central nervous system tumors: a single-center experience. *Childs Nerv Syst*. 2017;33(12):2109-2116. doi:10.1007/s00381-017-3572-1

37. Wilne S, Collier J, Kennedy C, Koller K, Grundy R, Walker D. Presentation of childhood CNS tumours: a systematic review and meta-analysis. *Lancet Oncol*. 2007;8(8):685-695. doi:10.1016/S1470-2045(07)70207-3

38. Elsman EBM, Al Baaj M, van Rens GHMB, et al. Interventions to improve functioning, participation, and quality of life in children with visual impairment: a systematic review. *Surv Ophthalmol*. 2019;64(4):512-557. doi:10.1016/j.survophthal.2019.01.010