CHILDHOOD BRAIN TUMORS

InSight in Sight



MYRTHE NUIJTS

Childhood brain tumors

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InSight in Sight

Myrthe Annelotte Nuijts

Colofon

ISBN: 978-94-6361-807-6
Design cover and chapter pages: Villa Grafica
Design study logo: Sammy Claessens
Layout and print: Optima Grafische Communicatie

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The research described in this thesis was financially supported by Stichting Kinderen Kankervrij (grant number 304).

Publication of this thesis was financially supported by Landelijke Stichting voor Blinden en Slechtzienden, Neurofibromatose Vereniging Nederland, Rotterdamse Stichting Blindenbelangen, Stichting Blindenhulp, Stichting STOPhersentumoren and Synga Medical.

Childhood brain tumors – InSight in Sight

Kinderhersentumoren – InZicht in Zicht

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 30 maart 2023 des middags te 2.15 uur

door

Myrthe Annelotte Nuijts

geboren op 28 februari 1994
te Leiderdorp

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To my shining star who has watched over me during this adventure,
to my dear mama

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LIST OF ABBREVIATIONS USED IN THIS THESIS

AUMC	Amsterdam University Medical Center
ATRT	Atypical teratoid rhabdoid tumor
AUC	Area under the curve
B	Beta regression coefficient
BCVA	Best corrected visual acuity
BEFIE	Behavioral visual field screening test
CCISS	Child central nervous tumours insight in sight
CF	Counting fingers
CI	Confidence interval
CP	Craniopharyngioma
CS	Case series
CT	Chemotherapy
EBAR	Examiner based assessment of reliability
EMC	Erasmus Medical Center
ETV	Endoscopic third ventriculostomy
EVD	External ventricular drain
GCC	Ganglion cell complex
GCL-IPL	Ganglion cell layer – inner plexiform layer
GCP	Good clinical practice
GKSR	Gamma knife stereotactic radiosurgery
Gy	Gray
HFA	Humphrey visual field analyzer
HH-OCT	Handheld optical coherence tomography
HM	Hand motion
ICP	Intracranial pressure
KP	Kay pictures
LGG	Low grade glioma
LogMAR	Logarithm of the minimal angle of resolution
MC	Multicenter
MCAR	Missing completely at random
MD	Mean deviation
MRI	Magnetic resonance imaging
NA	Not applicable
NF1	Neurofibromatosis type 1
NPL	No perception of light
NPV	Negative predictive value
NR	Not reported

NTR	Netherlands Trial Register
OCT	Optical coherence tomography
OPG	Optic pathway glioma(s)
OR	Odds ratio
OU	Both eyes
PL	Perception of light
PMC	Princess Máxima Center for Pediatric Oncology
PPR	Posterior pole retina
PPV	Positive predictive value
PRISMA	Preferred reporting items of systematic reviews and meta-analyses
PS	Prospective
PVF	Peripheral visual field
P-32	Phosphorus-32
QUADAS-2	Quality assessment of diagnostic accuracy
QUIPS	Quality in prognostic studies
RAPD	Relative afferent pupillary defect
RNFL	Retinal nerve fiber layer
RS	Retrospective
RT	Radiotherapy
SC	Single-center
SD	Standard deviation
SD-OCT	Spectral-domain optical coherence tomography
SF	Snellen fraction
SN	Sensitivity
SP	Specificity
STARD	Standards for reporting of diagnostic accuracy
STROBE	Strengthening the reporting of observational studies in epidemiology
TAC	Teller acuity cards
TD-OCT	Time-domain optical coherence tomography
UCVA	Uncorrected visual acuity
UK	United Kingdom
UMCU	University Medical Center Utrecht
USA	United States of America
VA	Visual acuity
VF	Visual field
VI	Visual impairment
VP shunt	Ventriculoperitoneal shunt
WHO	World Health Organization

CHAPTER 1

General introduction and aims of this thesis

GENERAL INTRODUCTION

A major part of all children with a brain tumor suffers from an impaired visual function.[1–3] This is mainly caused by damage to the visual pathway, increased intracranial pressure (ICP), cranial nerve palsies and various therapies such as neurosurgery, radiotherapy, chemotherapy and targeted therapy.[4,5]

Visual impairment poses a substantial burden on the health, quality of life, and participation in daily life of children with a brain tumor.[6,7] Ophthalmological evaluation at brain tumor diagnosis is of utmost importance to enable early detection of vision loss, to optimize decision-making about treatment, and, when applicable, the timely referral to a visual rehabilitation center. This requires reliable and feasible ophthalmological testing methods, which can also be applied in young and often acutely and/or severely ill children. This thesis focusses on the ophthalmological findings in children newly diagnosed with a brain tumor and on the potential role of retinal optical coherence tomography (OCT) to evaluate the visual function.

Background and epidemiology of childhood brain tumors

Cancer is one of the leading causes of death in childhood. Brain tumors are the most common solid tumors in children and adolescents and account for 15-20% of all childhood malignancies.[8] They represent a significant burden in terms of morbidity and mortality in children. The estimated age-adjusted incidence of childhood brain tumors is 6.21 per 100,000 with variations among gender and race/ethnicity.[9]

Brain tumors are classified as low grade or high grade (malignant) and graded from 1 to 4 according to the fifth edition of the World Health Organization (WHO) classification, which incorporates both histological and molecular data.[10,11] The most common types of childhood brain tumors include gliomas, embryonal tumors, sellar region tumors and germ cell tumors.[8,9,12] **Figure 1** shows the distribution in children and adolescents of all brain and other central nervous system tumors according to tumor location and tumor histology.

Survival rates in children with a brain tumor vary widely and depend on the type of brain tumor, grade, location and age of the child. Advances in the diagnostics and treatment of childhood brain tumors and enhanced supportive care have considerably improved long-term survival over the last decades. The current overall five-year survival rate reaches 75% in developed countries.[13,14] This increased survival rate stresses the emphasis on adverse effects caused by the brain tumor and its treatment. About 82% of childhood brain tumor survivors experience at least one adverse effect including neu-

rocognitive deficits (11-73%), visual impairment (45-67%), neurological complications (25-49%), hearing loss (25%) and hypothalamic-pituitary disorders (23%).[1,2,15–18] Hence, visual impairment is common in childhood brain tumor survivors. However, visual impairment is not only involved in long-term health outcome, but it can already occur early in the trajectory of children with a brain tumor as direct adverse effect of the brain tumor, increased ICP, and neurosurgical procedures.

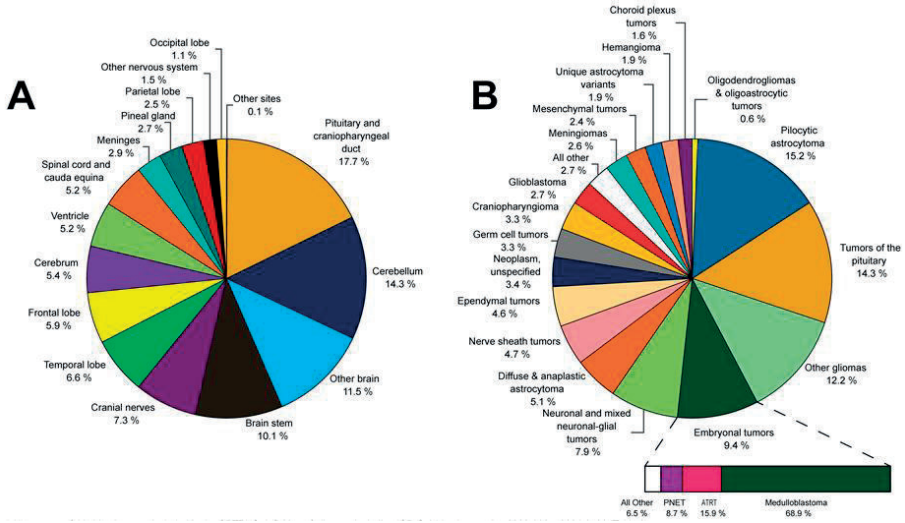


Figure 1. Distribution in children and adolescents (age 0-19 years) of all brain and central nervous system tumors by A) tumor location and B) tumor histology.
Note. Figure adapted from Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014-2018. *Neuro Oncol*. 2021;23:III1-III105.
Percentages may not add up to 100% because of rounding.

VISUAL IMPAIRMENT IN CHILDHOOD BRAIN TUMORS

Anatomy and development of the visual pathway

The visual pathway refers to all anatomical structures involved in the transduction of light into visual signals. It is composed of four neuronal elements: photoreceptors, bipolar cells, retinal ganglion cells, and fourth neuronal elements in the lateral geniculate body. Visual transduction begins in the photoreceptors (i.e. rods and cones) of the retina, the innermost thin tissue layer covering the back of the eye. Signaling continues through the bipolar cells with modulation by interneurons until the retinal ganglion cells are activated. The axons of the retinal ganglion cells combine into the optic nerve, and further posteriorly both optic nerves meet in the optic chiasm. In the optic chiasm, the axons of the nasal hemiretina cross to the contralateral optic tract, while the axons of

the temporal hemiretina continue through the ipsilateral optic tract. The main portion of ganglion cell axons (90%) forms the lateral root of the optic tract and proceeds their way to the lateral geniculate body. A small subset of axons (10%) forms the medial root of the optic tract and terminate in the superior colliculus and the pretectal nuclei. These axons are important for optic reflexes (e.g. the pupillary reflex and vestibulo-ocular reflex). From the lateral geniculate body axons spread out and continue their way via the optic radiation to the primary visual cortex, also known as striate area, V1 or visual area, located in the occipital lobe.[19,20] The processing of the visual signs then takes place in other areas of the brain, such as in the parietal lobes. A schematic overview of the visual pathway is shown in **Figure 2**.

Visual development progresses rapidly throughout the first years of life as a result of both genetically programmed neural development (i.e. changes in photoreceptor organization, myelination of the visual pathway and refinement of synaptic connections) and normal early visual experience. Because of these developments, visual acuity (VA) - *the clarity or sharpness of vision* - improves from approximately 20/600 in a newborn, to 20/120 by the age of 3 months and to adult levels of 20/20 by the age of 3-5 years.[21] In parallel with VA, the extension of the visual field (VF) - *the entire area that can be seen when an eye is fixed straight at a point* – expands in the first years of life, with the most developmental change in the temporal and inferotemporal field. The exact normal for age limits of the VF depend on the test method used, but adultlike levels are broadly reached by the age of 10-12 years.[22]

Partial damage or interruption of any part of the visual pathway corresponds to specific VF defects **(Figure 2)**. Lesions of the optic nerve prevent the transduction of light from the eye to higher levels of the visual pathway and therefore frequently cause monocular blindness. Lesions in the optic chiasm most often selectively damage crossing nasal ganglion cell axons producing bitemporal VF defects (e.g. bitemporal hemianopia). Damage or interruption of the retro-chiasmal pathway results in a homonymous VF defect, which means that the VF loss is on the same right or left hemifield in each eye.[20]

Mechanisms of visual impairment in children with a brain tumor

There are several mechanisms causing visual impairment in children with a brain tumor. Brain tumors mainly induce visual impairment by direct damage to the optic nerves, the optic chiasm and/or the retro-chiasmatic pathways, resulting in decreased VA and VF defects. The most frequent brain tumors involved in this mechanism are optic pathway gliomas (OPGs), craniopharyngiomas and germ cell tumors. OPGs are low-grade astrocytic tumors intrinsic to the precortical visual pathway (i.e. optic nerve, chiasm, tracts, and radiations) and sometimes involving other structures such as the thalamus

and/or hypothalamus. They represent 3-5% of all brain tumors in childhood. OPGs can occur sporadically or in association with neurofibromatosis type 1 (NF1) and are mostly diagnosed in children between 3 and 9 years of age. It concerns a chronic disease with unpredictable progression over time and although the five-year survival is high (89 to 95%), many children suffer from short- and long-term visual impairment (i.e. decreased VA and/or VF defects) having a significant impact on their quality of life.[23–26] Suprasellar localized craniopharyngiomas and germ cell tumors generally cause visual impairment by compression or invasion of the anterior part of the visual pathway. Children typically present with VF defects (e.g. bitemporal hemianopia) with or without decreased VA.[27,28] In addition, germ cell tumors located in the pineal region may induce diplopia by colliculi compression/invasion that results in Parinaud syndrome (i.e. vertical gaze palsy, convergence retraction nystagmus, pupil light-near dissociation, and bilateral lid retraction).[28] Besides an impaired visual function, children with a suprasellar tumor often suffer from hypothalamic and/or pituitary deficiencies.[29,30]

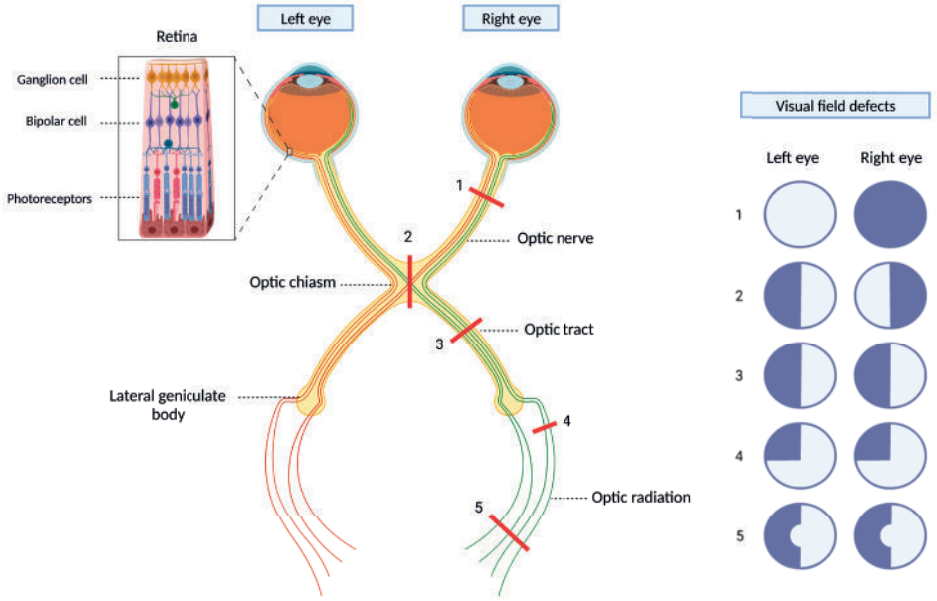


Figure 2. Schematic overview of the anatomy of the visual pathway and the type of visual field defects.
Note. Illustration created with BioRender.com.

Another mechanism of visual impairment in childhood brain tumors is the elevation of ICP due to obstructive hydrocephalus, mass effect of the tumor or resorption problems due to leptomeningeal disease.[4,5] Increased ICP can lead to the development of papill-edema and, if left untreated, to optic nerve atrophy and subsequent permanent vision loss.[31,32] Children with an infratentorial tumor and supratentorial tumor are particularly

at risk to develop papilledema, either by obstruction of the ventricular outflow at the relatively narrow Sylvian aquaduct or by mass effect of the tumor on the brain.[33]

Moreover, treatment of the brain tumor with neurosurgery, radiotherapy, chemotherapy or targeted therapy can also lead to ocular adverse effects and potentially to vision loss.[34] Even after relatively uneventful tumor resection, children may develop perioperative vision loss from direct surgical trauma to the visual pathways, a sudden decrease in ICP or interruption of the vascular supply of visual structures.[5,35–37] Radiation can also induce vision loss during or shortly after treatment, as a result of radiation-related edema and consequently compression of the visual pathways; or at a later stage, caused by radiation necrosis and damage to the vasculature resulting in optic neuropathy and/or retinopathy, or by damage to other ocular structures causing cataract, glaucoma or dry eye syndrome.[38–40] Conventional cytotoxic chemotherapy has been associated with diverse ocular adverse effects, such as conjunctivitis, keratitis, optic neuritis, blurred vision, optic neuropathy, papilledema, maculopathy, and cataract.[41,42] Ocular adverse effects of molecularly targeted agents are less defined in children and strongly depend on the type of molecularly target, and ranges from dry eyes and blepharitis to retinal vein occlusion and pigment epithelial detachment.[43,44]

Lastly, brain tumors can also cause eye movement disorders, including strabismus, gaze deficits and nystagmus.[45] In particular, tumors located in the pineal region, posterior fossa, diencephalic region and brainstem are commonly associated with eye movement disorders.[46] Strabismus may be due to temporary or permanent vision loss leading to loss of binocular function, (in)direct compression or damage of the tumor to the ocular motor pathways, or cranial nerve palsy due to increased ICP (e.g. sixth nerve palsies).[47–50] Due to the ongoing development of the visual system of young children, strabismus from an underlying brain tumor can lead to strabismic amblyopia and interruption of sensory fusion with subsequent permanent vision loss in children under eight years of age.[51] In addition, ptosis and treatment-related cataracts can lead to deprivation amblyopia.[5]

Clinical picture of children at diagnosis of a brain tumor

The presenting signs and symptoms of a brain tumor vary among children and depend on the location of the tumor, the developmental stage and ability of the child to communicate, and whether there is increased ICP. The various ways of presentation and relative rarity of childhood brain tumors often cause a diagnostic delay. In addition, many of the presenting signs and symptoms also occur with other more common and less severe pediatric diseases such as gastroenteritis, migraine and behavioral problems.[46,52,53] In general, children with a brain tumor often present with headache, nausea and vomiting, abnormal gait or coordination, and/or lethargy.[46] Visual signs and symptoms are

particularly present in children with a tumor located along the visual pathway, although it has also been reported in children with other types of brain tumors (e.g. infratentorial brain tumors).[1,46] **Figure 3** shows an overview of the presenting visual signs and symptoms in childhood brain tumors according to the tumor location. Previous studies demonstrated that certain abnormal ophthalmological findings, such as VF defects, remain unrecognized in a significant proportion of the children with a brain tumor.[1,54] In this thesis, we will further investigate if, and if so, what type of abnormal ophthalmological findings are present in children with a brain tumor who initially presented without visual signs or symptoms.

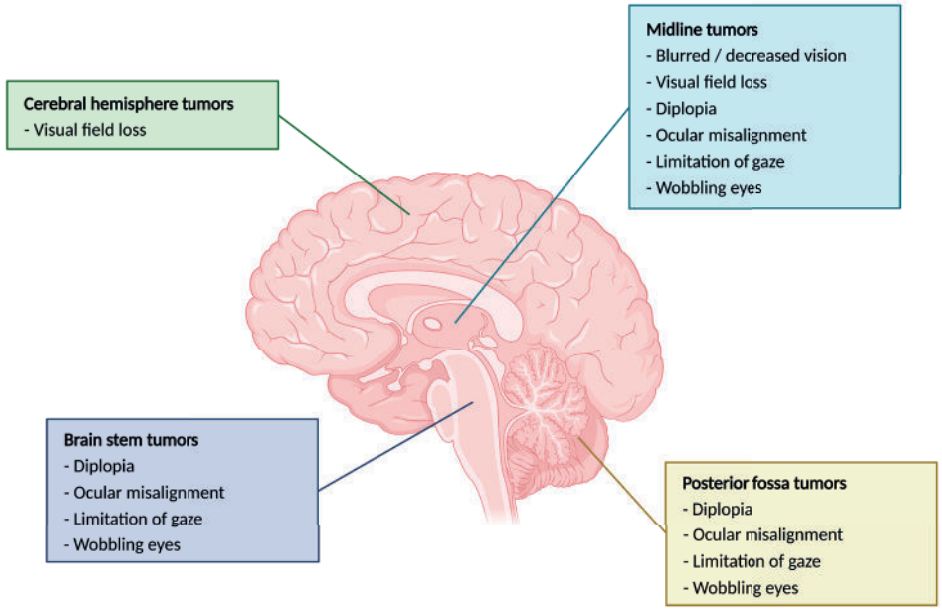


Figure 3. An illustration of the most common visual signs and symptoms at brain tumor diagnosis according to the tumor location.
Note. Illustration created with BioRender.com.

OPHTHALMOLOGICAL EVALUATION IN CHILDREN WITH A BRAIN TUMOR

Optimal ophthalmological evaluation in children with a brain tumor at diagnosis and during follow-up is warranted to enable early detection of vision loss, to optimize decision-making regarding treatment, and when applicable, the timely referral for visual rehabilitation therapy. Early detection of vision loss and the subsequent timely referral for visual rehabilitation is particularly important since this will improve regaining mobility and activities of daily living and improve quality of life in children with

visual impairment.[55] Here, multidisciplinary collaboration between ophthalmologists, pediatric neurologists, pediatric neuro-oncologists, neuroradiologists and pediatric neurosurgeons is crucial.

However, despite frequent visual impairment in children with a brain tumor, ophthalmological evaluation is not implemented in standard care for all children with a brain tumor.[1] Reasons for this lacking and/or suboptimal ophthalmological evaluation include lack of awareness of healthcare providers of the potential risk of visual impairment, the inability of children to properly recognize changes in vision, the capability to adapt to reduced vision, and the complexity to perform a complete and reliable ophthalmological examination in young, often acutely and/or severely ill children. In addition, national and international guidelines for ophthalmological evaluation in all different types of brain tumors are lacking. In this thesis we will investigate the ophthalmological referral rate and prevalence of abnormal ophthalmological findings in a retrospective cohort, as well as the prevalence of abnormal ophthalmological findings in a prospective consecutive national cohort of children newly diagnosed with a brain tumor. This will provide insight into the ophthalmological situation of those children who are not routinely referred for ophthalmological evaluation in current practice, but who may be at risk for abnormal ophthalmological findings.

Ophthalmological examination

The ophthalmological examination in children with a brain tumor consists of multiple tests which depend on the age and cooperation of the child. Generally it includes orthoptic evaluation, VA, pupillary responses, slit-lamp examination, funduscopy and visual fields. Imaging methods of the eye and functional tests that are sometimes performed are optical coherence tomography (OCT), electroretinogram and visually evoked potentials. The tests generally used in our research project are explained below.

- *Orthoptic evaluation* consists of inspection/observation of the patient, light reflex and cover tests, ocular motility and convergence, stereopsis, assessment of color vision, and refraction. It provides insight in the presence of eye movement disorders, such as strabismus, gaze deficits and nystagmus.
- *Visual acuity* refers to the clarity of vision and is measured using age-appropriate testing methods. The type of VA test chosen is based on the child's age, cognitive level and ability to cooperate. Teller Acuity Cards are used for infants and preverbal toddlers, whereas Kay Pictures, E-hooks, Snellen or numeral charts are used in children who can perform recognition VA tasks. To date, VA is one of the most important outcome measurements in evaluating the visual function in children with a brain tumor.

- *Pupillary responses* are evaluated with the swinging flashlight test that detects aberrant pupillary response in children with a brain tumor such as a relative afferent pupillary defect, a condition in which pupils respond differently to light due to unilateral or asymmetrical disease of the afferent pupillary pathway (e.g. in children with an OPG).[56]
- *Slit-lamp examination* is performed to evaluate the anterior segment of the eye. In children with a brain tumor, this test provides insight in the presence of e.g. Lisch nodules (e.g. in children with neurofibromatosis type 1) and corneal or conjunctival diseases (e.g. in children with seventh nerve palsy).
- *Funduscopy* is usually performed to assess the presence and severity of papilledema and optic atrophy in children with increased ICP and/or a brain tumor located along the visual pathway. The severity of papilledema is described with the modified Frisén Scale (Grade 0; normal optic disc, and Grade 5: severe degree of edema).[57] In children with optic atrophy, the extent of optic disc pallor is described.
- *Visual field examination* informs us about the area that a person can see when his/her eye is fixed on a single point. In children with a brain tumor, VF examination is commonly used to evaluate damage or interruption of the visual pathway. The VF of children described in this thesis is measured with age-appropriate testing methods including the Behavioral Visual Field (BEFIE) Screening test [58], the Humphrey Visual Field Analyzer (HFA) (SITA 24–2 FAST algorithm)[59], the semi-automatic static Peritest[60] or Goldmann kinetic perimetry.[61] Both from a patient as from a research point of view, standard computer assisted perimetry techniques are preferred, since these test are reliable and provide quantitative data. However, most of these techniques are difficult to perform in young and neurologically impaired and/or sick children, since they require comprehension and prolonged cooperation, concentration and visual fixation. Therefore, reliable and feasible alternative tests (e.g. BEFIE test and semi-automatic static Peritest) are chosen when it is not possible to perform computer assisted perimetry techniques.

Decisions about the management of a childhood brain tumor may depend on the results of ophthalmological examination. In particular in children with a tumor located along the visual pathway, changes in VA or VF will influence treatment decisions. Therefore, a reliable and feasible ophthalmological examination is of major importance. The above challenges (e.g. lack of cooperation and concentration leading to reduced test reliability) demonstrate the need for novel and objective tests to measure the visual function. These tests must also be easily obtained in (young) children who cannot cooperate with the traditional ophthalmological examination. Retinal optical coherence tomography (OCT) has been proposed as a potential test of the visual function in children with a brain tumor.

OPTICAL COHERENCE TOMOGRAPHY

OCT is a non-invasive imaging modality which provides high-resolution cross-sectional images of the retina and optic nerve by using low-coherence interferometry.[62,63] It comprises of A-scans and B-scans. An A-scan is an axial scan at a single point along the retina and a B-scan is a collection of A-scans to create cross-sectional 'slices' on a transverse plane. The scan resolution can be improved by either increasing the number of A-scans per B-scan, increasing the total number of B-scans, or decreasing the distance between the B-scans. The high resolution of modern OCT images enables clinicians to easily distinguish between the ten different retinal layers.[64] **Figure 4** provides an overview of the different retinal layers which can be identified on OCT.

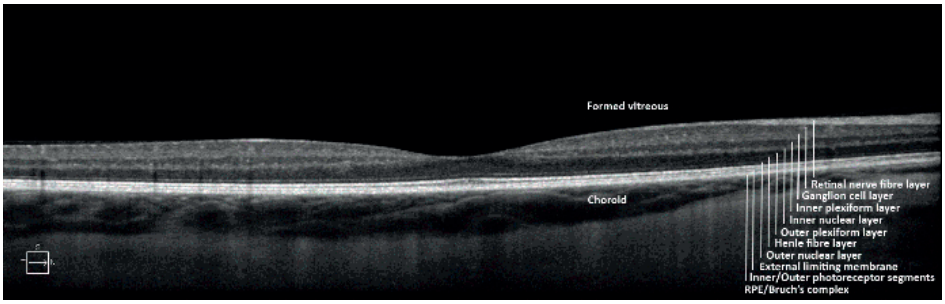


Figure 4. Spectral-domain optical coherence tomography (OCT) scan of the macula of a normal eye indicating the different retinal layers which can be identified on OCT.

Over the last decades OCT techniques have been evolved from time-domain OCT (TD-OCT) to spectral domain OCT (also known as Fourier domain OCT, and referred to as SD-OCT). Time-domain OCT devices have a relative slow acquisition speed of 400 A-scans per second, making them more susceptible to eye motion artifacts. Spectral domain OCT relies on real-time measurements of reflected light at different wavelengths. This results in higher acquisition speed (up to 40,000 A-scans per second) and better accuracy and resolution compared to TD-OCT.[64]

Like many other medical devices, OCT was originally developed for adults. The application of OCT has been limited in children because the traditional table-mounted OCT device requires the child's ability to fixate and cooperate. However, with the incorporation of eye tracking technology and the development of a handheld OCT device, OCT can nowadays be reliably used in the pediatric population. In young children who are not cooperative with OCT imaging when awake, OCT can be performed under general anesthesia.[64–67]

Imaging the retinal nerve fiber layer and ganglion cell layer – inner plexiform layer

Most researchers investigating the potential role of retinal OCT as surrogate marker of the visual function are interested in two retinal layers, the retinal nerve fiber layer (RNFL) and the ganglion cell layer – inner plexiform layer (GCL-IPL). The RNFL of the retina consists of the axons of retinal ganglion cells that form the optic nerve. OCT imaging can quantify axonal integrity with RNFL thickness measurements. This provides insight in pathological processes involving the optic nerve, such as papilledema and optic atrophy.[20,68] In addition, OCT imaging can be used for detailed visualization of the macula and multiple retinal layers. Researchers studying VA loss and VF defects are mainly interested in measuring the combined GCL-IPL thickness.[20,68] Potential advantages of measuring the GCL-IPL thickness compared to RNFL thickness are that the GCL-IPL layer is generally less affected by optic nerve edema and contains fewer blood vessels that may cause artifacts.[64]

The applicability of retinal OCT in children with a brain tumor

In patients with a tumor located along the visual pathway, retinal OCT may play a role in early diagnosis of vision loss, monitoring of the visual function and prediction of long-term visual outcomes. Previous studies in adults with parachiasmal tumors have shown that thinning of the RNFL and GCL-IPL precedes VF changes and that RNFL and GCL-IPL thickness measurements can predict post-operative VF improvement. In some patients, thinning of the GCL-IPL was detected before loss of RNFL thickness. The pattern of RNFL and GCL-IPL thinning on OCT imaging corresponded to the type of VF defects (e.g. binasal thinning of the GCL-IPL in adults with bitemporal VF defects).[20,69,70] In addition, in adults with papilledema, RNFL thickness measurements can be used to monitor the severity of edema over time.[68]

Studies investigating the potential value of retinal OCT in children with a brain tumor mainly focus on children with OPG or craniopharyngioma. These studies have shown that RNFL thickness and GCL-IPL thickness measurements can discriminate between children with a normal and abnormal visual function.[71–76] **Figure 5** shows an example of magnetic resonance imaging, VF examination and OCT imaging in a child with a craniopharyngioma.

Thus, OCT has great potential to be a surrogate test of the visual function in children with a tumor along the visual pathway. The significance of thickness changes in the RNFL and GCL-IPL on OCT with respect to ICP remains to be defined. For children unable to complete traditional ophthalmological examination, OCT may be helpful to provide indirect information about the child's visual status and assist in treatment decisions.

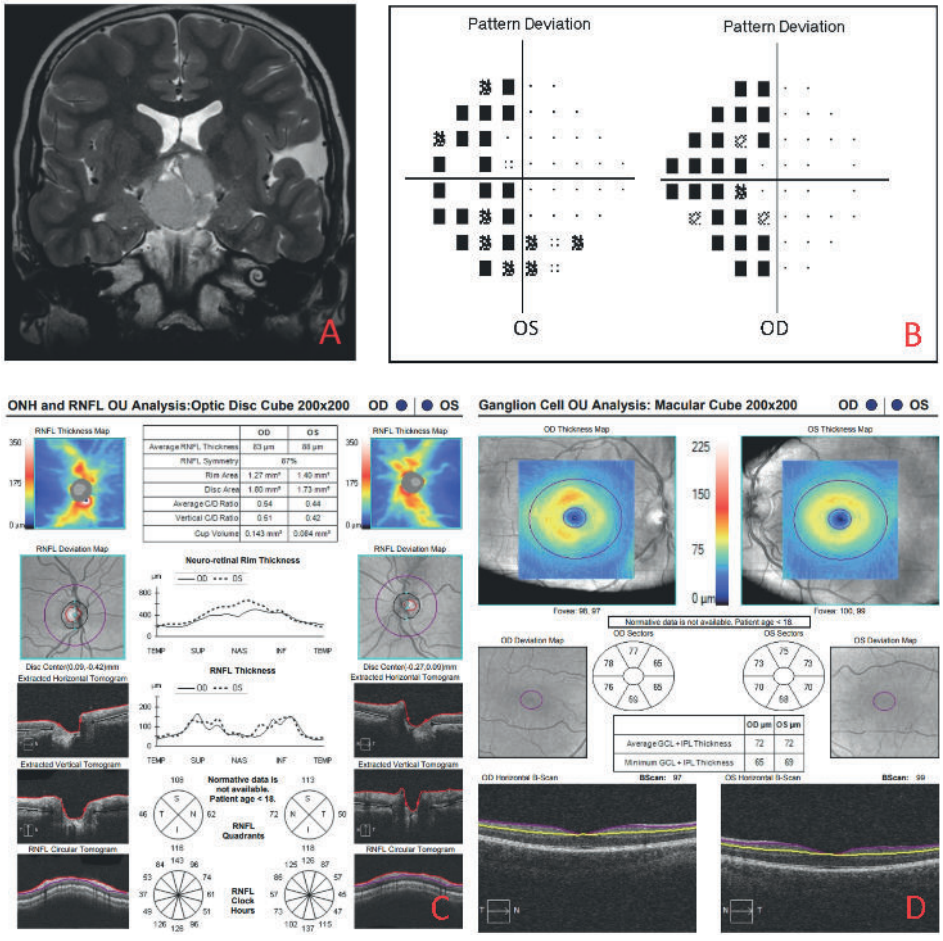


Figure 5. A 13-year old boy presented with growth failure. The coronal T2-weighted magnetic resonance image (A) demonstrated a large suprasellar mass suggestive for a craniopharyngioma. The optic chiasm was identifiable and stretched over the tumor on the ventral side. There was compression by the mass on the left optic nerve. Orthoptic examination and visual acuity measurement were normal. Funduscopy showed mild bilateral temporal pallor of the optic disc. Visual field examination with the Humphrey Visual Fields Analyzer revealed homonymous hemianopia (B). The spectral-domain optical coherence tomography scans showed thinning of the retinal nerve fiber layer (C) and the ganglion cell layer-inner plexiform layer (D) in both eyes.
Abbreviations: C/D Ratio, cup to disc ratio; GCL, ganglion cell layer; IPL, inner plexiform layer; OD, oculus dexter; ONH, optic nerve head; OS, oculus sinister; RNFL, retinal nerve fiber layer.

Another imaginable future advantage of OCT is that by detecting RNFL and GCL-IPL thinning, impending vision loss may be identified and early treatment can be provided. However, to include OCT imaging as part of clinical decision making and patient care, the promising results of previous studies have to be confirmed in larger prospective studies with long-term follow-up and standardized ophthalmological examination. In addition, no studies have investigated the value of OCT imaging in children with other types of brain tumors yet. Also, the maturation of the visual pathway in childhood might

be a factor that can lead to age-dependent interpretation of OCT imaging and the visual function in comparison with adults.

AIMS AND OUTLINE OF THIS THESIS

In this thesis we aimed to gain new insights in the ophthalmological evaluation and abnormal ophthalmological findings in children with a brain tumor, and to investigate the potential role of retinal OCT as surrogate marker of the visual function at brain tumor diagnosis and during follow-up. In **chapter 2** we systematically review the literature to better understand the visual function in children with craniopharyngioma at diagnosis, a rare slow-growing (supra)sellar tumor near the optic chiasm that often causes visual impairment. In **chapter 3** we retrospectively assess the ophthalmological referral rate and prevalence of abnormal ophthalmological findings at brain tumor diagnosis, and investigate whether demographic and tumor-related characteristics are associated with abnormal ophthalmological findings in these children. A reliable and feasible ophthalmological examination is a prerequisite for an adequate estimation of the visual function. This highly depends on the cooperation of the child, which can be challenging in young and/or acutely or severely ill children. Since retinal OCT imaging might be a more objective method for measuring the visual function, in **chapter 4,** we systematically review the diagnostic accuracy and prognostic value of retinal OCT for the detection of a decreased visual function in children with a brain tumor. To gain better insight in the true prevalence and type of abnormal ophthalmological findings in children with a brain tumor and the potential role of OCT, a prospective longitudinal study including standardized ophthalmological examination is needed. **Chapter 5** describes the rationale and design of the nationwide prospective CCISS study, *'Child Central nervous tumors InSight in Sight'*. The results of comprehensive and standardized ophthalmological examination in children at brain tumor diagnosis, performed as first part of the CCISS study, are presented in **chapter 6.** By comparing these results with the findings of the retrospective historical cohort of chapter 3, we improve insight in which children are not referred for ophthalmological evaluation in current practice, however occur at risk for ophthalmological abnormalities. In **chapter 7** we prospectively investigate the diagnostic accuracy of retinal OCT to differentiate between a normal and abnormal visual function in children newly diagnosed with a brain tumor. Finally, in **chapter 8** we discuss the main findings of this thesis, and provide insight in our ideas for future ophthalmological research in children with a brain tumor.

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CHAPTER 2

Visual functions in children with craniopharyngioma at diagnosis: A systematic review

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PLoS One. 2020 doi: 10.1371/journal.pone.0240016

ABSTRACT

Childhood craniopharyngioma is a rare and slow growing brain tumour, often located in the sellar and suprasellar region. It commonly manifests with visual impairment, increased intracranial pressure and hypothalamic and/or pituitary deficiencies. Visual impairment in childhood adversely affects a child's daily functioning and quality of life. We systematically reviewed the literature to provide an extensive overview of the visual function in children with craniopharyngioma at diagnosis in order to estimate the diversity, magnitude and relevance of the problem of visual impairment. Of the 543 potentially relevant articles, 84 studies met our inclusion criteria. Visual impairment at diagnosis was reported in 1041 of 2071 children (50.3%), decreased visual acuity was reported in 546 of 1321 children (41.3%) and visual field defects were reported in 426 of 1111 children (38.3%). Other ophthalmological findings described were fundoscopic (32.5%) and orthoptic abnormalities (12.5%). Variations in ophthalmological testing methods and ophthalmological definitions precluded a meta-analysis. The results of this review confirm the importance of ophthalmological examination in children with craniopharyngioma at diagnosis in order to detect visual impairment and provide adequate support. Future studies should focus on long-term visual follow-up of childhood craniopharyngioma in response to different treatment strategies to provide insight in risks and ways to prevent further loss of vision.

INTRODUCTION

Childhood craniopharyngioma (CP) is a rare and slow growing epithelial brain tumour (World Health Organization grade I).[1] It is thought to arise from embryonic remnants of Rathke's pouch, located along the craniopharyngeal duct. CP is commonly located in the sellar and/or suprasellar region of the brain.[2,3] The incidence of CP is 0.5–2.0 new patients per million persons per year, with a bimodal distribution in children (5–14 years) and adults (50–74 years).[2-5] Despite the benign histological grade I classification, CP often recurs and may cause severe morbidity due to its close anatomic relation with important visual and endocrinological structures. Affected children commonly present with visual impairment, increased intracranial pressure (ICP) and hypothalamic and/or pituitary deficiencies.[2,3,6] An impaired visual function is a primary manifestation in 62–84% of all children diagnosed with a CP.[3] Nevertheless, it often takes years after the onset of symptoms before children actually get diagnosed.[4,6]

Craniopharyngioma mainly causes visual impairment by direct infiltration and/or compression of the visual pathway. Damage of the visual pathway commonly manifests as decreased visual acuity (VA), visual field (VF) defects, typically bitemporal hemianopia, and/ or abnormal pupillary reponses.[5-11] Increased intracranial pressure as a result of obstructive mass effect of the tumour can lead to papilledema with subsequent optic atrophy and permanent vision loss as potential complications.[8,12,13] In addition, therapeutic interventions for CP such as tumour resection or post-surgical radiation therapy can lead to further visual loss. In particular, gross total tumour resection has a high risk of visual loss as a result of direct damage to visual structures or disruption of its vascularization.[2-4,9,14-16]

As described above, CP and its therapy commonly causes severe and permanent visual impairment, as well as hypothalamic-pituitary dysfunction. These tumour sequelae have a major impact on a child's health and quality of life.[12,13,17-19] Therefore, early detection of visual impairment together with adequate treatment and support is of major relevance as it may reduce irreversible visual sequelae and improve long-term visual outcome and quality of life.[12,13,20] Early detection of visual abnormalities requires timely referral to an ophthalmologist for ophthalmological examination. Previous studies have already demonstrated the importance of ophthalmological examination in children with a brain tumour at time of diagnosis and during follow-up.[12,13,17,18,20]

Several non-systematic reviews have summarized ophthalmological findings in children and adults with CP. However, an extensive overview in subtopics like VA, VF, fundoscopy and orthoptic examination has never been published. With this systematic review we aim to provide a broad overview of the visual function in children with CP at diagnosis in order to estimate the diversity, magnitude and relevance of the problem of visual impairment in children with CP.

METHODS

Protocol and registration

A review protocol was developed based on the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement.[21] The systematic review was prospectively registered in the international prospective register of systematic reviews (PROSPERO) on April 23, 2020 (ID: 150419). In accordance with Dutch guidelines, no institutional ethical review board approval was required.

Information sources and search strategy

We conducted a systematic search in the Cochrane Library, Embase and PubMed in order to identify all eligible studies. The electronic databases were last searched on October 2, 2019 for a combination of the following key search terms and/or their synonyms: 'craniopharyngioma', 'vision', 'visual acuity', 'visual fields', 'optic chiasm', 'optical coherence tomography', fundoscopic abnormalities (e.g. 'papilledema') and orthoptic abnormalities (e.g. 'diplopia'). The full search strategies are presented in **S1 Appendix**. We did not apply date, language or publication status restrictions. We limited search terms to presence in title or abstract to reduce the number of irrelevant articles. Reference lists of the included studies were reviewed for possible relevant articles. We did not search any trial registries for unpublished trials and no study authors were contacted to identify additional studies. All records identified were managed using Rayyan QCRI.[22]

Study selection

Two authors (M.N. and N.V.) independently screened titles and abstracts of studies identified from the electronic searches for potential inclusion. Full-text articles were obtained from potentially relevant abstracts and were assessed for eligibility by the two authors. Discrepancies were resolved by discussion. Both review authors were unmasked to article authors, journal, institution and trial results during the assessment.

Eligibility criteria

We included all study types except case reports in which < 2 patients were included. Studies were included if patients were diagnosed with a CP and if data from children could be specifically extracted. Studies including patients who had received treatment before study participation and/or had recurrent CP were excluded.

Outcome measures

The primary outcome measures of this systematic review were the presence of visual impairment, VA and VF at diagnosis. Secondary outcome measures of our study were results of fundoscopy and orthoptic examination at diagnosis.

Risk of bias in individual studies

Risk of bias of the included studies was assessed by two reviewers (M.N. and N.V) independently of each other, using the Newcastle-Ottawa Scale (NOS).[23] Any discrepancies between the reviewers were resolved by discussion. The NOS uses a star rating system for risk of bias assessment of three main parameters: selection and definition of study groups; comparability of study groups; and outcome assessment. The star ranking method in our review was based on predefined criteria, in which a total of 7 stars could be awarded. A detailed description of the risk of bias assessment is given in **Table 1**.

Table 1. Detailed description of risk of bias assessment using Newcastle-Ottawa Scale (NOS)

Domains		Predefined criteria	Maximum number of stars per domain
Selection	Representativeness of exposed cohort (children with CP and visual impairment)	* Cohort truly representative of the average child with a primary CP aged 0-18 or 0-21 years in the community together with a description of key characteristics (age, gender, tumour type etc.) - Selected group of children with CP (e.g. only giant CP) - No description of key characteristics	****
	Selection of non-exposed cohort (children with CP without visual impairment)	* Cohort drawn from the same community as the exposed cohort - Cohort drawn from a different source - No description of the derivation of the non-exposed cohort	
	Ascertainment of exposure (CP)	* Medical records / histological confirmation - No description	
	Demonstration that outcome of interest (visual impairment) was not necessarily present at start of study	* Outcome of interest was not an inclusion criterion for study - Outcome of interest was an inclusion criterion for study	
Comparability	Comparability of cohorts on the basis of the design of analysis	NA or for studies with > 1 cohort: * Only children (aged 0-21 years) included in both cohorts * Tumour locations were reported in both cohorts	NA or **
Outcome	Assessment of outcome	* VA and VF were reported - Only global information about visual function at diagnosis	*
	Was follow-up long enough for outcomes to occur	NA	
	Adequacy of follow-up of cohorts	NA	

Abbreviations: CP, craniopharyngioma; NA, not applicable. Items do not apply to the research question and design of this review.

Data analysis and synthesis

All data from the included studies were extracted in duplicate by two authors (M.N. and N.V.) independently. A standard data extraction form was used, including study characteristics (e.g. study size, study design, age, gender, tumour location) and outcome measures (e.g. VA, VF, fundoscopy and orthoptic examination) with associated outcome definitions if available. We quantified the extracted data per item and presented numbers for each item in two tables. Variations between studies and its outcome measures precluded a meta-analysis.

RESULTS

Study selection

We identified 3653 records through the literature search in PubMed, Embase and the Cochrane Library. After removal of duplicates, 2372 records were screened by title and abstract. In total, 494 full-text articles should be assessed for eligibility. However, full-text articles of 117 potential relevant abstracts were not available in the electronic databases. In attempt to retrieve these full-text articles, we searched the Utrecht University Library, Sci-Hub and contacted the corresponding author by mail and/or ResearchGate. Of these 117 potential relevant abstracts, 62 abstracts were published between 1956 and 2000 and 55 abstracts were published between 2001 and 2018. Finally, 377 full-text articles were assessed for eligibility.

Together with 15 studies identified through reference screening[24-38], this resulted in 92 studies eligible for inclusion. However, we found that 18 studies reporting about patients diagnosed and treated for CP in the following hospitals (Hospital for Sick Children, Toronto; Boston Children's Hospital; General Navy Hospital, Beijing; Hospital National de Pediatria 'Prof. Juan P. Garrahan'; Institute of Neurological Sciences, Glasgow; Hôspital Necker-Enfants Malades; Great Ormond Street Children's Hospital; Johns Hopkins Hospital). Of these 18 studies, sixteen studies had overlapping periods of patient inclusion.[10,14,29,31,39-50] To avoid double inclusion of single patients, we decided to exclude the studies with the shortest period of patient inclusion and/or the least availability of visual data. This resulted in the exclusion of the following 8 studies: Abrams (1997)[44]; Banna (1973)[50]; Cohen (2013)[36]; Hetelekidis (1993)[45]; Sainte-Rose (2005)[40]; Thompson (2005)[41]; Yu (2015)[46] and Zuccaro (2005).[49]

Finally, 84 studies met the eligibility criteria and were included in our review. A detailed overview of the selection process for included studies and reasons for exclusion after full-text screening is shown in **Fig 1**.

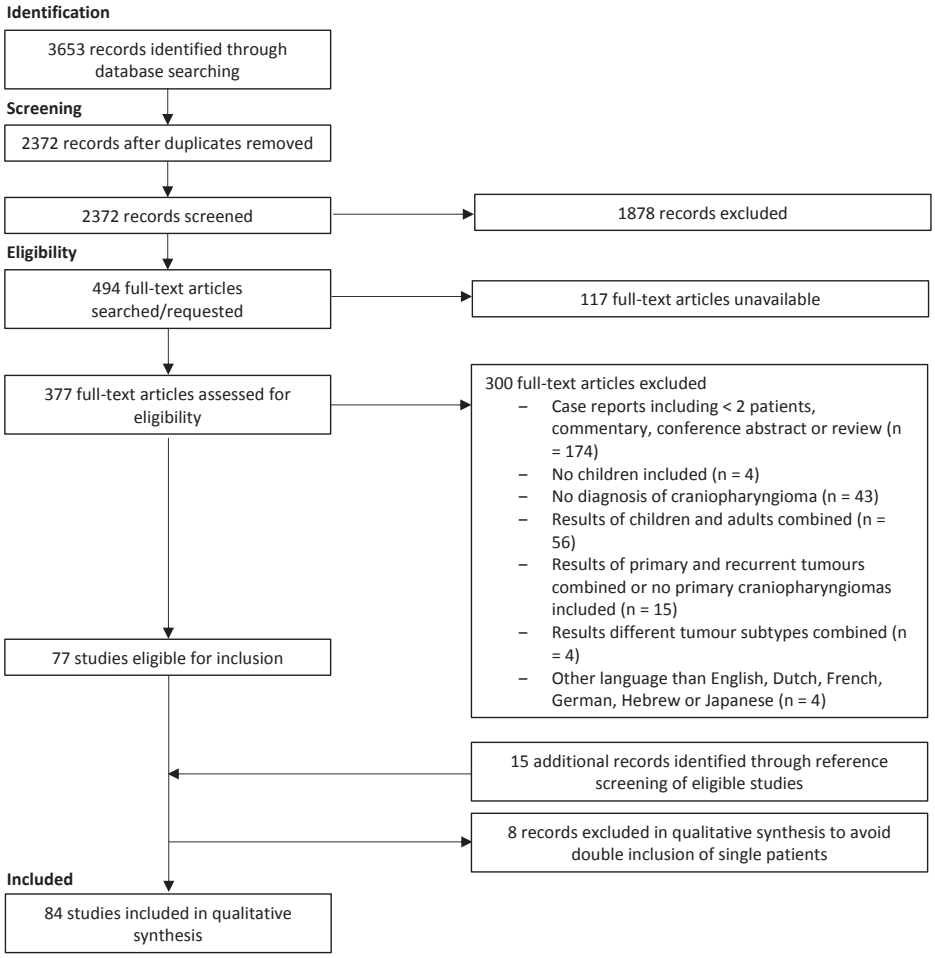


Fig 1. PRISMA flow chart for identification and selection of studies.

Study characteristics

Characteristics of the 84 included studies are shown in detail in **Table 2** and **Table 3**. Altogether, the studies included a total of 3531 children with CP with sample sizes ranging from 2 to 411 children, with a mean study sample of 42 children (median of 21 children). Studies were published between 1955 and 2019; 40 of the 84 studies were published in the past 10 years. Twenty-two studies were conducted in the United States of America (USA)[28,32,34,35,37,49,51-66]; 7 studies in Germany[26,29,67-71]; 6 studies in the United Kingdom (UK)[9,38,39,42,48,72] and France[14,24,33,46,73,74]; 5 studies in China[30,75-78]; 4 studies in India[27,79-81], Israel[82-85] and Japan[19,86-88]; 3 studies in Canada[10,25,89], Italy[90-92] and the Netherlands[93-95]; 2 studies in Australia[6,96], Korea[97,98], Saudi Arabia[99,100], Turkey[32,101]; 1 study in Bulgaria[102], Denmark[103], Iran[104], Lithuania[105], Malaysia[7], Romania[106], Spain[107] and Taiwan[108]; and

for 1 study the country was not reported[109]. With regard to the included children with CP, 1236 were females and the mean age ranged from 0[39,93] to 23 years[99]. Data about gender or age were missing in respectively 19[6,9,26,33,35,39,51,52,67-69,73,82,91,92,96,102,103,107] and 7 studies.[9,26,33,52,68,82,100v]

All studies had a retrospective study design, of which 5 studies also had a prospective follow up.[14,25,70,72,92] In most of the studies, a cohort of children was reviewed. These cohorts were generally obtained by screening medical records in single-centre and in some studies multicentre hospitals. We also included twelve case series[10,38,69,75,83,86,92,94,97,104,105,109] and two studies discussing more than one case report.[79,80]

There was a large variety between research aims of the included studies. In the majority of studies, visual function in children with CP at diagnosis was not a primary outcome measure, but details about visual function at diagnosis could be obtained from tables containing baseline characteristics. Precisely 10 studies reported primarily visual function and/or long term visual outcomes in children with CP.[6,7,10,39,52,53,72,83,102,107]

Risk of bias assessment

Table 4 shows the results of the risk of bias assessment by the Newcastle-Ottawa Scale (NOS) for the included studies. Overall, total scores ranged between 1 to 6 stars of a possible 7 stars. Eleven studies were awarded 1–3 stars, 72 studies 4–5 stars and one study 6 stars. These scores indicate that most of the included studies were of moderate quality. Quality was predominately limited by missing or incomplete information about VA testing and/or VF testing.[14,19,26–28,30,33–35,51,54–56,62,67,68,70,74,77,85,93,97,100,104,108] Other important reasons for weaker quality were studies who included only patients who are known to have an impaired visual function[83,100], studies who included only patients who are known to have a CP at a specific location[46,54,71,75,76,80,81,86,108] and studies who included only patients with giant or extensive CP.[46, 67, 79, 99, 104] We were not able to score comparability for 82 studies, because no cohorts were compared in these studies. Puget (2007)[14] and Tan (2017)[42] were the only two studies we could rate for comparability, since they included two and three cohorts, respectively.

Table 2. General characteristics of the included studies

	Study	Study design, setting and country	Number of children, subtype if available	Mean age (years) at diagnosis, range/SD (years)	Gender (M/F)	Tumour location
1	Al-Mefty, 1985[99]	RS, 1 cohort, SC, Saudi Arabia	20	(2-17), except one 23-year old man	10/10	NR
2	Albright, 2005[51]	RS, 1 cohort, SC, USA	44	Micro neurosurgical tumour resection: 11, 12 (6-18)*; P-32: 7, 7 (3-17)*; GKSR: 13, 13 (5-18)*	NR	NR
3	Ali, 2013[54]	RS, 1 cohort, SC, USA	7	9.6 (5-14)	6/1	Sellar and suprasellar 5 (71.4%), suprasellar 1 (14.3%), suprasellar and third ventricle 1 (14.3%)
4	Ammirati, 1988[71]	RS, 1 cohort, SC, Germany	3	13 (8-17)	0/3	Retrochiasmatic 4 (100%)
5	Anderson, 1989[53]	RS, 1 cohort, SC, USA	2	13.5 (12-15)	2/0	NR
6	Ansari, 2016[62]	RS, 1 cohort, SC, USA	9	6.7 (3-15)	6/3	NR
7	Artero, 1984[107]	RS, 1 cohort, SC, Spain	24	24 patients < 20 years	NR	NR
8	Ashkenazi, 1990[82]	RS, 1 cohort, SC, Israel	12	NR (only for children & adults together)	NR (for all ages: 11/9)	NR For children & adults: sellar extension 19/20, third ventricular 14/20
9	*Bartlett, 1971*[35]	*RS, 1 cohort, SC, USA*	*30*	*< 15 years*	*NR (for all ages: 42/43)*	*NR*
10	Behari, 2003[81]	RS, 1 cohort, SC, India	2	13.5 (11-16)	2/0	Intraventricular 2 (100%)
11	Bialer, 2013[84]	RS, 1 cohort, SC, Israel	20	6.5, SD 3.88	10/10	NR

Table 2. General characteristics of the included studies (*continued*)

	Study	Study design, setting and country	Number of children, subtype if available	Mean age (years) at diagnosis, range/SD (years)	Gender (M/F)	Tumour location
12	Boekhoff, 2019[70]	RS, 1 cohort (PS follow-up), MC, Germany	218 Adamantinomatous	9.5 (1.3-17.9)*: Symptomatic CP 9.6 (1.3-17.9) Incidental CP 8.1 (3.7-15.2)	104/114: symCP 101/113 incCP: 3/1	SymCP: extrasellar 44 (20.6%), intra- and extrasellar 153 (71.5%), intrasellar 3 (1.4%), not applicable 14 (6.5%); IncCP: extrasellar 2 (50%), intra- and extrasellar 2 (50%)
13	Cai, 2019[76]	RS, 1 cohort, SC, China	5	9.4 (3-13)	4/1	NR
14	Caldarelli, 2005[90]	RS, 1 cohort, SC, Italy	52	9 (1.67-15.8)	33/19	Intrasellar 3 (5.8%), sellar/suprasellar with prominent prechiasmatic growth 24 (46.2%), retrochiasmatic/third ventricular 14 (26.9%), giant (with an extension into the middle and/or posterior cranial fossae) 11 (21.2%)
15	Capatina, 2018[106]	RS, 1 cohort, SC, Romania	35	12.6, SD 4.2	16/19	NR
16	Chamlin, 1955[52]	RS, 1 cohort, SC, USA	18	NR	NR	NR
17	Chen, 2003[6]	RS, 1 cohort, SC, Australia	17 9 Squamous 6 Adamantinomatous 2 NR	10	NR (for all ages: 17/19)	Children & adults: suprasellar 35 (97.2%), sellar 1 (2.8%)
18	Cherninkova, 1990[102]	RS, 1 cohort, SC, Bulgaria	50	9.5	NR	NR

Table 2. General characteristics of the included studies (*continued*)

	Study	Study design, setting and country	Number of children, subtype if available	Mean age (years) at diagnosis, range/SD (years)	Gender (M/F)	Tumour location
19	d'Avella, 2019[91]	RS, 1 cohort, SC, Italy	8	10.8 (8-16)	NR (8/4 including patients who had been previously surgically treated)	Supradiaphragmatic preinfundibular 2 (25%), supradiaphragmatic preinfundibular suprasellar 1 (12.5), supradiaphragmatic retroinfundibular 1 (12.5) infradiaphragmatic intra-suprasellar 3 (37.5%), infradiaphragmatic intra para-suprasellar 1 (12.5%)
20	Drimtzias, 2014[72]	PS and RS, 1 cohort, SC, UK	20	7.3 (1.25-13.75)	10/10	Suprasellar 20 (100%)
21	Erşahin, 2005[101]	RS, 1 cohort, MC, Turkey	87	10.2 (1.67-18)	51/36	Suprasellar 57 (66%), extended to third ventricle 22 (25%), temporal fossa 1 (1%), anterior cranial fossa 1 (1%), retroclival 4 (5%), temporal and posterior cranial fossa 2 (2%)
22	Fisher, 1998[43]	RS, 1 cohort, SC, USA	30 Adamantinomatous	8.5, SD 5.3. 8.2 (0.74-18.9)*	14/16	Suprasellar 14 (47%), suprasellar and sellar 16 (53%)
23	Fouda, 2019[63]	RS, 1 cohort, SC, USA	135	8.5* (1-21)	70/65	Suprasellar 135 (100%): sellar extension 53 (39%) and third ventricular extension 56 (41%)
24	Gautier, 2012[73]	RS, 1 cohort, two-centre, France	65	< 10 years: 5.5 (4-6)*; 10-18 years: 12.5 (11-15)*	NR	< 10 year: intrasellar 1 (3.1%), extrasellar 9 (28.1%), intra/extrasellar 24 (75%); 10-18 year: intrasellar 3 (10.3%), extrasellar 8 (27.6%), intra/extrasellar 18 (62.1%)
25	Gerganov, 2014[67]	RS, CS, SC, Germany	1 Adamantinomatous	14	NR	Suprasellar, retrosellar and intraventricular 1/1
26	Goldenberg-Cohen, 2011[83]	RS, CS, SC, Israel	4	4.9 (2.5-7.1)	2/2	NR

Table 2. General characteristics of the included studies (*continued*)

	Study	Study design, setting and country	Number of children, subtype if available	Mean age (years) at diagnosis, range/SD (years)	Gender (M/F)	Tumour location
27	*Gonc, 2004*[31]	*RS, 1 cohort, SC, Turkey*	*66*	*8.4 (0.33-16.2)*	*30/36*	*Supra- and intrasellar 38 (58.5%), suprasellar 26 (41%), intrasellar 1 (1.5%)*
28	Greenfield, 2015[60]	RS, 1 cohort, SC, USA	24	7 (2-17.8)*	12/12	NR
29	Haghighatkhah, 2010[104]	RS, CS, NR, Iran	5	8.2 (6-12)	2/2	Suprasellar and sellar 2 (40%), suprasellar 2 (40%), posterior cranial fossa 1 (20%)
30	Hakuba, 1985[86]	RS, CS, SC, Japan	3	7.7 (6-10)	3/0	Suprasellar 3 (100%)
31	*Hoff, 1972*[37]	*RS, 1 cohort, SC, USA*	*16*	*(0.18-13)*	*6/10*	*NR*
32	*Hoffman, 1977*[25]	*RS, 1 cohort, SC, Canada*	*48*	*N = 17: (2-6)* *N = 31: (7-16)*	*24/24*	*NR*
33	Hoffman, 1992[89]	RS, 1 cohort, SC, Canada	50	At time of surgery: 9.39 (1.83-17.58)	28/22	Prechiasmatic 25 (50%), retrochiasmatic 23 (46%), sellar 2 (4%)
34	Hoffmann, 2015[68]	RS, 1 cohort (PS follow-up), MC, Germany	411	NR	NR	Intrasellar 5 (1,2%), suprasellar 61 (14,8%), intra- and suprasellar 169 (41,1%).
35	*Honegger, 1999*[26]	*RS, 1 cohort, SC, Germany*	*30*	*NR*	*NR*	*NR*
36	Hoogenhout, 1984[93]	RS, 1 cohort, SC, The Netherlands	12	(0-15)	9/3	Children & adults: intra- and extrasellar 7 (25%), extrasellar 22 (75%)
37	Im, 2003[97]	RS, CS, SC (except one case who had been treated at another hospital), Korea	6	10.7 (5-14)	2/4	Intrasellar (pre-chiasmatic) 6 (100%)
38	Jane Jr., 2010[64]	RS, 1 cohort, SC, USA	11	12.3 (7-16)	6/5	Sellar and/or suprasellar 10 (90.9%), third ventricle 1 (9.1%)

Table 2. General characteristics of the included studies (*continued*)

	Study	Study design, setting and country	Number of children, subtype if available	Mean age (years) at diagnosis, range/SD (years)	Gender (M/F)	Tumour location
39	Jung, 2010[98]	RS, 1 cohort, SC, Korea	17	12 (4-18)*	12/5	Suprasellar 10 (58.8%), supra- and intrasellar 7 (41.2%)
40	Karavitaki, 2005[48]	RS, 1 cohort, MC, UK	42	10 (2.5-15)* available in n= 35	23/19	Intrasellar 1 (2.9%), extrasellar 13 (38.2%), intra- and extrasellar 20 (58.8%) available in n = 34
41	Kennedy, 1975[39]	RS, 1 cohort, SC, UK	14	(0-13)	NR (for all ages: 22/23)	NR
42	Kiran, 2008[79]	RS, case reports (2x), SC, India	2	8 (6-10)	1/1	Suprasellar with extension into the third ventricle and subtemporal extension to the left side with posterior extension 1 (50%), suprasellar with extension into third ventricle and posterior fossa 1 (50%)
43	*Kramer, 1960[38]*	*RS, CS, MC, UK*	*6*	*10 (6.5-14)*	*5/1*	*Suprasellar 4 (66.7%)*
44	Lee, 2008[108]	RS, 1 cohort, SC, Taiwan	66	8.02, SD 4.28; 7.0 (1.42-17.58)*	40/26	Intrasellar 27 (40.9%), third ventricular 39 (59.1%)
45	*Lena, 2005[24]*	*RS, 1 cohort, SC, France*	*47*	*N = 7: < 3 years* *N = 10: (3-5)* *N = 18: (6-10)* *N = 12: > 10 years*	*27/20*	*Intrasellar 14 (29.8%): anterosuperior extension 9, pure intrasellar 3 and intrasphenoidal extension 2; infundibulotuberous 25 (53.2%); pure intraventricular 1 (2.1%); global/giant 7 (14.9%)*
46	Leng, 2012[58]	RS, 1 cohort, SC, USA	3	10.3 (5-15)	2/1	Sellar, suprasellar, retrochiasmatic 2 (67%); sellar, suprasellar, subchiasmatic 1 (33%)
47	Merchant, 2002[65]	RS, 1 cohort, SC, USA	30	8.6 (1-15)*	13/17	NR
48	Mohd-Ilham, 2019[7]	RS, 1 cohort, SC, Malaysia	11	9.5 (3-16)	7/4	Suprasellar 11 (100%)
49	*Mottolese, 2001[33]*	*RS, 1 cohort, SC, France*	*14*	*NR*	*NR*	*NR*

Table 2. General characteristics of the included studies (*continued*)

	Study	Study design, setting and country	Number of children, subtype if available	Mean age (years) at diagnosis, range/SD (years)	Gender (M/F)	Tumour location
50	Nielsen, 2012[103]	RS, 1 cohort, MC, Denmark	39	< 15 years	NR	Intrasellar 27 (75%), intrasellar only 1 (2.7%), parasellar 10 (28.6%), suprasellar 36 (97.3%)
51	*Ohmori, 2007[28]*	*RS, 1 cohort, SC, USA*	*27*	*9.0 (2-17)*	*17/10*	*NR*
52	Ono, 1996[87]	RS, 1 cohort, SC, Japan	19 Adamantinomatous	8.1 (2-17)*	11/8	Prechiasmatic 11 (45.8%), retrochiasmatic 7 (29.2%), sellar 1 (4.2%)
53	Pascual, 2018[55]	RS, 1 cohort, SC, USA	35 Adamantinomatous	11.4 (5-18)	18/17	Suprasellar pseudointraventricular 7 (20.0%), infundibulo-tuberal 6 (15.8%), sellar/suprasellar-secondary intraventricular 15 (39.5%), sellar/suprasellar 6 (15.8%), all intracranial spaces (giant) 1 (2.63%)*
54	Patel, 2017[56]	RS, 1 cohort, SC, USA	10	11.5 (5.9-15.0)	6/4	Sellar- and suprasellar 4 (40%), sellar, suprasellar and intraventricular 1 (10%), sellar, suprasellar and subchiasmatic 1 (10%), suprasellar 3 (30%), extracranial, infrasellar, nasal cavity and sphenoid sinus 1 (10%)
55	Puget, 2007[14]	RS and PS, 2 cohorts, SC, France	88	RS cohort: 7.4 (1-16)*; PS cohort: 8 (2.8-14)*	RS cohort: 42/24; PS cohort: 13/9	Prechiasmatic 20 (30%), retrochiasmatic 60 (91%), intraventricular 45 (68%), intrasellar 46 (70%)
56	Qi, 2012[77]	RS, 1 cohort (2 subgroups), SC, China	81	Group A: 8.26 ± 4.03; Group B: 9.15 ± 3.83	Group A: 23/11 Group B: 26/21	Group A: intra- and infrasellar 34 (42.0%); Group B: third ventricle: 47 (58%)
57	Quon, 2019[57]	RS, 1 cohort, SC, USA	16	11.8 (5.9-16)*	11/5	Suprasellar extension 15 (94%), NR 1 (6%)
58	Rath, 2013[96]	RS, 1 cohort, SC, Australia	10 Adamantinomatous	9.4 (2.4-17.6)	NR	NR

Table 2. General characteristics of the included studies (*continued*)

	Study	Study design, setting and country	Number of children, subtype if available	Mean age (years) at diagnosis, range/SD (years)	Gender (M/F)	Tumour location
59	Richmond, 1980[61]	RS, 1 cohort, SC, USA	21	0-4 years: 4/21, 5-8 years: 4/21, 9-12 years: 8/21, 13-16 years: 1/21, 17-20 years: 4/21	11/10	NR
60	Salunke, 2016[80]	RS, case reports, SC, India	2	12.3 (8-18)	2/1	Suprasellar 2 (66%); suprasellar with erosion of sphenoid bone 1 (33%)
61	*Sankhla, 2015*[27]	*RS, cohort, SC, India*	*6*	*13 (10-15)*	*4/2*	*NR*
62	Shammari, 2012[100]	RS, 1 cohort, SC, Saudi Arabia	2	NR (only for children & adults together)	1/1	Suprasellar 2 (100%)
63	Shi, 2017[78]	RS, 1 cohort, SC, China	348 Adamantinomatous	9.17	218/130	NR
64	Sogg, 1977[109]	RS, CS, centre NR, country NR	2	7.5 (6-9)	0/2	Third ventricle, tuber cinereum and the pituitary stalk 1 (50%), NR 1
65	*Stahnke, 1984*[29]	*RS, cohort, SC, Germany*	*28*	*8.4, SD 3.3 (2.5-14.5)*	*17/11*	*Suprasellar 13 (46.4%), intra- and suprasellar 11 (39.3%), intrasellar 4 (14.3%)*
66	Suharwardy, 1997[9]	RS, cohort, SC, UK	5	NR	NR	NR
67	Synowitz, 1977[69]	RS, CS, SC, Germany	3	8.3 (6-12)	NR	Sellar 1 (33%), suprasellar 1 (33%), NR 1 (33%)
68	Tamasauskas, 2014[105]	RS, CS, SC, Lithuania	9 Adamantinomatous 8, Papillary 1	8.0 (0.83-17)	6/3	Suprasellar 3 (33%), suprasellar and intrasellar 3 (33%), suprasellar, intrasellar and parasellar 1 (11%), suprasellar, parasellar and retrosellar 1 (11%), suprasellar and parasellar 1 (11%)

Table 2. General characteristics of the included studies (*continued*)

	Study	Study design, setting and country	Number of children, subtype if available	Mean age (years) at diagnosis, range/SD (years)	Gender (M/F)	Tumour location
69	Tan, 2017[42]	RS, 3 cohorts, MC, UK	185	Group A: 6.60 (1.00-16.40), 7.70 (NA), Group B: 8.60 (7.23-9.99), 9.01 (3.83-16.00), 10.6 (3.50-16.20), 10.80 (1.50-15.50)	85/100	NR
70	Taphoorn, 2002[94]	RS, CS, SC, The Netherlands	3	10.3 (6-13)	2/1	Foramen intraventricular 1 (33%), suprasellar with chiasm compression & enlargement ventricles 1 (33%), sellar 1 (33%)
71	Taylor, 2012[74]	RS, 1 cohort, SC, France	56	7.5 (6.6-8.5); 7.0 (4.9-9.9)*	36/20	NR
72	*Thomsett, 1980[32]*	*RS, 1 cohort, SC, USA*	*42*	*9.2 (1.8-17.2)*	*24/18*	*NR*
73	Tomita, 2005[66]	RS, 1 cohort, SC, USA	54	8.2 (0.92-16)*	28/26	NR
74	Villani, 1997[92]	RS, 1 cohort (PS follow-up), SC, Italy	27	11 (6-16)	NR	Intrasellar 2 (7.4%), intrasuprasellar 13 (48.2%), suprasellar extraventricular 7 (25.9%), intra- and extra-ventricular 4 (14.8%), intraventricular 1 (3.7%)
75	Vries de, 2003[85]	RS, 1 cohort, SC, Israel	36	9.2. 7.8 (0.3-22.2)*	19/17	NR
76	Wan, 2018[10]	RS, CS, SC, Canada	59	9.4 (0.7-18.0)	27/32	NR
77	Weiss, 1989[59]	RS, 1 cohort, SC, USA	31	9.9 (1-19)*	12/19	NR
78	Wijnen, 2017[95]	RS, 1 cohort, SC, The Netherlands	63	8 (5-12)*	25/38	Intrasellar 3 (5%), suprasellar 23 (38%), intra- and suprasellar 34 (57%)
79	*Winkfield, 2011[34]*	*RS, 1 cohort, SC, USA*	*79*	*At initial treatment: 8.5 (0.8-24.7)**	*43/36*	*NR*

Table 2. General characteristics of the included studies (*continued*)

	Study	Study design, setting and country	Number of children, subtype if available	Mean age (years) at diagnosis, range/SD (years)	Gender (M/F)	Tumour location
80	Yamada, 2018[88]	RS, 1 cohort, SC, Japan	45	At time of surgery: 9.6 (0.8-17.9)	37/28	Subdiaphragmatic 26 (58%): 3 sellar, 23 suprasellar; supradiaphragmatic 19 (42%): 1 purely intraventricular
81	Yano, 2016[19]	RS, 1 cohort, SC, Japan	26	7.3 (4-14)	10/16	NR
82	Yu, 2015[46]	RS, 1 cohort, SC, France	15	6.9 (0.25-14)	9/6	Sellar region with extension to the posterior cranial fossa 15 (100%)
83	*Zhang, 2008*[30]	*RS, 1 cohort, SC, China*	*202*	*9.3 ± 3.6 (1-15)*	*115/87*	*NR*
84	Zhou, 2009[75]	RS, CS, SC, China	5	12 (9-18)	3/2	Posterior fossa 5 (100%): sellar 5 (100%), extension to cerebellopontine angle 5 (100%), infraclivus 2 (40%)

Abbreviations: CS, case series; UK, United Kingdom; USA, United States of America; GKSR, gamma knife stereotactic radiosurgery; MC, multicentre; NR, not reported; PS, prospective; P-32, phosphorus-32; RS, retrospective; SC, single-centre.
Studies in italics indicate studies retrieved by reference screening.
*Median age.

Table 3. Overview of visual function in children with craniopharyngioma at diagnosis

	Study	Children with availability of vision data	Visual disturbance as symptom	Visual impairment	Decreased VA with description
1	Al-Mefty, 1985[99]	VA: 15/20 VF: 9/20	NR	NR	15/15: Severe decrease in both eyes 8/15, totally blind in both eyes 5/15, totally blind in one eye with decreased VA in the other eye 2/15
2	Albright, 2005[51]	NR	NR	Intracavitary irradition P-32: 4/44 Microneurosurgical tumour resection and GKSR: VI was one of the predominant neurological symptoms	NR
3	Ali, 2013[54]	NR	2/7	4/7	Blurry vision 1/7
4	Ammirati, 1988[71]	2/3	1/3	2/3	2/3: VA 20/100: 1/4 eyes, VA 20/200: 1/4 eyes, LP: 1/4 eyes
5	Anderson, 1989[53]	2/2	1/2	2/2	2/2: VA 20/25; CF at 1 foot 1/2, VA: 20/300; CF at 2 feet 1/2
6	Ansari, 2016[62]	NR	5/9	5/9	NR
7	Artero, 1984[107]	VA: 21/24, VF: 18/24	5/24	22/24	Decreased VA 17/21
8	Ashkenazi, 1990[82]	NR	5/12	NR	Decreased VA 5/12
9	*Bartlett, 1971*[35]	*NR*	*23/30*	*NR*	*NR*
10	Behari, 2003[81]	2/2	2/2	2/2	2/2 6/24: 1/4 eyes, 6/18: 2/4 eyes, 6/12: 1/4 eyes

Decreased VF with description	Orthoptic examination	Fundoscopy	Other vision related defects	Ophthalmological examination	Ophthalmological definitions
Bitemporal defects 6/9, only central VF 1/9	NR	Papilledema 7, optic atrophy 7, Foster-Kennedy syndrome 3	NR	NR	NR
NR	NR	NR	NR	NR	NR
NR	Diplopia 1/7	NR	NR	Yes (not specified)	NR
Bitemporal hemianopia 2/3	NR	NR	NR	NR	NR
Homonymous hemianopia 1/2, temporal hemianopia 1/2	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR
16/18: Homonymous defects 5/18, temporal defects 14/18 (of whom 7/18 had bitemporal defects)	Diplopia 2/24	Abnormal ocular fundus 19/24, optic atrophy or pallor 14/24 (unilateral 6/24), papilledema 7/24	NR	VA and campimetric determinations, fundoscopy and examination of ocular motility when the age and/or clinical condition allowed them to be performed.	NR
Reduction 3/12	NR	NR	NR	NR	NR
NR	*NR*	*Papilledema 13/30*	*NR*	*NR*	*NR*
NR	Bilateral sixth nerve palsy 1/2	Bilateral papilledema 1/2	NR	NR	NR

Table 3. Overview of visual function in children with craniopharyngioma at diagnosis (*continued*)

	Study	Children with availability of vision data	Visual disturbance as symptom	Visual impairment	Decreased VA with description
11	Bialer, 2013[84]	13/20	1/11	4/11	≤ 20/200 in at least one eye 7/11
12	Boekhoff, 2019[70]	NR	Symptomatic CP 54/214	Symptomatic CP 54/214, Incidental CP 1/4	NR
13	Cai, 2019[76]	NR	NR	3/5	NR
14	Caldarelli, 2005[90]	NR	NR	17/52	Reduction of VA 13/52
15	Capatina, 2018[106]	NR	NR	NR	22/35: Defect 11/35, decrease 15/35, uni- or bilateral blindness 7/35
16	Chamlin, 1955[52]	NR	NR	NR	Loss of central VA 12/18

Decreased VF with description	Orthoptic examination	Fundoscopy	Other vision related defects	Ophthalmological examination	Ophthalmological definitions
Bilateral temporal 4/15, unilateral temporal 3/15, right inferior homonymous quadrantanopia 1/15	RAPD 8/13, unilateral exotropia 6/13, sixth nerve palsy 2/13, monocular nystagmus 1/13, diplopia 3/13	Papilledema 3/13, optic disc pallor 10/13: bilateral 7, unilateral 3	NR	BCVA, Humphrey Field Analyzer	NR
Incidental CP: impaired VF right side 1/4	NR	NR	NR	NR	NR
NR	NR	NR	NR	VA and VF testing.	Visual outcome was graded as improved, stable, or deteriorated.
9/52	Sixth nerve deficit 5/52, third nerve deficit 1/52, nystagmus 2/52	NR	NR	NR	NR
18/35	NR	NR	NR	Yes (not specified)	NR
Bitemporal hemianopia 18/18	NR	Optic atrophy 14/18, papilledema 4/18	Proptosis 1/18	VF, optic discs, central VA (Snellen) and other ocular signs (extraocular muscle palsies, pupillary changes, involvement of NV, papilledema, proptosis, nystagmus)	As an indication of visual loss they took a very definite drop in VA (e.g. from a known 20/20 to 20/40 or less), or a reliable statement from the patient that his vision was definitely failing.

Table 3. Overview of visual function in children with craniopharyngioma at diagnosis (*continued*)

	Study	Children with availability of vision data	Visual disturbance as symptom	Visual impairment	Decreased VA with description
17	Chen, 2003[6]	16/17	15/17	13/17	< 6/12: 6/17 (40%), ≥ 6/12: 10/17 (60%)
18	Cherninkova, (1990)[102]	NR	NR	NR	Reduced VA 32/46. Bilaterally reduced VA: under 0.1 6/50; over 0.1 17/50, amaurosis in one eye and reduced VA in the other 2/50, amaurosis in one eye and normal VA in the other 3/50, bilateral amaurosis 1/50, reduced VA in one eye and normal in the other 3/50
19	d'Avella, 2019[91]	NR	7/8	NR	Left eye VA reduction 1/8
20	Drimtzias, 2014[72]	VA: 20/20 VF: 14/20	12/20	12/20	11/20: Mild-moderate 8/40 eyes, severe 13/40 eyes, normal 19/40 eyes
21	Erşahin, 2005[101]	NR	NR	NR	Blindness 13/87, visual disturbance and decreased VA 21/87
22	Fisher, 1998[43]	NR	19/30	19/30	Loss of VA 17/30

	Decreased VF with description	Orthoptic examination	Fundoscopy	Other vision related defects	Ophthalmological examination	Ophthalmological definitions
	Bitemporal hemianopia 9/17, unilateral hemianopia 1/17, homonymous hemianopia 1/17, normal VF 3/17, data NA 3/17	Strabismus 3/17, RAPD 10/17	Bilateral (optic) atrophy 10/17, bilateral papilledema 4/17	NR	BCVA, Ishihara colour testing, RAPD, fundoscopy, cranial nerve examination, perimetry testing with Humphrey field analyser, Goldman perimetry or Bjerrum screen.	Normal if BCVA ≥ 6/12
	VF defects 21/31. Bitemporal hemianopia 5/31, amaurosis of one eye and temporal defect of the other eye 3/31, bilateral temporal narrowing of perimeters 5/31, homonymous hemianopia 2/31, bilateral concentric narrowing of the visual field 5/32, other defects 1/31	Nystagmus 4/50, paresis of cranial nerve 6/50	Optic nerve atrophy: unilateral 7/50, bilateral 19/50, congestive optic papilla 11/50	NR	Ophthalmological examinations were performed by routine methods. In small children and patients in a serious condition a thorough study was not always possible.	NR
	Bitemporal hemianopia 3/8, bilateral superior quadrantanopia 1/8, right temporal hemianopia 1/8	NR	NR	Right amauro-sis 1/8	VA, computerized VF examination.	NR
	10/14: bitemporal hemianopia 5/14	NR	Optic atrophy 12/20, bilateral papilledema 6/20	NR	BCVA (logMAR or Preferential Looking charts). VF with Goldmann perimetry	VA: normal (grade 8), mild-moderate visual loss (grade 5, 6, 7), severe visual loss (grade 1, 2, 3, 4).
	10/87	Abducens paralysis 2/87, nystagmus 3/87, diplopia and squint 7/87	Papilledema 5/87, optic atrophy 29/87	NR	NR	NR
	Loss of VF 14/30	NR	NR	NR	NR	NR

Table 3. Overview of visual function in children with craniopharyngioma at diagnosis (*continued*)

	Study	Children with availability of vision data	Visual disturbance as symptom	Visual impairment	Decreased VA with description
23	Fouda, 2019[63]	NR	56/135	56/135	Impaired VA 26/135
24	Gautier, 2012[73]	53/65	40/53	40/53	Only reported together with VF 40/53
25	Gerganov, 2014[67]	NR	1/1	1/1	NR
26	Goldenberg-Cohen, 2011[83]	3/4	2/4	3/4	3/4
27	*Gonc, 2004[31]*	*64/66*	*23/66*	*NR*	*20/64: Unilateral 14/64, bilateral 6/64*
28	Greenfield, 2015[60]	NR	NR	21/24	VA and VF deficits 16/24, legally blind (BCVA <20/200) 1/24
29	Haghighatkhah, 2010[104]	NR	NR	2/5	Visual loss 1/5, left eye blindness 1/5
30	Hakuba, 1985[86]	NR	1/3	1/3	Failing vision 1/3
31	*Hoff, 1972[37]*	*12/16*	*NR*	*7/12*	*NR*
32	*Hoffman, 1977[25]*	*NR*	*47/48*	*47/48*	*Significantly reduced unilaterally 17/48, significantly reduced bilaterally 11/48*
33	Hoffman, 1992[89]	NR	29/50	29/50	Decreased in one or both eyes 21/50, blind in one eye 4/50
34	Hoffmann, 2015[68]	130/411	161/291	NR	NR

Decreased VF with description	Orthoptic examination	Fundoscopy	Other vision related defects	Ophthalmological examination	Ophthalmological definitions
Impaired VF 39/135	NR	Papilledema 51/135	NR	NR	NR
Only reported together with VA 40/53	NR	NR	NR	NR	Blindness: VA of 1/10 or less in both eyes.
NR	NR	NR	NR	Uniformly subjected preoperative ophthalmological assessment	NR
NR	Diplopia 1/4, esotropia 1/4, exotropia 1/4, mono-nystagmus 1/4	Papilledema 1/4, optic atrophy 2/4, mild pallor 1/4	NR	BCVA and a comprehensive neuro-ophthalmologic evaluation.	Severe visual loss was defined as counting fingers or less.
Bitemporal hemianopia 22/64	*Diplopia 3/66*	*Optic atrophy 27/64, papilledema 26/64*	*NR*	*NR*	*NR*
VA and VF deficits 16/24	Diplopia 8/24	NR	NR	NR: only at follow-up.	Legally blind if corrected VA <20/200 in the better eye.
NR	NR	NR	NR	NR	NR
Bitemporal hemianopia 1/3	NR	Papilledema 2/3	NR	NR	NR
NR	*NR*	*Papilledema 2/12, optic atrophy 7/12*	*NR*	*Satisfactory eye examination in 12/16 children.*	*NR*
Hemianopia 33/48: bitemporal 25/48, homonymous 4/48, unilateral temporal 4/48	*Seesaw nystagmus 3/48*	*Papilledema 13/48*	*NR*	*NR*	*VA ≥ 20/40 bilaterally (mild visual loss); VA < 20/40 in one eye (moderate visual loss); VA < 20/40 bilaterally (severe visual loss).*
19/50: bitemporal hemianopia 8/50	Diplopia 4/50, seesaw nystagmus 2/50	NR	NR	No	NR
NR	NR	NR	NR	NR	NR

Table 3. Overview of visual function in children with craniopharyngioma at diagnosis (*continued*)

	Study	Children with availability of vision data	Visual disturbance as symptom	Visual impairment	Decreased VA with description
35	*Honegger, 1999*[26]	*NR*	*10/30*	*NR*	*NR*
36	Hoogenhout, 1984[93]	NR	7/12	NR	NR
37	Im, 2003[97]	NR	5/6	NR	NR
38	Jane Jr., 2010[64]	NR	NR	NR	NR
39	Jung, 2010[98]	NR	NR	4/17	NR
40	Karavitaki, 2005[48]	41/42	NR	NR	Decreased 16/39
41	Kennedy, 1975[39]	VA 12/14, VF NR	NR	NR	Diminished vision 7/14
42	Kiran, 2008[79]	2/2	1/2	1/2	6/9 bilateral: 1/2
43	*Kramer, 1960*[38]	*6/6*	*3/6*	*3/6*	*2/6: 6/60: 1/6*
44	Lee, 2008[108]	NR	21/66: Intrasellar 15/27; third ventricular 6/39	NR	NR
45	*Lena, 2005*[24]	*NR*	*32/47*	*32/47*	*Blindness: bilateral 2/47, unilateral 3/47*

Decreased VF with description	Orthoptic examination	Fundoscopy	Other vision related defects	Ophthalmological examination	Ophthalmological definitions
NR	*NR*	*NR*	*NR*	*NR*	*NR*
NR	NR	NR	NR	Visual fields	NR
NR	NR	NR	NR	NR	NR
4/11	NR	NR	NR	Formal visual field testing for patients with visual complaints.	NR
NR	NR	NR	NR	Method used described by Fahlbusch and Schott to analyze ophthalmological findings (VA and VF).	NR
19/41 VF defects: bitemporal hemianopia 11/41	NR	Papilledema 12/41, optic atrophy 2/41	NR	NR	NR
7/14	Strabismus 5/14; rotatory nystagmus 1/14	Optic atrophy 9/14, papilledema 6/14	NR	VA, ocular movements, pupil reactions, ophthalmoscopy and VF testing using the Bjerrum screen.	NR
NR	NR	Optic atrophy 1/2	NR	VA, pupils and fundus examination	NR
Bitemporal hemianopia 2/6, loss of right nasal field 1/6	*Right vertical and left rotatory nystagmus 1/6*	*Papilledema 3/6, optic atrophy 3/6*	*NR*	*Yes (not specified)*	*NR*
NR	NR	NR	NR	NR	NR
Pure VF defect 3/47, VF defect and decreased VA 23/47	*NR*	*Papilledema 13/47*	*NR*	*Yes (not uniformly performed on all patients due to young age and emergency presentation).*	*NR*

Table 3. Overview of visual function in children with craniopharyngioma at diagnosis (*continued*)

	Study	Children with availability of vision data	Visual disturbance as symptom	Visual impairment	Decreased VA with description
46	Leng, 2012[58]	NR	1/3	1/3	NR
47	Merchant, 2002[65]	NR	17/30	NR	NR
48	Mohd-Ilham, 2019[7]	11/11	4/11	4/11	BCVA ≥ 6/6-6/12: 13/22 eyes, BCVA 6/15-6/60: 3/22 eyes, BCVA < 6/60: 6/22 eyes
49	*Mottolese, 2001[33]*	*NR*	*2/20*	*2/20*	*NR*
50	Nielsen, 2012[103]	NR	NR	NR	Reduction 21/32, blindness 1/39
51	*Ohmori, 2007[28]*	*NR*	*15/27 (55%)*	*NR*	*NR*
52	Ono, 1996[87]	NR	NR	15/19. Mean visual score at diagnosis 68.4.	NR
53	Pascual, 2018[55]	NR	35/35	35/35	NR

Decreased VF with description	Orthoptic examination	Fundoscopy	Other vision related defects	Ophthalmological examination	Ophthalmological definitions
NR	NR	NR	NR	Neuro-ophthalmological evaluation and formal visual field testing when possible.	NR
NR	NR	NR	NR	NR	NR
Temporal hemianopia 5/22 eyes: bilateral 2/22 eyes, unilateral 3/22 eyes; scotoma 3/22 eyes: central 2/22 eyes, inferior 1/22 eyes; quadrantanopia 2/22 eyes; constricted 1/22 eyes. VF is NA in 5 patients	Squint 2/11, diplopia 1/11, RAPD 7/11	Optic atrophy 11/11, papilledema 2/11	Colour defect 4/11	BCVA, VF (confrontational test or Humphrey visual field test), colour vision, light brightness, RAPD, fundus examination and cranial nerves examination.	BCVA ≥ 6/12 (good) during presentation. Visual loss was defined as blurring of vision in both eyes.
NR	*NR*	*NR*	*NR*	*NR*	*NR*
Reduction 12/26	NR	NR	Ophthal-moplegia 5/31	VA and VF testing.	NR
NR	*NR*	*NR*	*NR*	*For 21 patients only initial outcome data is available. 6 patients underwent extensive outcome analysis, including ophthalmological testing.*	*NR*
NR	NR	NR	NR	VA and VF testing. Visual scores were assigned in order to evaluate visual functions digitally assessing both VA and VF (0-100 points).	NR
NR	Diplopia 14/35, sixth nerve palsy 1/35	NR	NR	Yes (not specified)	NR

Table 3. Overview of visual function in children with craniopharyngioma at diagnosis (*continued*)

	Study	Children with availability of vision data	Visual disturbance as symptom	Visual impairment	Decreased VA with description
54	Patel, 2017[56]	NR	7/10	7/10	NR
55	Puget, 2007[14]	NR	RS cohort: 30/66 PS cohort: 14/22	NR	Blindness 10/66
56	Qi, 2012[77]	NR	Group A: 34/34 Group B: 24/47	57/81	Unilateral/bilateral blindness or light perception: Group A: 12/34 Group B: 3/47.
57	Quon, 2019[57]	NR	NR	11/16	Vision loss 4/16, blurry vision 2/16
58	Rath, 2013[96]	10/10	4/10	7/10	Mild VA deficit or field cut 4/10, unilateral blindness, homonymous hemianopia or bitemporal hemianopia 2/10, bilateral blindness or near functional blindness (unrelated) 1/10
59	Richmond, 1980[61]	NR	9/21	NR	Decreased VA: bilateral 2/21, unilateral 7/21 (3 blind). Unilateral blind 3/21.
60	Salunke, 2016[80]	2/2	2/2	2/2	2/2: 6/18: 2/4 eyes, 6/24: 1/4 eyes, PL plus 1/4 eyes
61	*Sankhla, 2015[27]*	*NR*	*3/6*	*NR*	*NR*

Decreased VF with description	Orthoptic examination	Fundoscopy	Other vision related defects	Ophthalmological examination	Ophthalmological definitions
NR	NR	Papilledema 1/10	NR	NR	NR
NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR
Bilateral hemianopia 1/16, bitemporal hemianopia 2/16; VF deficit 3/16	NR	Papilledema 3/16, optic nerve compression 1/16	Proptosis 1/16	Complete work-up by an ophthalmologist when visual symptoms or signs were present.	NR
Mild VA deficit or field cut 4/10, unilateral blindness, homonymous hemianopia or bitemporal hemianopia 2/10, bilateral blindness or near functional 2 blindness (unrelated) 1/10	Right exotropia 1/10	Papilledema 1/10	NR	NR	1) Normal acuity and fields (3/10); 2) Mild acuity deficit or field cut (4/10); 3) Unilateral blindness, homonymous hemianopia or bitemporal hemianopia (2/10); 4) Bilateral blindness or near functional blindness (1/10)
12/21 (3 of them had a combination of two findings). Temporal: unilateral 4/21; bilateral 3/21, homonymous 4/21, scotoma 1/21	NR	Optic atrophy: unilateral 2/21; bilateral 5/21, papilledema 2/21	NR	Yes (not further specified)	NR
Bitemporal hemianopia 2/2	NR	NR	NR	NR	NR
NR	*NR*	*NR*	*NR*	*NR*	*NR*

Table 3. Overview of visual function in children with craniopharyngioma at diagnosis (*continued*)

	Study	Children with availability of vision data	Visual disturbance as symptom	Visual impairment	Decreased VA with description
62	Shammari, 2012[100]	NR	2/2	1/2	NR
63	Shi, 2017[78]	NR	NR	99/348	NR
64	Sogg, 1977[109]	2/2	2/2	2/2	2/2: 20/100: 1/4 eyes, 20/50: 1/4 eyes, 20/400: 1/4 eyes, 20/200: 1/4 eyes
65	*Stahnke, 1984[29]*	*NR*	*12/28*	*24/28*	*Decreased VA 11/28*
66	Suharwardy, 1997[9]	5/5	1/5	5/5	6/24 2/10 eyes, NPL 1/10 eyes, 6/12 2/10 eyes, 6/9 1/10 eyes, 6/6 2/10 eyes, 1/60 1/10 eyes, HM 1/10 eyes
67	Synowitz, 1977[69]	3/3	3/3	3/3	Fingerzahlen right/1 m and Handbewegung left/50 cm (1/3), LP (1/3), NR (1/3)
68	Tamasauskas, 2014[105]	7/9	4/9	4/9	RE=LE= 5/10: 1, RE= 1 and LE=1/1000: 1

Decreased VF with description	Orthoptic examination	Fundoscopy	Other vision related defects	Ophthalmological examination	Ophthalmological definitions
NR	Rotatory nystagmus 1/2, horizontal pendular nystagmus 1/2	Temporal disc pallor both eyes 2/2	NR	Ophthalmic records were reviewed.	NR
NR	NR	NR	NR	NR	NR
Bitemporal hemianopia 2/2	NR	Papilledema 1/2, optic pallor 1/2	NR	VA and VF testing (red test and large white test objects; Goldmann perimetry), fundoscopy.	NR
VF defect 16/28	*NR*	*Optic atrophy 11/28, papilledema 4/28*	*NR*	*Ophthalmological examination.*	*NR*
VF in the better eye: temporal defect 1/5, bitemporal hemianopia 1/5, asymmetric binasal loss with enlarged blind spots 1/5, right probable temporal loss 1/5, left supero-temporal loss 1/5	RAPD 5/5	Bilateral optic atrophy 1/5, papilledema 2/5, left disc pallor 1/5, bilateral disc pallor 1/5	NR	A full ophthalmological examination including VA and VF testing (in most cases possible with a Snellen chart and Goldmann field respectively), optic discs, colour vision and pupil responses.	NR
NR	Nystagmus 2/3	Optic atrophy 2/3, papilledema 2/3	NR	Yes (not further specified)	NR
Bitemporal hemianopia 2/9, homonymous hemianopia 1/9	NR	NR	NR	VA and VF testing before surgery and after surgery.	NR

Table 3. Overview of visual function in children with craniopharyngioma at diagnosis (*continued*)

	Study	Children with availability of vision data	Visual disturbance as symptom	Visual impairment	Decreased VA with description
69	Tan, 2017[42]	136/185	90/136	90/136	NR
70	Taphoorn, 2002[94]	3/3	1/3	3/3	Decreased VA 1/3
71	Taylor, 2012[74]	NR	27/56	NR	Reduced VA
72	*Thomsett, 1980*[32]	*NR*	*15/42*	*15/42*	*Decreased VA 14/33*
73	Tomita, 2005[66]	NR	23/54	23/54	Decreased VA 13/54: monocular 10, binocular 11.
74	Villani, 1997[92]	NR	16/27	16/27	Decreased VA 16/27
75	Vries de, 2003[85]	NR	8/36	NR	NR
76	Wan, 2018[10]	59/59	18/59	25/59	Visual impairment in at least 1 eye 25/59, binocular visual impairment 16/59, legally blind in both eyes 4/59
77	Weiss, 1989[59]	NR	24/31	24/31	VA and/or VF 19/31
78	Wijnen, 2017[95]	VA: 46/63 VF: 39/63	NR	NR	33/46

Decreased VF with description	Orthoptic examination	Fundoscopy	Other vision related defects	Ophthalmological examination	Ophthalmological definitions
NR	NR	NR	NR	VA and VF were assessed by experienced ophthalmologists. Children unable to cooperate were given a score based on visual evoked potentials.	NR
Bitemporal hemianopia 1/3, partial homonymous hemianopia 2/3	Diplopia 1/3	Papilledema 2/3	NR	NR	NR
NR	Strabismus, nystagmus	NR	NR	NR	NR
VF defect 13/32	*Cranial nerve palsy 12/42*	*Optic atrophy 11/29, papilledema 9/42*	*NR*	*NR*	*NR*
VF defect 2/54	Diplopia 3/54, strabismus 2/54	NR	NR	NR	NR
11/27	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR
NR	Diplopia or strabismus 7/59	Optic nerve edema 25/59, optic nerve pallor 24/59	NR	VA (preferential looking if vision too poor or pre-verbal) and VF testing (automated Humphrey, dynamic Goldmann or confrontation), fundoscopy.	Visual decline: defined as a move from a higher to lower category of visual function in 1 or 2 eyes. Visual outcomes were grouped normal, impaired and legally blind.
VA and/or VF 19/31	Sixth nerve deficit 4/31: unilateral 2, bilateral 2	Asymptomatic papilledema or optic atrophy 5/31	NR	NR	NR
23/39	NR	NR	NR	VA was determined after correction for refraction disorders. Goldmann perimetry for VF testing.	NR

Table 3. Overview of visual function in children with craniopharyngioma at diagnosis (*continued*)

	Study	Children with availability of vision data	Visual disturbance as symptom	Visual impairment	Decreased VA with description
79	*Winkfield, 2011*[34]	*NR*	*46/79*	*NR*	*NR*
80	Yamada, 2018[88]	42/45 (3 patients could not be assessed due to their young age)	12/45	28/42	NR
81	Yano, 2016[19]	NR	14/26	NR	NR
82	Yu., 2015[46]	14/15	NR	13/15	Decreased vision 13/14
83	*Zhang, 2008*[30]	*NR*	*NR*	*113/202*	*NR*
84	Zhou, 2009[75]	NR	4/5	1/5	NR

Abbreviations: BCVA, best corrected visual acuity; GKSR, gamma knife stereotactic radiosurgery; HM, hand motion; NA, not available; NPL, no perception of light; NR, not reported; OU, both eyes; PL, perception of light; P-32, phosphorus-32; VA, visual acuity; VF, visual field; VI, visual impairment.
Studies in italics indicate studies retrieved by reference screening.

	Decreased VF with description	Orthoptic examination	Fundoscopy	Other vision related defects	Ophthalmological examination	Ophthalmological definitions
	NR	*NR*	*Papilledema 25/76*	*NR*	*NR*	*NR*
	NR	NR	NR	NR	Yes (except the youngest in whom testing was difficult): VA and VF testing before and 2 weeks after surgery.	NR
	NR	NR	NR	NR	NR	NR
	NR	Cranial nerve palsy 3/15	NR	NR	NR	NR
	NR	*NR*	*NR*	*NR*	*NR*	*NR*
	Hemianopia 1/5	Diplopia 1/5, bidiplopia 1/5, dilated pupil on the left 2/5	Bipapilledema 3/5	NR	NR	NR

Table 4. Risk of bias assessment for cohort studies using the New-Ottawa Scale (NOS)

Number	Study	Selection				Comparability		Outcome		Total number of stars
		Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
1	Al-Mefty, 1985[99]		*	*	*	NA	*	NA	NA	4
2	Albright., 2005[51]	*	*	*	*	NA		NA	NA	4
3	Ali, 2013[54]		*	*	*	NA		NA	NA	3
4	Ammirati, 1988[71]		*	*	*	NA	*	NA	NA	4
5	Anderson, 1989[53]	*	*	*	*	NA	*	NA	NA	5
6	Ansari, 2016[62]	*	*	*	*	NA		NA	NA	4
7	Artero, 1984[107]	*	*	*	*	NA	*	NA	NA	5
8	Ashkenazi, 1990[82]	*	*		*	NA	*	NA	NA	3
9	*Bartlett,1971*[35]	*	*	*	*	*NA*		*NA*	*NA*	*4*
10	Behari, 2003[81]		*	*	*	NA	*	NA	NA	4
11	Bialer, 2012[84]	*	*	*	*	NA	*	NA	NA	5
12	Boekhoff, 2019[70]	*	*	*	*	NA		NA	NA	4
13	Cai, 2019[76]		*	*	*	NA	*	NA	NA	4
14	Caldarelli, 2005[90]	*	*	*	*	NA	*	NA	NA	5
15	Capatina, 2018[106]	*	*	*	*	NA	*	NA	NA	5
16	Chamlin, 1955[52]	*	*	*	*	NA	*	NA	NA	5
17	Chen, 2003[6]	*	*	*	*	NA	*	NA	NA	5
18	Cherninkova, 1990[102]	*	*	*	*	NA	*	NA	NA	5
19	d'Avella, 2019[91]	*	*	*	*	NA	*	NA	NA	5
20	Drimtzias, 2014[72]	*	*	*	*	NA	*	NA	NA	5

Table 4. Risk of bias assessment for cohort studies using the New-Ottawa Scale (NOS) (*continued*)

Number	Study	Selection				Comparability	Outcome			Total number of stars
		Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
21	Erşahin, 2005[101]	*	*	*	*	NA	*	NA	NA	5
22	Fisher, 1998[43]	*	*	*	*	NA	*	NA	NA	5
23	Fouda, 2019[63]	*	*	*	*	NA	*	NA	NA	5
24	Gautier, 2012[73]	*	*	*	*	NA	*	NA	NA	5
25	Gerganov, 2014[67]		*	*	*	NA		NA	NA	3
26	Goldenberg-Cohen, 2011[83]	*		*		NA	*	NA	NA	3
27	*Gonc, 2004[31]*	*	*	*	*	*NA*	*	*NA*	*NA*	*5*
28	Greenfield, 2015[60]	*	*	*	*	NA	*	NA	NA	5
29	Haghighatkhah, 2010[104]		*		*	NA		NA	NA	2
30	Hakuba, 1985[86]		*	*	*	NA	*	NA	NA	4
31	*Hoff, 1972[37]*	*	*	*	*	*NA*	*	*NA*	*NA*	*5*
32	*Hoffmann, 1977[25]*	*	*	*	*	*NA*	*	*NA*	*NA*	*5*
33	Hoffmann, 1992[89]	*	*	*	*	NA	*	NA	NA	5
34	Hoffmann, 2015[68]	*	*	*	*	NA		NA	NA	4
35	*Honegger, 1999[26]*	*	*	*	*	*NA*		*NA*	*NA*	*4*
36	Hoogenhout, 1984[93]	*	*	*	*	NA		NA	NA	4
37	Im, 2002[97]	*	*	*	*	NA		NA	NA	4
38	Jane jr., 2010[64]	*	*	*	*	NA	*	NA	NA	5
39	Jung, 2010[98]	*	*	*	*	NA	*	NA	NA	5
40	Karavitaki, 2005[48]	*	*	*	*	NA	*	NA	NA	5

Table 4. Risk of bias assessment for cohort studies using the New-Ottawa Scale (NOS) (*continued*)

Number	Study	Selection			Comparability	Outcome			Total number of stars
		Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
41	Kennedy, 1975[39]	*	*	*	*	NA	*	NA	NA	5
42	Kiran, 2008[79]		*	*	*	NA	*	NA	NA	4
43	*Kramer, 1960*[38]	*	*	*	*	*NA*	*	*NA*	*NA*	*5*
44	Lee, 2008[108]		*	*	*	NA		NA	NA	3
45	*Lena, 2005*[24]	*	*	*	*	*NA*	*	*NA*	*NA*	*5*
46	Leng, 2012[58]	*	*	*	*	NA	*	NA	NA	5
47	Merchant, 2002[65]	*	*	*	*	NA	*	NA	NA	5
48	Mohd-Ilham, 2019[7]	*	*	*	*	NA	*	NA	NA	5
49	*Mottolese, 2001*[33]	*	*	*	*	*NA*		*NA*	*NA*	*4*
50	Nielsen, 2013[103]	*	*	*	*	NA	*	NA	NA	5
51	*Ohmori, 2007*[28]	*	*	*	*	*NA*		*NA*	*NA*	*4*
52	Ono, 1996[87]		*	*	*	NA	*	NA	NA	4
53	Pascual, 2018[55]	*	*	*	*	NA		NA	NA	4
54	Patel, 2017[56]	*	*	*	*	NA		NA	NA	4
55	Puget, 2007[14]	*	*	*	*	*		NA	NA	5
56	Qi, 2012[77]	*	*	*	*	NA		NA	NA	4
57	Quon, 2019[57]	*	*		*	NA	*	NA	NA	4
58	Rath, 2012[96]	*	*	*	*	NA	*	NA	NA	5
59	Richmond, 1980[61]		*	*	*	NA	*	NA	NA	4
60	Salunke, 2016[80]		*		*	NA	*	NA	NA	3

Table 4. Risk of bias assessment for cohort studies using the New-Ottawa Scale (NOS) (*continued*)

Number	Study	Selection				Comparability	Outcome			Total number of stars
		Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
61	*Sankhla, 2015*[27]		*	*	*	*NA*		*NA*	*NA*	*3*
62	Shammari, 2012[100]	*				NA		NR	NA	1
63	Shi, 2017[78]	*	*	*	*	NA	*	NA	NA	5
64	Sogg, 1977[109]	*	*		*	NA	*	NR	NA	4
65	*Stahnke, 1984*[29]	*	*	*	*	*NA*	*	*NA*	*NA*	*5*
66	Suharwardy, 1997[9]	*	*	*	*	NA	*	NA	NA	5
67	Synowitz, 1977[69]	*	*	*	*	NA	*	NA	NA	5
68	Tamasauskas, 2014[105]	*	*	*	*	NA	*	NA	NA	5
69	Tan, 2017[42]	*	*	*	*	*	*	NA	NA	6
70	Taphoorn, 2000[94]	*	*	*	*	NA	*	NA	NA	5
71	Taylor, 2012[74]		*	*	*	NA		NA	NA	3
72	*Thomsett, 1980*[32]	*	*	*	*	*NA*	*	*NA*	*NA*	*5*
73	Tomita, 2005[66]	*	*	*	*	NA	*	NA	NA	5
74	Villani, 1997[92]	*	*	*	*	NA	*	NA	NA	5
75	Vries de, 2003[85]		*	*	*	NA		NA	NA	3
76	Wan, 2018[10]	*	*	*	*	NA	*	NA	NA	5
77	Weiss, 1989[59]	*	*	*	*	NA	*	NA	NA	5
78	Wijnen, 2017[95]	*	*	*	*	NA	*	NA	NA	5
79	*Winkfield, 2011*[34]	*	*	*	*	*NA*		*NA*	*NA*	*4*
80	Yamada, 2018[88]	*	*	*	*	NA	*	NA	NA	5

Table 4. Risk of bias assessment for cohort studies using the New-Ottawa Scale (NOS) (*continued*)

Number	Study	Selection				Comparability	Outcome			Total number of stars
		Represen-tativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
81	Yano, 2016[19]	*	*	*	*	NA		NA	NA	4
82	Yu, 2015[46]		*	*	*	NA	*	NA	NA	4
83	*Zhang, 2008[30]*	*	*	*	*	*NA*		*NA*	*NA*	*4*
84	Zhou, 2009[75]		*	*	*	NA	*	NA	NA	4

Abbreviations: NA, not applicable, i.e. items do not apply to the research question and design of this review.
Studies in italics indicate studies retrieved by reference screening.
*The study met an item of the NOS.

Tumour location

Fourty-seven of the 84 studies described the CP location in a total of 1895 children (**Table 2**), although different anatomical terms, without strict definitions of terminology, were used. In 3 studies it was not clear if tumour location was concerned for child or adult CP: Ashkenazi (1990) reported 19 CP with sellar extension and 14 third ventricular CP[82], Chen (2003) reported 35 suprasellar CP and one sellar CP[6] and Hoogenhout (1984) reported 22 extrasellar CP and 7 intra- and extrasellar CP.[93]

Craniopharyngioma was located (intra)sellar in 153 children (8.1%). In 34 children CP was located intra- and infrasellar (1.8%). Villani (1997)[92] reported 4 intra- and extra-ventricular CP (0.2%). (Intra)sellar and suprasellar CP were reported in 244 children (15.9%) and sellar and/or suprasellar CP in 20 children (1.1%). Sellar, suprasellar and intraventricular CP were reported in 16 children (0.8%).[55,56]. Extrasellar CP was reported in 76 children (4.0%) and intra-and extrasellar in 217 children (11.5%).

Suprasellar CP was reported in 477 children (25.2%), of which 27 CP were not purely supra- sellar. Intraventricular CP was reported in 49 children (2.6%). Quon (2009)[57] reported 15 CP with suprasellar extension and one CP without tumour location. Seven patients had a suprasellar extraventricular CP.[92] In a study by Tamasauskas (2014), 2 of 9 children had respectively a suprasellar, intrasellar and parasellar CP and a suprasellar, parasellar and retrosellar CP.[105] Gerganov (2014) reported one suprasellar, retrosellar and intraventricular CP.[67] Taphoorn (2002) reported one suprasellar CP with enlargement of ventricles and chiasm compression.[94] Lastly, Kiran (2008) reported one suprasellar CP with extension to the third ventricle and subtemporal extension to the left side with posterior extension.[79]

Craniopharyngioma was located third ventricular or extended to the third ventricle in 110 children (5.8%). Retrochiasmatic CP was reported in 94 children (5.0%), with a sellar and suprasellar component in 2 patients in a study by Leng (2012).[58] Caldarelli (2005) reported 14 retrochiasmatic or third ventricular CP.[90] Twenty-four children (1.5%) had a CP located in or with extension to the posterior cranial fossa, namely 2 CP were located at the temporal and posterior cranial fossa[101], 1 suprasellar CP with extension to the posterior cranial fossa and third ventricle[79], 15 sellar CP with extension to the posterior cranial fossa[46] and 5 sellar CP with extension to the cerebellopontine angle and the posterior cranial fossa, as well as infraclivus extension in 2 of 5 patients.[75]

Prechiasmatic CP was reported in 80 children (4.2%). Of these, 24 CP were sellar or suprasellar with prominent prechiasmatic growth.[90] D'Avella (2019)[91] reported 23 supradiaphragmatic CP (2 preinfundibular, 1 preinfundibular and suprasellar, 1 retroinfundibular) and 4 infradiaphragmatic CP (3 intra-suprasellar, 1 intra-para-suprasellar).

Nielsen (2012) reported 10 parasellar CP (0.5%).[103] Erşahin reported 4 retroclival CP (0.2%).[101] Lena (2005)[24] and Pascual (2019)[55] reported 31 infundibulo-tuberous CP (1.6%) in 31 children (1.6%). In a study by Taphoorn (2008) one of three CP was located in the foramen intraventriculare (0.05%).[94] In a study by Erşahin (2005) one of 87 CP (0.05%) was located in the anterior cranial fossa and 3 CP (0.2%) were located in the temporal fossa (2 also with posterior cranial fossa extension).[101] In a study by Patel (2017) one of 10 CP was located extracranial, infrasellar, in the nasal cavity and the sphenoid sinus (0.05%).[56]

Tumour subtypes

Information about histological tumour subtype was available for 9 of 84 studies (**Table 2**).[6,43,55,61,67,70,78,87,105] Adamantinomatous CP was present in 675 of 685 children (98.5%). Nine of 685 children (1.3%) had squamous CP[6] and one child (0.15%) had a papillary CP.[105]

Visual impairment

Of the 84 studies eligible for data extraction, in 56 studies authors provided the total number of patients in whom visual function was impaired (**Table 3**). For these studies, visual impairment was described in 1041 of 2071 children (50.3%) with CP at diagnosis. Authors used different terms to describe visual impairment, for instance 'visual impairment', 'visual defects', 'vision loss' and 'visual complaints'. If a definition for impaired visual function was provided by the authors, this is shown in **Table 3**. Twenty-eight studies did not mention the total number of children with visual impairment in general, nevertheless data about one or more subdomains of visual function (visual acuity, visual field, fundoscopy or orthoptic examination) was available for these studies. Sixty-two studies reported about visual disturbance as an anamnestic symptom at diagnosis in 1135 of 2267 (50.0%) children with a CP.

Visual acuity

We identified 53 studies describing VA in children with CP at diagnosis (**Table 3**). Authors used different definitions and grading systems to describe VA. Four authors described the applied VA testing method, namely by Snellen test[9,52], LogMAR charts[72] or preferential looking charts.[10,72] Seven studies explicitly reported about best corrected VA (BCVA) instead of VA.[6,7,60,72,83,84,95] Authors of the other 46 studies did not describe whether they

used BCVA or uncorrected VA (UCVA). The VA testing methods and definitions are shown in **Table 3**.

Decreased VA was reported in 546 of 1321 tested children (41.3%). Five studies reported about combined VF and VA data, therefore it was impossible to extract VA of these studies.[24,59,60,73,96] Furthermore, Taylor (2012) only reported about reduced VA without providing the number of patients.[74] Seven studies expressed decreased VA in eyes instead of in patients. Ammirati (1988) reported decreased VA in 3 of 4 eyes: VA 20/100 in one eye, VA 20/ 200 in one eye and perception of light (PL) in one eye.[71] Behari (2003) reported for a total of 4 eyes a VA of 6/24 in one eye, a VA of 6/18 in two eyes and a VA of 6/12 in one eye.[81] Drimtzias (2014) described deceased VA in 11 of 20 patients (40 eyes in total), with mild-moderate visual loss in 8 of 40 eyes, severe visual loss in 13 of 40 eyes and a normal VA in 19 of 40 eyes.[72] Mohd-Ilham (2019) reported the BCVA in 22 eyes, which was ≥ 6/6-6/12 in 13 eyes, 6/15-6/60 in 3 eyes and < 6/60 in 6 eyes.[7] In a study by Sogg (1977), two children both had decreased VA (20/100, 20/50, 20/400 and 20/200).[109] Salunke (2016) described decreased VA in two children, with VA 6/18 in 2 eyes, VA 6/24 in one eye and PL plus in one eye.[80] Suharwardy (1997) reported decreased VA in 10 eyes, namely VA of 6/24 in 2 eyes; VA of 6/12 in 2 eyes; VA of 6/9 in one eye; VA of 6/6 in 2 eyes; VA of 1/60 in one eye; no PL in one eye and hand motion in one eye.[9]

Twenty-nine studies described decreased VA in one or both eyes without giving any further details about the degree of VA reduction in 365 of 831 children (43.9%). Visual loss was found in 31 of 68 children (45.6%).[39,43,57,86,104] Blindness in one or two eyes with or without PL was present in 71 of 515 children with CP (13.8%).[10,14,24,61,77,89,96,99,101,103,104,106] Ali (2013)[54] and Quon (2019)[57] described blurry vision in 3 of 23 patients (13.0%). Loss of central VA was reported in 12 of 18 children by Chamlin (1955).[52] Multiple studies described VA by using VA scales. In a study by Chen (2003) 6 patients had a VA < 6/12 (35.3%) and 10 patients had a VA ≥ 6/12 (58.8%).[6] In two studies, 10 of 55 patients had a VA of ≤ 20/200 in one or both eyes (18.2%).[60,84] Kiran (2008)[79] reported VA of 6/9 in one of 2 patients and Kramer (1960)[38] VA of 6/60 in one of 6 patients. Tamasauskas (2014) described two children with a VA of 5/10 and 1/1000.[105] Two children with CP in a study by Anderson (1989) had respectively a VA of 20/25 and counting fingers (CF) at 1 foot, and a VA of 20/300 and CF at 2 feet.[53] Finally, Synowitz (1977) presented VA data of 3 CP patients: one patient had no VA defects; one patient had only PL and the last patient could CF with his right eye at 1 m and could see hand movements with his left eye at 50 cm.[69]

In summary, different grading systems and testing methods were used to report about decreased VA in 41.3% of children, with no specification of VA reduction in 43.9%. Blindness in one or both eyes was reported in 13.8% of children.

Visual fields

A total of 46 studies provided data about visual field testing in children with CP (**Table 3**). Nine authors described which VF test is performed in their study, namely the Humphrey Field Analyzer[6,7,10,84], Goldmann perimetry[6, 9,10,72,95,109], Bjerrum screen[6,39], confrontation method[7,10] and/or the red test and large white test objects.[9]

Visual field defects were reported in 426 of 1111 tested children (38.3%). Mohd-Ilham (2019) reported about VF per eye instead of per patient: temporal hemianopia was found in 5 of 22 eyes, scotoma in 3 of 22 eyes, quadrantanopia in 2 of 22 eyes and a constricted VF in 1 of 22 eyes.[7] Five studies reported VF data together with VA data, therefore VF data from these studies could not be extracted.[24,59,60,73,96] In 8 studies VF defects were reported in 121of 400 children (30.3%) without providing descriptions of the VF defects.[39, 63, 64, 90, 92, 95, 101, 106] In nine studies a VF defect (no further specification), reduction or loss was present in 82 of 320 children (25.6%).[24,29,32,43,48,66,82,89,103] The remaining studies reported the type of the VF defect in detail. Bitemporal hemianopia was reported in 98 of 332 patients (29.5%)[6,9,25,31,38,48,52,57,61,71,72,80,84,86,89,91,94,96,99,102,105,107,109]. Twenty-three of 177 children (13.0%) were diagnosed with an unitemporal hemianopia.[6,25,53,61,84,94,96,102,105] For 11 of 33 children (33.3%) it was not specified whether their temporal hemianopia was uni- or bilateral, these are reported as having a temporal hemianopia.[9,53,91,107] Zhou (2009) found hemianopia in one of 5 children (20%).[75] Quadrantopia was described in 2 of 23 children (8.7%).[84,91] Richmond (1980) described the presence of a scotoma in one of 21 children.[61] Kramer found loss of right nasal field in one of 6 patients.[38] Impaired VF was reported in one of 4 patients by Boekhoff (2019).[70] Artero (1984) found homonymous defects in 5 of 18 patients (27.8%).[107] Suharwardy (1997) described an asymmetric binasal loss with enlarged blind spots and a supero-temporal loss in one of 5 patients.[9] Concentric narrowing of the VF or only central VF was reported in 6 of 41 patients (14.6%).[99,102] Cherninkova (1990) reported 'other defects' for one of 21 patients with VF defects among their patients.[102]

Despite the fact that 8 studies did not specify the VF defects in 30.3% of children with CP, uni- and/or bitemporal hemianopia is the most frequent VF defect in 132 of 542 children (24.4%).

Fundoscopy

In 37 studies fundoscopy was performed (**Table 3**). Fundoscopic abnormalities were reported in 520 of 1601 examined children (32.5%). Papilledema (uni- or bilateral), also mentioned as optic disc or nerve oedema, was present in 254 of 986 patients (25.8%). Optic atrophy or pallor was reported in 239 of 534 (44.8%). Weiss (1989) reported about asymptomatic papilledema or optic atrophy in 5 of 31 patients (16.1%).[59] Optic nerve compression was found in 1 of 16 patients (6.25%) by Quon (2019).[57] Al-Mefty (1985) reported about the presence of the Foster-Kennedy syndrome in 3 of 15 patients (20%).[99] An abnormal ocular fundus without further specificity was reported by Artero (1984) in 19 of 24 patients (79.2%).[107]

Summarizing this, fundoscopic abnormalities were reported in 32.5% of children. Among these, papilledema (25.8%) and optic nerve atrophy or pallor (44.8%) were the most common fundoscopic abnormalities.

Orthoptic examination

Twenty-nine studies provided data about orthoptic examination at diagnosis in children with CP (**Table 3**) In these studies, orthoptic abnormalities were reported in 163 of 1304 children (12.5%) with CP at diagnosis. Taylor (2012) was the only study that did not provide numbers of children in whom an orthoptic abnormality was found, they only mentioned nystagmus and strabismus as the orthoptic abnormalities seen among their study participants.[74]

Fourty-three of 296 children experienced diplopia (14.5%)[7,31,54,55,60,66,75,83,84,89,94,107], 21 of 127 children (16.5%) were diagnosed with strabismus (also called squint by some studies)[6,7,39,66,83,84,96] and in 22 of 331 children (6.6%) nystagmus (monocular, seesaw, horizontal pendular or rotatory) was seen during orthoptic examination.[25,38,39,69,83,84,89–102] Sixth nerve deficits or palsy were present in 15 of 220 patients (6.8%)[55,59,81,84,90,101] and other cranial nerve deficits or palsies in 22 of 159 patients (13.8%).[32,46,90,102] Proptosis was reported in one of 16 children (6.3%) with CP by Quon (2019).[57] Four studies mentioned a relative afferent pupillary defect (RAPD) in 30 of 46 children (65.2%).[6,7,9,84] Wan (2018) reported for diplopia and strabismus together in 7 of 59 patients (11.9%).[10] In a study by Erşahin (2005) diplopia and squint were reported together which was seen in 7 of 87 (8.0%) patients.[101]

The overall findings in children with orthoptic abnormalities (12.5%) showed diplopia in 14.5%, strabismus in 16.5% and nystagmus in 6.6% of the children.

Other vision related abnormalities

Apart from the abovementioned ophthalmological findings, some studies have described other vision related abnormalities as well (**Table 3**). Colour vision defects were reported by Mohd-Ilham (2019) in 4 of 11 patients (18.2%).[7] Nielsen (2012) described ophthalmoplegia in 5 of 31 patients (16.1%).[103] Right amaurosis was reported by d'Avella (2019)[91] in 1 of 8 patients (12.5%) and Chamlin (1955)[52] reported ptosis in 1 of 18 patients (0.05%). These vision related abnormalities were not the main focus of our study and were not analysed and/or reported in any of the other studies included in our systematic review.

DISCUSSION

Our review was designed to provide a detailed overview of the currently available evidence about visual function in children with CP at diagnosis. To the best of our knowledge, this is the first review that systematically describes the visual function in subtopics like VA, VF, fundoscopy and orthoptic examination. We included 84 studies, with 56 studies explicitly providing data about visual impairment in general, and 55 studies providing specific data about VA and/or VF. We found a high rate of visual impairment in children with CP at time of diagnosis (50.3%). Considerable rates were also reported for decreased VA (41.3%) and VF loss (38.3%). Papilledema (25.8%) and optic nerve atrophy (44.8%) were common fundoscopic findings in our review. The most common abnormalities in orthoptic examination (12.5%) were strabismus, diplopia and cranial nerve deficits. These findings are in agreement with several non-systematic reviews of Bogusz (2018), who concluded that more than 50% of children with CP had visual impairment at diagnosis[110], and with Müller (2008) who described visual impairment, VF defects, papilledema and optic atrophy in respectively 62–84%, 36%, 20–35% and 35–45% of children with CP.[4] Drapeau (2019) described even higher rates for decreased VA and VF defects, namely in 70–80% of children with CP. In particular, Drapeau (2019) reported bitemporal hemianopia and papilledema in respectively 50% and 20% of children with CP.[111]

The presented data in our review supports the importance of awareness in doctors for the fact that CP commonly induce visual impairment in children, as well as the importance of ophthalmological examination at diagnosis. Visual impairment due to damage of the optic nerves, optic chiasm and visual pathways often results in lifelong effects for children and their family, by affecting domains including childhood development, education, employment and self-perception.[12,112-114] Visual problems may be reversible in early stages of visual impairment. Therefore, timely monitoring of visual function and early detection of visual impairment in children with CP is of major importance

to preserve visual function and provide adequate treatment.[12,13,17,18,20] In children with irreversible visual impairment, timely referral for visual rehabilitation may reduce the adverse effects of visual impairment on health and/or vision related quality of life.[115,116] The impact of an impaired visual function on quality of life has also been reported in children with visual impairment with ophthalmological origin, for example, children who suffer from glaucoma and cataract.[117,118]

Moreover, visual impairment has been reported as one of the factors that may lower the level of physical activity.[119] Especially in children with craniopharyngioma in whom hypothalamic damage can be severe, resulting in endocrine deficiencies and obesity, physical activity is crucial (40–50%).[119-123] Both visual impairment and severe obesity negatively affect quality of life in childhood CP survivors.[119,124,125]

Limitations of the included studies

Overall there was moderate quality evidence for the presence of visual impairment in children with CP at diagnosis in our review. Although there were serious limitations to the data due to e.g. retrospective design of the studies, moderate risk of bias for some included studies and potential publication/reporting bias, the overall quality of evidence was raised by the number of included studies, study sizes, availability of confirmatory evidence and representativeness of study patients. Nevertheless, there are some issues that need to be discussed. First, different terminology was used to describe tumour locations and no concrete insights were given in the relationship between tumour location and visual loss. Therefore, we were not able to relate a more suprasellar tumour location involving the optic chiasm with the type and degree of visual loss. Second, no standardized ophthalmological examination was performed in a large proportion of included studies, and if performed, there was no uniformity in testing methods between the studies. Visual acuity and VF were described with different definitions and cut-off values per study, which makes grouping of results difficult. In the absence of standardized ophthalmological examination, it could be questioned whether we can presume that those children reported without visual impairment really have a normal visual function. In addition, performing reliable VA and VF testing in young and non-cooperative children is often very complicated.[126,127] Therefore, it is likely that these data were frequently missing in the included studies. Both of these issues, no standardized ophthalmological examination and difficulties with reliable VA and VF testing, could be reasons for underreporting of visual impairment in our review. Additionally, we were not able to compare the feasibility of different VA and VF testing methods for different age groups, because only a few studies provided information about the used tests and in these studies the authors often did not specify which testing methods were used for the different age groups. Furthermore, study authors reported the number of children per

abnormality found by either fundoscopy or orthoptic testing. For this reason, the exact number of children with fundoscopic or orthoptic abnormalities is unclear, because one child might have more than one fundoscopic or orthoptic abnormality. Finally, authors used different cut-off values for the age limit of children. We initially planned to include studies only when patients were aged between 0 and 18 years. However, during study selection we encountered multiple studies still referring to patients as 'children' when aged < 24 years. We decided to include those studies as well, aiming to provide an extensive overview of visual function in children with CP at diagnosis. Nevertheless, heterogeneity in age ranges for children across studies may lower their comparability.

Strengths and limitations of this systematic review

The findings of the present systematic review should be interpreted by its strengths and limitations. We planned this review a priori and registered our review in PROSPERO with clearly defined selection criteria. We conducted a comprehensive literature search and reviewed all reference lists of included studies. Two reviewers independently of each other performed the literature screening, data extraction and risk of bias assessment. In this way we retrieved and summarized the visual data of 3531 children with a newly diagnosed CP. We also encountered some possible limitations for the methodology of our review. By screening references of included studies, we identified a relatively high number of additional studies eligible for inclusion (n = 15). Therefore, it might be possible that in our search we missed studies, though our cross reference search would in that case have identified those articles. Furthermore, full-text articles of 117 potential relevant abstracts found by our search in the electronic databases were not available despite searching the Utrecht University Library, Sci-Hub and contacting the corresponding author by mail and/or ResearchGate. Possible reasons for this could be that the abstracts are dated (we did not use a publication date filter) or that the full-text did not exist. Lastly, we did not review visual function at follow-up as we initially planned for in our PROSPERO registration. This was because many authors within our study selection, described visual follow-up data only in patients who received tumour treatment.

RECOMMENDATIONS

For future research, it is relevant to investigate the visual function at diagnosis and during long-term follow-up of childhood CP in response to surgery, radiotherapy and other treatment strategies, first by systematically reviewing the literature as well as in prospective collaborative studies. This will provide insight in risks and benefits of treatment regarding vision in children with CP, for professionals, patients and their caregivers. Furthermore, future studies should focus on reliable ophthalmological testing

methods for young and non-cooperative children. As we have shown, the majority of studies did not report the methods they used for ophthalmological testing. Therefore, unfortunately, we were not able to compare feasibility of testing methods for different age groups due to lacking data. For future studies, it is important that all studies must use the correct testing methods for VA and VF and report these as such in the paper. Additionally, optical coherence tomography with analysis of the retinal layers might be applied as objective testing method in addition to VA and VF testing.[84,128-130]

CONCLUSION

Children diagnosed with CP have at least 50% risk of visual impairment at diagnosis regarding VA, VF, fundoscopy and/or orthoptic examination. Complete structured evaluation of visual function at diagnosis should be performed routinely in all children diagnosed with craniopharyngioma. However, large, well designed studies with standardized ophthalmological examination and uniform reporting with grading are needed to gain more insight in the visual function of these patients at diagnosis, after therapeutic interventions and during follow-up.

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SUPPLEMENTARY DATA

S1 Appendix. Search strategies for electronic databases.

Search strategy for the Cochrane Library

(((“amblyopia”:ti,ab OR lazy eye*:ti,ab OR “binocular vision”:ti,ab OR “strabismus”:ti,ab OR eye movement*:ti,ab OR “diplopia”:ti,ab OR “double vision”:ti,ab OR orthoptic*:ti,ab OR hemianop*:ti,ab OR “ocular”:ti,ab OR vision*:ti,ab OR visual*:ti,ab OR ophthal*:ti,ab OR oculo*:ti,ab OR optic*:ti,ab OR optic chiasm*:ti,ab OR chiasma optic*:ti,ab OR optic decussation*:ti,ab OR optic compression*:ti,ab OR chiasm compression*:ti,ab OR chiasmal compression*:ti,ab OR OCT:ti,ab OR “optic coherence tomography”:ti,ab OR “optical coherence tomography”:ti,ab OR RNFL:ti,ab OR “GCL-IPL”:ti,ab OR retinal nerve fiber layer*:ti,ab OR ganglion cell layer*:ti,ab OR retinal layer*:ti,ab) OR (MeSH descriptor: [Amblyopia] OR MeSH descriptor: [Strabmismus] OR MeSH descriptor: [Vision, Binocular] OR MeSH descriptor: [Eye Movements] OR MeSH descriptor: [Diplopia] OR MeSH descriptor: [Orthoptics] OR MeSH descriptor: Tomography, Optical Coherence OR MeSH descriptor: [Optic Chiasm] OR MeSH descriptor: [Visual acuity] OR MeSH descriptor: [Visual Fields] OR MeSH descriptor: [Vision, Ocular] OR MeSH descriptor: [Orthoptics] OR MeSH descriptor: [Hemianopsia])) AND (MeSH descriptor: [Craniopharyngioma] OR craniopharyng*:ti,ab))

Search strategy for Embase database

(((‘amblyopia’:ti,ab,kw OR ‘lazy eye*’:ti,ab,kw OR ‘binocular vision’:ti,ab,kw OR ‘strabismus’:ti,ab,kw OR ‘eye movement*’:ti,ab,kw OR ‘diplopia’:ti,ab,kw OR ‘double vision’:ti,ab,kw OR ‘orthoptic*’:ti,ab,kw OR ‘hemianop*’:ti,ab,kw OR ‘ocular’:ti,ab,kw OR ‘vision*’:ti,ab,kw OR ‘visual*’:ti,ab,kw OR ‘ophthal*’:ti,ab,kw OR ‘oculo*’:ti,ab,kw OR ‘optic*’:ti,ab,kw OR ‘optic chiasm*’:ti,ab,kw OR ‘chiasma optic*’:ti,ab,kw OR ‘optic decussation*’:ti,ab,kw OR ‘optic compression*’:ti,ab,kw OR ‘chiasm compression*’:ti,ab,kw OR ‘chiasmal compression*’:ti,ab,kw OR ‘OCT’:ti,ab,kw OR ‘optic coherence tomography’:ti,ab,kw OR ‘optical coherence tomography’:ti,ab,kw OR ‘RNFL’:ti,ab,kw OR ‘GCL-IPL’:ti,ab,kw OR ‘retinal nerve fiber layer*’:ti,ab,kw OR ‘ganglion cell layer*’:ti,ab,kw OR ‘retinal layer*’:ti,ab,kw) OR (‘Amblyopia’/exp OR ‘Strabismus’/exp OR ‘Binocular Vision’/ex OR ‘Eye Movement’/exp OR ‘Diplopia’/exp OR ‘Orthoptics’/exp OR ‘Optical Coherence Tomography’/exp OR ‘Optic Chiasm’/exp OR ‘Visual Acuity’/exp OR ‘Visual Field’/exp OR ‘Vision’/exp OR ‘Orthoptics’/exp OR ‘Hemianopia’/exp)) AND (‘craniopharyngioma’/exp OR ‘craniopharyng*’:ti,ab,kw))

Search strategy for PubMed database

(((((amblyopia[tiab] OR lazy eye*[tiab] OR strabismus[tiab] OR "binocular vision"[tiab] OR eye movement*[tiab] OR diplopia[tiab] OR "double vision"[tiab] OR orthoptic*[tiab] OR hemianop*[tiab] OR ocular[tiab] OR vision*[tiab] OR visual*[tiab] OR ophthal*[tiab] OR oculo*[tiab] OR optic*[tiab] OR optic chiasm*[tiab] OR chiasma optic*[tiab] OR optic decussation*[tiab] OR optic compression*[tiab] OR chiasm compression*[tiab] OR chiasmal compression*[tiab] OR OCT[tiab] OR "optic coherence tomography" [tiab] OR "optical coherence tomography"[tiab] OR RNFL[tiab] OR "GCL-IPL" [tiab] OR retinal nerve fiber layer*[tiab] OR ganglion cell layer*[tiab] OR retinal layer*[tiab]))) OR (("Amblyopia"[Mesh] OR "Strabismus"[Mesh] OR "Vision, Binocular"[Mesh] OR "Eye Movements"[Mesh] OR "Diplopia"[Mesh] OR "Orthoptics"[Mesh] OR "vision, ocular"[Mesh] OR "visual fields"[Mesh] OR "Tomography, Optical Coherence"[Mesh] OR "Optic Chiasm"[Mesh] OR "visual acuity"[Mesh] OR "visual fields"[Mesh]))))) AND (("craniopharyngioma"[Mesh] OR craniopharyng*[tiab]))

S2 Appendix. PRISMA checklist.

Weblink: https://doi.org/10.1371/journal.pone.0240016.s002

S3 Appendix. Systematic research protocol.

Weblink: https://doi.org/10.1371/journal.pone.0240016.s003



CHAPTER 3

Ophthalmological evaluation in children presenting with a primary brain tumor

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J Neuroophthalmol. 2022 doi: 10.1097/WNO.0000000000001421

ABSTRACT

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.

BACKGROUND

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 Utrecht 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–≤1.0 logMAR), severe VI (BCVA >1.0–≤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. Visual field 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 ±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 abovementioned 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.

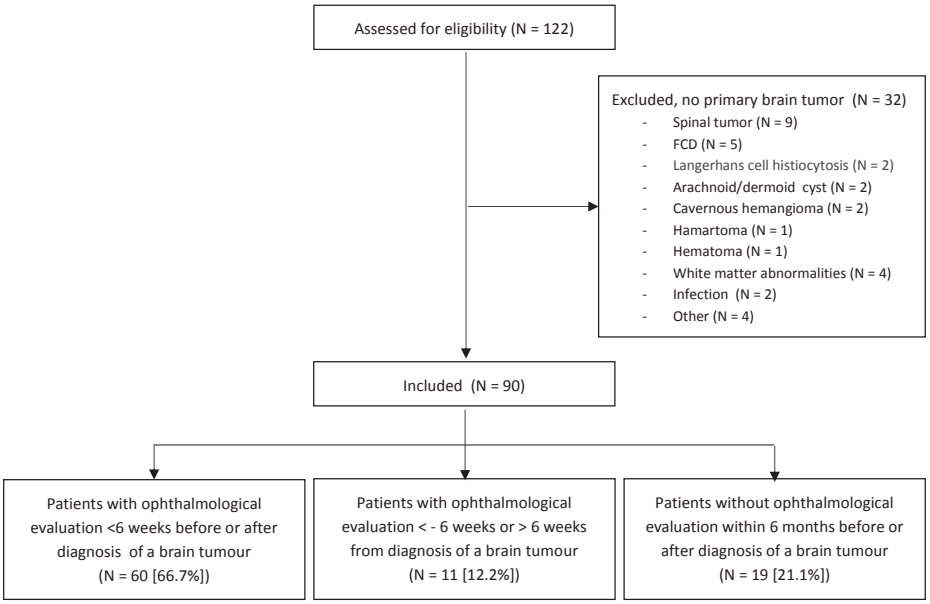


Fig 1. Patient flow demonstrating the patient selection and grouping process.

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 OPG (N = 5 [5.6%]) and non-optic 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 non-optic 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 (78.3%) 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 (36.2%) 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 fundoscopic findings were present after neurosurgical intervention in patients who were seen before and after neurosurgical intervention. Visual field examination was completed in 31 of 60 patients (51.7%). Visual field examination was performed before neurosurgical intervention in 15 patients (48.4%) and after neurosurgical intervention in 16 patients (51.6%). In particular, the 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.

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

Covariate	Patients with eye examination within 6 weeks before or after diagnosis	Patients with eye examination < -6 weeks or > 6 weeks from diagnosis	Patients without eye examination
	n = 60 (66.7)	n = 11 (12.2)	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, years			
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

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

Covariate	Patients with eye examination within 6 weeks before or after diagnosis	Patients with eye examination < -6 weeks or > 6 weeks from diagnosis	Patients without eye examination
	n = 60 (66.7)	n = 11 (12.2)	n = 19 (21.1)
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)II
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

Abbreviations: ATRT, atypical teratoid rhabdoid tumor; OPG, optic pathway glioma.
Data are presented as number (%) unless otherwise noted.
*Pineoblastoma (1), schwannoma (1).
†Meningioma (1).
‡Radiological suspicion of OPG (4).
§Radiological suspicion of OPG (1).
IIRadiological 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.

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 – 0.82]
Worst eye		0.10 [-0.18 – 2.52]

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

	Number*	n (%)
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)

Abbreviations: BCVA, best corrected visual acuity; LogMAR, logarithm of minimal angle of resolution; VF, visual field; VI, visual impairment; RAPD, relative afferent pupillary defect.
Data are presented as number (%) 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.

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.

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

	Seen for ophthalmological evaluation within 6 weeks before or after 6 diagnosis n = 60	Not seen for ophthalmological evaluation within 6 weeks 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)*

Abbreviations: CI, confidence interval; OR, odds ratio.
Data are presented as number (%) or median [range] with OR (95% CI).
*Statistical significant OR.
†Decreased vision, diplopia, wobbling eyes, ocular misalignment and visual field loss.

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.

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 – 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 – 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 – 0.17)	1 (20.0)	0.57 (0.05 – 6.61)
Suprasellar	4 (12.9)	ref	11 (25.0)	0.07 (-0.08 – 0.22)	3 (60.0)	ref

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 (continued)

	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)II	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)II	10 (55.6)	2.81 (0.63 – 12.61)
Tumor location				
Infratentorial	17 (65.4)	9.11 (1.77 – 46.78)II	6 (33.3)	ref
Supratentorial	7 (26.9)	13.13 (1.92 – 89.52)II	2 (11.1)	0.56 (0.07 – 4.76)
Suprasellar	2 (8.7)	ref	10 (55.6)	1.68 (0.34 – 8.26)

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

Data are presented as number (%) with OR (95% CI) or as number (%) 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.

§Data presented as median [range].

†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.

IIStatistical significant OR.

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 presented without visual symptoms at diagnosis. Visual impairment adversely affects physical, psychological, and social wellbeing 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.

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 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, fundoscopy, 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 non-cooperative children with OPG or craniopharyngioma.[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 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 find-

ings 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.

ACKNOWLEDGMENTS

The authors would like to thank the pediatric ophthalmologists and orthoptists at University Medical Center Utrecht for their dedication and data registration used in this work.

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CHAPTER 4

The diagnostic accuracy and prognostic value of OCT for the evaluation of the visual function in children with a brain tumor: A systematic review

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PLoS One. 2021 doi: 10.1371/journal.pone.0261631

ABSTRACT

Purpose

To systematically review the evidence on the diagnostic accuracy and prognostic value of retinal optical coherence tomography (OCT) to detect visual acuity (VA) or visual field (VF) loss in children with a brain tumour.

Methods

PubMed, Embase and Cochrane Library databases were searched from inception to February 2021. We included studies evaluating retinal OCT and standard visual function parameters (VA and or VF) in children with a brain tumour. Two authors independently extracted data from each included study. They also assessed the methodological quality of the studies using the QUADAS-2 or QUIPS tool. The diagnostic accuracy of OCT was evaluated with receiver operating characteristic analysis, sensitivity, specificity, positive predictive value and negative predictive value. The prognostic value of OCT was evaluated with predictive measures (odds ratio).

Results

We included five diagnostic studies, with a total of 186 patients, all diagnosed with optic pathway glioma. No prognostic studies were eligible for inclusion. Included studies evaluated either retinal nerve fiber layer (RNFL) thickness or ganglion cell layer-inner plexiform layer (GCL-IPL) thickness. There was considerable heterogeneity between OCT devices, OCT protocols, visual function parameters and threshold values. Sensitivity and specificity for RNFL thickness measurement ranged from 60.0% to 100.0% and 76.6% to 100%, respectively. For GCL-IPL thickness measurement, area under the curve ranged from 0.91 to 0.98 for different diameters.

Conclusion

The literature regarding the diagnostic accuracy and prognostic value of OCT parameters in children with a brain tumour is scarce. Due to heterogeneity and a considerable risk of bias of included studies, we cannot draw solid conclusions regarding the accuracy of retinal OCT. Future research should investigate the potential of OCT as diagnostic and prognostic tool for the evaluation of the visual function and detection of visual impairment in children with any type of brain tumour.

INTRODUCTION

Optical coherence tomography (OCT) is a non-invasive, in vivo, imaging modality which provides high-resolution cross-sectional images of ocular tissues by using low-coherence interferometry.[1,2] The high resolution of modern OCT images enables the clinician to easily distinguish between multiple retinal layers around the optic nerve head and the macula. Numerous clinicians have used OCT to measure the peripapillary retinal nerve fiber layer (RNFL) thickness and the ganglion cell layer-inner plexiform layer (GCL-IPL) thickness as a surrogate marker for optic nerve swelling and or retinal ganglion cell damage.[3-5] In adults with compressive optic neuropathies or glaucoma, OCT was shown to detect a decrease in RNFL and GCL-IPL thickness, which correlates with a decline of visual function (i.e. visual field (VF) defects).[6,7] Furthermore, the high inter-visit reproducibility of OCT measurements validates its utility for the follow-up of these patients.[6-8]

In recent years, there has been increasing information about the diagnostic and prognostic ability of RNFL thickness and GCL-IPL thickness measurements for the detection of visual acuity (VA) and VF loss in children with a brain tumour. This applies particularly to children with a brain tumour located along the visual pathway, including low-grade gliomas, craniopharyngiomas and germ cell tumours.[3,9-15] An impaired visual function often has important long-term implications for the development, quality of life and later prospects in childhood brain tumour survivors.[16,17] Therefore, early detection of an impaired visual function and timely initiation of treatment or referral for visual rehabilitation are important to preserve visual function and improve coping in daily life.[18,19]

Regrettably, ophthalmological examination for the objective measurement of disease progression and evaluation of the visual function is challenging in children with a brain tumour. Formal VA and VF testing has limitations because these testing methods need full cooperation and cognitive ability of the patient.[18,20,21] Also, previous studies showed that 2D tumour volume changes on magnetic resonance imaging (MRI) do not relate to VA or VF loss.[22,23] In these children, OCT measurements may be helpful to provide indirect information about the child's visual status and assist in treatment decisions by the ophthalmologist and neuro-oncologist. The application of OCT has been limited in children because the traditional table-mounted OCT device requires the child's ability to fixate and cooperate. However, with the incorporation of eye tracking technology and the development of a handheld OCT (HH-OCT) device this technique can now be successfully used in the paediatric population as well, even in very young children under general anaesthesia.[3,24-29] In this study, we systematically review the diagnostic accuracy and prognostic value of retinal OCT to detect VA or VF loss in children with any type of brain tumour.

METHODS

Protocol and registration

This systematic review was registered in the international prospective register of systematic reviews (PROSPERO) on April 11, 2019 (ID: 125785). Results were reported according to the principles of the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement.[30] In accordance to Dutch guidelines, no institutional ethical review board approval was required.

Information sources and search strategy

We conducted a systematic search in the Cochrane Library, Embase and PubMed on February 2, 2021. The electronic databases were searched for a combination of the following key search terms and or their synonyms: 'glioblastoma', 'optic pathway glioma (OPG)', 'astrocytoma', 'craniopharyngioma', 'germ cell tumor', 'pineal tumor', 'medulloblastoma', 'ependymoma', 'atypical teratoid rhabdoid tumor', 'diffuse intrinsic pontine glioma', 'choroid plexus tumor', 'primitive neuroectodermal tumor', 'brain tumor', 'visual pathway', 'chiasm compression' and 'optical coherence tomography'. The full search strategies are presented in **S1 File**. There were no date or publication restrictions. We manually searched the reference lists of the included studies to ensure that no relevant studies were missed by our search strategy. No language restrictions were applied. No trial registries were sought for unpublished trials and study authors were not contacted to identify additional studies.

Study selection

Two reviewers (M.N. and N.V.) independently screened titles and abstracts of studies identified from the electronic searches using Rayyan QCRI.[31] Full-text articles of definitely or potentially relevant abstracts were obtained and reviewed for eligibility by the same two reviewers. Discrepancies were resolved by consensus or by discussion with a third reviewer (I.S.). The reviewers were unmasked for article authors, journal, institution and study results during the assessment.

Eligibility criteria

We included studies of all designs that produce estimates of test accuracy and prognostic factor measurement or provide sufficient data from which these estimates can be computed: cross-sectional, longitudinal, cohort and case-control studies. To evaluate diagnostic accuracy, we included studies with VA and VF as reference standard and retinal OCT parameters (RNFL thickness and GCL-IPL thickness) as index test. Studies including only patients older than 18 years of age, studies including only patients without a brain tumour, case reports including < 2 patients and studies lacking data on VA,

VF and OCT parameters were excluded. In addition, studies providing insufficient data to construct 2x2 tables to estimate sensitivity (SN), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) were excluded.

Outcome measures

The primary outcome measures of this systematic review were retinal OCT parameters (RNFL and GCL-IPL thickness measurements), VA and VF. The diagnostic accuracy of OCT was evaluated with SN, SP, PPV, NPV and receiver operating characteristic (ROC) analysis. The prognostic value was assessed with predictive measures (odds ratio). If these numbers were not reported by the authors, we calculated them with the available data.

Assessment of methodological quality

Risk of bias and applicability concerns were assessed by two reviewers (M.N. and N.V.) independently, using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool[32] and the Quality In Prognostic Studies (QUIPS) tool.[33] Any disagreements between the reviewers were resolved by consensus.

The QUADAS-2 tool was designed to assess the methodological quality of primary diagnostic accuracy studies and facilitates assessment across four domains: patient selection, index test, reference standard and flow and timing. Each domain was assessed in terms of risk of bias and the first three domains were also assessed in terms of applicability concerns. The risk of bias within each domain was based on signalling questions and was expressed as high (+), low (-) or unclear (?). Risk of bias was rated as high if one or more items were answered with 'no', as low if all items were answered with 'yes' and as 'unclear' in all other instances. The definitions used for assessing the methodological quality of diagnostic accuracy studies with the QUADAS-2 tool are shown in **S1 Table**.

The QUIPS tool was developed for evaluating the methodological quality of prognostic studies. The following six domains were assessed: study participation, study attrition, prognostic factor measurement, outcome management, study confounding and statistical analysis and reporting. Each domain consisted of multiple items that were judged separately. The risk of bias within each domain was based on the ratings of these items and was expressed as high (+), low (-) or unsure (?). Risk of bias was rated as high if one or more items were answered with 'no', as low if all items were answered with 'yes' and as 'moderate' in all other instances. The definitions used for assessing the methodological quality of prognostic studies with the QUIPS tool are shown in **S2 Table**.

Data analysis and synthesis

All data were extracted independently by two review authors (M.N. and N.V.). A standardized data extraction form was used, including the following items: author, country, study design, study size, gender and age of patients, type of brain tumour, presence of NF1, type of ophthalmological testing methods, type of OCT device and protocol, follow-up period and ophthalmological outcome measures. Authors of the eligible primary studies were contacted to obtain additional study data if there was insufficient data for study inclusion. We quantified the extracted data per item and presented numbers for each item in different tables.

RESULTS

Results of the search

We identified 4542 records through our literature search. After deduplication and assessment of title and abstracts, we assessed 147 records via full-text screening. Of these, we removed 129 records that included the wrong or an unclear study population (N = 93), did not contain original data (N = 10), did not contain OCT data (N = 3), case reports including <2 patients (N = 12) and records of which the full-text was not available (N = 9) or that were written in Chinese or Russian (N = 2). Of the remaining 18 studies, 13 studies including both patients with and without the target condition were excluded, because they provided insufficient data to construct 2x2 tables to estimate SN, SP, PPV and NPV (**S3 Table).** The remaining five studies were included in this review. No additional studies were included after reference screening. A detailed overview of the identification and selection process for included studies and reasons for exclusion after full-text screening is shown in **Fig 1**.

Study and patient characteristics

We found no studies evaluating the prognostic value of OCT. All five included studies assessed the diagnostic accuracy of OCT (**Table 1**). The studies were prospectively conducted, two were longitudinal cohort studies[12,13] and three were cross-sectional studies.[34-36] Studies were published in English between 2013 and 2018 and were conducted in the United States of America[13,35,36], Iran[12] and Italy.[34]

The included studies comprised in total 186 children (301 eyes) and study sample sizes ranged from 23 to 53 children (mean of 37 children [60 eyes]). With regard to the included children, 73 children were males[12,34-36] and one study reported the inclusion of 20 male eyes and 35 female eyes.[13] Mean age ranged from 5.3 to 7.6 years[12,13,34,36] and median age ranged from 4.8 to 8.7 years.[35] All children were diagnosed with an OPG (sporadic or NF1

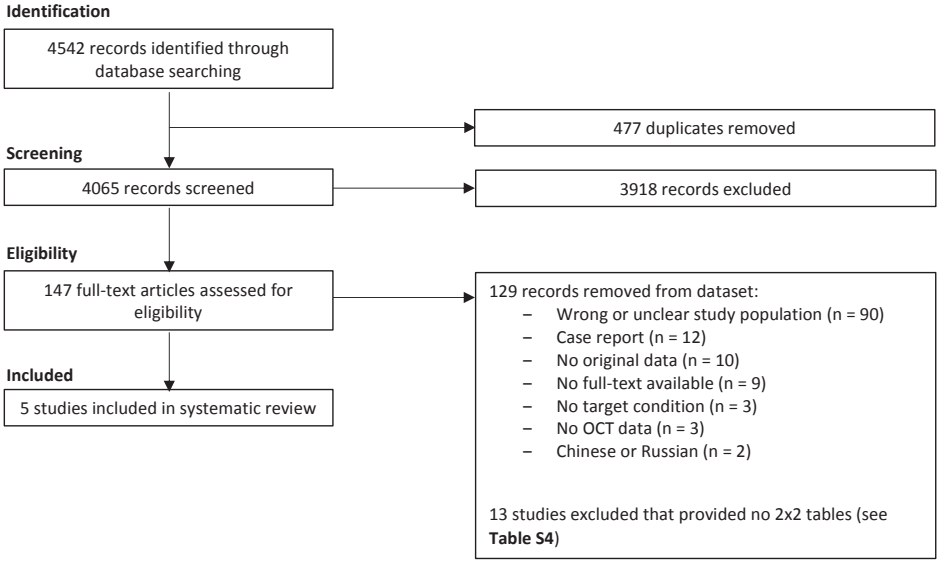


Fig 1. PRISMA flow chart for identification and selection of studies.

related). The included studies investigated whether there was a relation between the visual function (VA, VF) and structural changes (OCT parameters).

Visual outcome measures and definitions of included studies

The cut-off values for VA and VF loss varied between the studies. Two studies considered a loss of ≥ 0.2 logMAR compared to the baseline visit as significant decline in VA[12,13], two studies defined abnormal VA as ≥ 0.2 logMAR below age-based norms[35,36] and one study considered an abnormal VA as any VA below age-based norms.[34] With regard to VF, one study considered progressive VF loss as 3 or more contiguous points reaching significance ($P < 0.05$) using Humphrey 24–2 or as any constriction greater than 10 degrees across a minimum of 3 contiguous 15-degree vectors using the V-4-E or I-4-E isopter on Goldmann kinetic perimetry[13], one study defined progressive VF loss if mean VF mean deviation worsened by 5 dB or more[12], two studies predefined an abnormal VF as a VF defect in any quadrant[35,36] and in one study the definition for abnormal VF was unclear.[34]

Type of OCT device differed between the included studies (**Table 2**). Two studies used handheld SD- OCT (HH-OCT) (Bioptigen)[35,36], two studies used tabletop SD-OCT (Spectralis, Heidelberg Engineering)[12,34] and one study used HH-OCT (Bioptigen) as well as tabletop SD-OCT (Spectralis, Heidelberg Engineering).[13] A detailed overview of the used OCT protocols is presented in Table 2. With regard to the three cross-sectional studies, abnormal RNFL and GCL-IPL thickness was determined as the lower fifth and first percentile in the normal-vision OPG group in two studies[35,36] and one study calculated

Table 1. Characteristics of included studies and their patient population

First author (year)	Study design	Diagnostic or prognostic	Country	No. of patients/ no. of eyes	No. of patients with NF-1	Gender (M/F)	Mean age (years)	Tumour type	Follow-up time (months)
Avery (2014)[35]	Cross-sectional case-control study	Diagnostic	USA	53/95 OPG: 33/64 Control group: 20/31	25	28/25	OPG: median 4.8 (1.8-12.6) Control group: median 8.7 (1.7-16.7)	OPG	NA
Avery (2015)[13]	Longitudinal cohort study	Diagnostic	USA	46/55 Stable vision 39/45 New vision loss: 7/10	31 eyes Stable vision: 29 eyes New vision loss: 2 eyes	20/35 eyes	Stable vision: 6.5 (1.2-17.1) New vision loss: 6.9 (1.1-17.8)	OPG	New vision loss: mean 16.5 (6.1-34.1); Stable vision: 13.4 (5.7-23.7)
Fard (2013)[12]	Longitudinal cohort study	Diagnostic	Iran	23/38	6	11/12	5.8 (4-9.3)	OPG	24
Gu (2014)[36]	Cross-sectional cohort study	Diagnostic	USA	26/47 Normal vision: 19/31 Abnormal vision: 11/16	20 Normal vision: 16/19 Abnormal vision: 4/11	15/15 Normal vision: 9/10 Abnormal vision: 6/5	Normal vision: 5.3 (2.5-12.6) Abnormal vision: 6.1 (2.6-12.8)	OPG	NA
Parrozzani (2018)[34]	Cross-sectional cohort study	Diagnostic	Italy	38/66	38	19/19	7.6±3.6	OPG	NA

Abbreviations: NA, not applicable; NF-1, Neurofibromatosis type 1; OPG, optic pathway glioma; USA, United States of America.

Table 2. Visual function and OCT parameters as reported in included studies

First author (year)	OCT device	OCT protocol	Comparison (no. of patients/ no. of eyes)	Visual function parameters	OCT parameters	Baseline VA	Baseline VF
Avery (2014)[35]	HH-OCT (Bioptigen)	6x6 mm rectangular scan centered on the optic nerve head using 1000 A-scans across 100 B-scans. 1 participant was imaged using 6x6 mm 300 A-scans per 300 B-scans.	Normal vision (49 eyes) vs abnormal vision (15 eyes) in OPG patients OR OPG (33/64) vs control subjects (20/31)	VA, VF	RNFL	Abnormal vision (15/33 OPG patients): 1 eye abnormal VA only, 7 eyes both abnormal VA and VF	Abnormal vision (15/33 OPG patients): 7 eyes abnormal VF only,7 eyes abnormal VF and VA
Avery (2015)[13]	HH-OCT (Bioptigen) or SD-OCT (Spectralis, Heidelberg Engineering)	HH-OCT: 6x6x2 mm volume scan 300 A-scans across 300 B-scans (2.5 s acquisition time) or 1000 A-scans across 100 B-scans (2.8 s acquisition time). Table-top OCT: TruTrack eye tracking (3.5 mm circle over the optic nerve head). Scans were acquired with high-speed mode (768 A-scans) with an automatic real-time setting of 16.	Stable vision (39/45) vs new vision loss (7/10)	VA, VF	RNFL	NA	NA
Fard (2013)12	SD-OCT (Spectralis, Heidelberg Engineering)	40.000 A scans/second, scan beam with a wavelength of 870 nm.	Stable vision (18/30) vs vision loss/radiological tumour progression (5/8)	BCVA, VF	RNFL, PPR	Stable vision: 0.52±0.38 logMAR (*n*=20); vision loss or radiological tumour progression: 0.53±0.18 logMAR (*n*=6 eyes); *p*=0.96	Stable vision, MD: -8.4±2.5 dB (*n*=11); vision loss or radiological tumour progression , MD: -7.75±2.2 dB (*n*=4 eyes); *p*=0.6
Gu (2014)[36]	HH-OCT (Bioptigen)	6x6 mm image using 1000 A-scans per 100 B-scans. 3 participants were imaged using 300 A-scans per 300 B-scans.	Normal vision (19/31) vs abnormal vision (11/16)	VA, VF	RNFL, GCL-IPL	Normal VA/normal VF: 31/31 eyes; abnormal VA/ normal VF: 3/16 eyes; normal VA/abnormal VF 6/16 eyes; abnormal VA/ abnormal VF 7/16 eyes Abnormal VA 10/16 eyes	Normal VA/normal VF: 31/31 eyes; abnormal VA/ normal VF: 3/16 eyes; normal VA/abnormal VF 6/16 eyes; abnormal VA/ Abnormal VF 7/16 eyes
Parrozzani (2018)[34]	SD-OCT (Spectralis, Heidelberg Engineering)	High speed peripapillary RNFL circle scans (circle scan size, 3.5 mm).	NF-1 with OPG and normal VA (43 eyes) vs NF-1 with OPG and abnormal VA (23 eyes)	VA	RNFL	0.2±0.3 logMAR (range, 0.0-1.4 logMAR; 95% CI: 0.11-0.26 logMAR). Normal VA: 43 eyes; abnormal VA: 23 eyes.	NA

Table 2. Visual function and OCT parameters as reported in included studies (continued)

First author (year)	Baseline RNFL thickness	Baseline GCL-IPL thickness	Follow-up VA	Follow-up VF	Follow-up RNFL thickness	Follow-up GCL-IPL thickness	Cut off value
Avery (2014)[35]	Average RNFL: normal vision 125.1±13.9 µm; abnormal vision 75.8±16.8 µm (p<0.001: patients with and without vision loss); control 128.1±11.0 µm (p>0.05: control vs normal vision OPG)	NA	NA	NA	NA	NA	Abnormal VA: VA ≥ 0.2 logMAR below age-based norms. Abnormal VF: VF defect in any quadrant. Abnormal RNFL thickness: lower fifth and first percentile in the normal-vision OPG group.
Avery (2015)[13]	Global RNFL: stable vision 104.7 ± 30.5 µm; new vision loss 84.7 ± 21.0 µm	NA	NA	NA	Stable vision: 103.3 ± 29.5 µm; new vision loss: 66.5 ± 18.3 µm	NA	VA loss: decline ≥ 0.2 logMAR compared to the baseline visit. VF loss: Humphrey 24-2: 3 or more contiguous points reaching significance (P < 0.05) (Humphrey 24-2) or any constriction greater than 10 degrees across a minimum of 3 contiguous 15-degree vectors using the V-4-E or I-4-E isopter (Goldmann kinetic perimetry). Change in global RNFL thickness: ≥ 10% compared to baseline visit.
Fard (2013)[12]	Average RNFL: stable vision 59.26±8.54 µm (*n*=30); vision loss or radiological tumour progression: 53.87±3.68 µm (*n*=8); *p*=0.09	NA	Stable vision: 0.54±0.37 logMAR (*n*=20); vision loss or radiological tumour progression: 1.13±0.2 logMAR (*n*=6); *p*=0.001	Stable vision: MD: -8.86±2.34 dB (*n*=11); vision loss or radiological tumour progression: MD: -14.00±2.1 dB (*n*=4); *p* = 0.002	Stable vision: 57.46±8.59 µm (*n*=30); vision loss or radiological tumour progression; 45.25±3.45 µm (*n*=8); *p*=0.0004	NA	VA loss: ≥ 0.2 logMAR compared to baseline viit. VF loss: mean VF mean deviation worsened ≥5 dB Change in average RNFL thickness > 5µm in eyes with progressing OPG.

Table 2. Visual function and OCT parameters as reported in included studies (continued)

First author (year)	Baseline RNFL thickness	Baseline GCL-IPL thickness	Follow-up VA	Follow-up VF	Follow-up RNFL thickness	Follow-up GCL-IPL thickness	Cut off value
Gu (2014)[36]	Average RNFL: normal vision: outer 4.5 mm, 34.3±5.3 µm; inner 3.0 mm, 27.7±4.1 µm; center 1.5mm, 13.5±2.1 µm. Average RNFL: abnormal vision: outer 4.5 mm, 18.1±7.2 µm; inner 3.0 mm, 16.7±5.3; center 1.5mm, 9.9±2.2 µm.	Average GCL-IPL: normal vision: outer 4.5 mm, 71.6±7.9 µm; inner 3.0 mm, 92.1±9.1 µm; center 1.5mm, 74.3±9.0 µm. Abnormal vision: outer 4.5 mm, 52.2±5.0 µm; inner 3.0 mm, 60.0±7.9 µm; center 1.5mm, 44.6±12.8 µm	NA	NA	NA	NA	Abnormal VA: VA of ≥ 0.2 logMAR below age-based norms. Abnormal VF: VF defect in any quadrant. Normal vision: normal VA and VF Abnormal vision: abnormal VA and or VF. Abnormal RNFL and GCL-IPL: lower fifth and first percentile in the normal-vision group.
Parrozzani (2018)[34]	Global RNFL: 78.7±23.3 µm Normal VA: 88.14±22.6 µm vs Abnormal VA: 61.07±11.6 µm (p=0.0001)	NA	NA	NA	NA	NA	Abnormal VA: any VA below age-based norms.

Abbreviations: AUC, area under the curve; BCVA, best corrected visual acuity; CI, confidence interval; GCL-IPL, ganglion cell-inner plexiform layer; HH-OCT, Handheld Spectral Domain Coherence Tomography; MD, mean deviation; NA, not applicable; NF-1, Neurofibromatosis type 1; OCT, optical coherence tomography; OPG, optic pathway glioma; PPR, posterior pole retina; RNFL, retinal nerve fiber layer; SD, standard deviation; SD-OCT, Spectral Domain Optical Coherence Tomography; VA, visual acuity; VF, visual field.

a ROC curve to determine the cut-off value of the RNFL thickness between the normal VA group and the abnormal VA group.[34] In the two longitudinal studies, change of RNFL thickness was defined as a decline of ≥ 10% in global RNFL thickness compared to the baseline visit[13] or as a decline of > 5 µm in average RNFL thickness compared to the previous visit.[12]

Methodological quality of included studies

The risk of bias of the included diagnostic studies was assessed by the QUADAS-2 tool and the results are shown in **Figs 2** and **3**. We were not able to apply the QUIPS tool for the risk of bias assessment, because we could not include any prognostic studies in this review. Of the five studies included, one study was judged to have a low or unclear risk of bias for all domains.[13] The other studies all had a high risk of bias for at least two of the four domains assessed with the QUADAS-2 tool.[12,34-36] Two studies had a high risk of bias for the patient selection domain, due to their case-control design and inappropriate reasons for exclusion of patients.[34,35] Four studies were judged to have a high risk of bias regarding the index test, because the authors did not specify thresholds for the index test in advance.[12,34-36] For the reference standard domain, no studies had a high risk of bias. Three studies had a high risk of bias for flow and timing, because not all patients received the same reference standard or not all patients were included in the final analysis.[12,35,36] Applicability concerns were rated low or unclear for four studies.[12,13,34,36] One study was judged to have high applicability concerns for patient selection, because also patients without a brain tumour were included (serving as controls).[35]

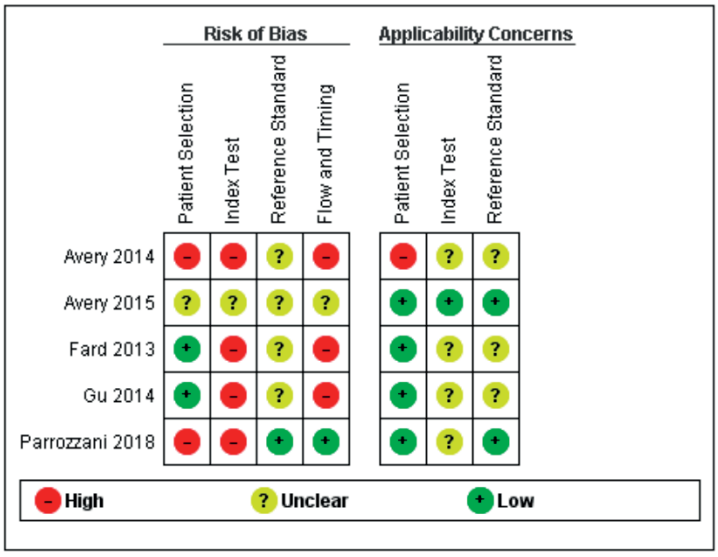


Fig 2. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.

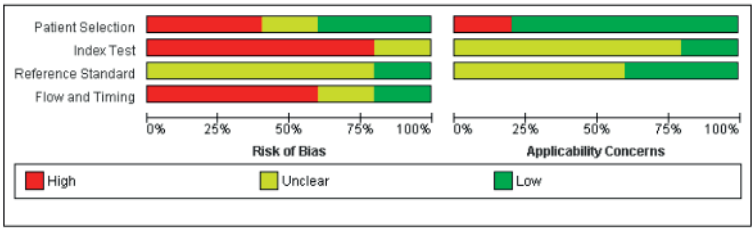


Fig 3. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.

Diagnostic accuracy of retinal OCT

One study used VA as reference standard[34], four studies used a combination of both VA and VF as reference standard.[12,13,35] Four studies used the RNFL thickness as index test[12,13,34,35] and one study used both the RNFL thickness and GCL-IPL thickness as index tests[36] (**Table 2 and Table 3**). Using criteria for abnormality as less than 5% and less than 1%, Avery et al. (2014) reported an AUC for the average RNFL thickness of 0.96 and 0.97, respectively. Estimates of diagnostic accuracy were highest in patients with RNFL thickness in two or more anatomic quadrants meeting less than 5% (SN = 93.3%; SP = 97.9%; PPV = 93.3%; and NPV = 97.9%) and less than 1% (SN = 93.3%; SP = 100%; PPV = 100%; and NPV = 98.0%) criteria.[35] In the study of Avery et al. (2015) they reported the highest diagnostic accuracy estimates for global average RNFL thickness (SN = 60%; SP = 100%; PPV = 100%; and NPV = 92%) and the inferior quadrant RNFL thickness (SN = 50%; SP = 100%; PPV = 100%; and NPV = 90%) using a threshold of ≥ 10% decline in RNFL thickness. Sensitivity, SP, PPV and NPV for vision loss when 2 or more anatomic quadrants were affected was 70%, 100%, 100% and 94%, respectively.[13] Fard et al. (2013) reported an AUC of 0.94 for the average RNFL thickness. Using a decline of more than 5 µm in RNFL thickness, SN and SP was 100% and 90%, respectively.[12] Using a threshold of less than 5%, Gu et al. (2014) reported an AUC of 0.98 for the GCL-IPL inner macula quadrants and an AUC of 0.94 for the RNFL inner quadrants with PPV of 88.9% and 93.8% and NPV of 100% and 96.8%, respectively.[36] Finally, Parrozzani et al. (2018) reported a best balanced cut-off value of the global RNFL thickness of 76.25 µm (SN = 91%; SP = 76%; PPV = 67%; and NPV = 94%) with an AUC of 0.86. Considering the best balanced cut-off values, estimates of diagnostic accuracy were highest in the superior and inferior RNFL quadrants (superior: SN = 87.0%; SP = 81.4%; PPV = 71.4%; and NPV = 92.1%; inferior: SN = 87.0%; SP = 79.1%; PPV = 69.0%; and NPV = 91.9%).[34]

Table 3. Sensitivity, specificity, positive predictive value, negative predictive value and area under the curve of RNFL and GCL-IPL thickness measurements reported in included studies

First author (year)	SN (%)	SP (%)	PPV (%)	NPV (%)	AUC (95% CI)
Avery (2014)[35]	*RNFL thickness* All quadrants, <5%, <1%: 93.3, 93.3 Superior, <5%, <1%: 86.7, 73.3 Nasal, <5%, <1%: 66.7, 60 Inferior, <5%, <1%: 86.7, 86.7 Temporal, <5%, <1%: 73.3, 73.3	*RNFL thickness* All quadrants, <5%, <1%: 81.6, 95.9 Superior, <5%, <1%: 95.9, 97.9 Nasal, <5%, <1%: 95.9, 100 Inferior, <5%, <1%: 93.8, 97.9 Temporal, <5%, <1%: 93.8, 100	*RNFL thickness* All quadrants, <5%, <1%: 60.8, 87.5 Superior, <5%, <1%: 86.7, 91.6 Nasal, <5%, <1%: 83.3, 100 Inferior, <5%, <1%: 81.2, 92.9 Temporal, <5%, <1%: 78.5, 100	*RNFL thickness* All quadrants, <5%, <1%: 97.5, 97.9 Superior, <5%, <1%: 95.9, 92.3 Nasal, <5%, <1%: 90.3, 90.7 Inferior, <5%, <1%: 95.8, 96.0 Temporal, <5%, <1%: 92.0, 92.4	*RNFL thickness* All quadrants, <5%, <1%: 0.96, 0.97 Superior, <5%, <1%: 0.91, 0.85 Nasal, <5%, <1%: 0.81, 0.79 Inferior, <5%, <1%: 0.90, 0.92 Temporal, <5%, <1%: 0.83, 0.86
Avery (2015)[13]	*RNFL thickness* Global: 60 Superior: 60 Nasal: 60 Inferior: 50 Temporal: 40 ≥ 2 anatomic quadrants with ≥ 10% decline: 70	*RNFL thickness* Global: 100 Superior: 93 Nasal: 98 Inferior: 100 Temporal: 96 ≥ 2 anatomic quadrants with ≥ 10% decline: 100	*RNFL thickness* Global: 100 Superior: 66 Nasal: 86 Inferior: 100 Temporal: 67 ≥ 2 anatomic quadrants with ≥ 10% decline: 100	*RNFL thickness* Global: 92 Superior: 91 Nasal: 92 Inferior: 90 Temporal: 88 ≥ 2 anatomic quadrants with ≥ 10% decline: 94	NA
Fard (2013)[12]	*RNFL thickness* Decrease average > 5 µm: 100	*RNFL thickness* Decrease average > 5 µm: 90	NR	NR	*RNFL thickness* Average: 0.94
Gu (2014)[36]	NR	NR	*RNFL thickness* Outer, <5%, <1%: 92.9, 100 Inner, <5%, <1%: 93.8, 100 Center, <5%, <1%: 90.9, 100 *GCL-IPL thickness* Outer, <5%, <1%: 88.9, 93.3 Inner, <5%, <1%: 88.9, 100 Center, <5%, <1%: 93.3, 100	*RNFL thickness* Outer, <5%, <1%: 90.9, 83.8 Inner, <5%, <1%: 96.8, 86.1 Center, <5%, <1%: 83.3, 81.6 *GCL-IPL thickness* Outer, <5%, <1%: 100, 93.8 Inner, <5%, <1%: 100, 96.9 Center, <5%, <1%: 93.8, 91.2	*RNFL thickness* Outer, <5%, <1%: 0.89 (0.76-0.96), 0.81 (0.66-0.90) Inner, <5%, <1%: 0.94 (0.82-0.98), 0.84 (0.71-0.93) Center, <5%, <1%: 0.78 (0.64-0.89), 0.78 (0.64-0.89) *GCL-IPL thickness* Outer, <5%, <1%: 0.97 (0.88-0.99), 0.92 (0.82-0.98) Inner, <5%, <1%: 0.98 (0.92-1.0), 0.96 (0.88-0.99) Center, <5%, <1%: 0.91 (0.79-0.97), 0.90 (0.79-0.97)

Table 3. Sensitivity, specificity, positive predictive value, negative predictive value and area under the curve of RNFL and GCL-IPL thickness measurements reported in included studies (continued)

First author (year)	SN (%)	SP (%)	PPV (%)	NPV (%)	AUC (95% CI)
Parrozzani (2018)[34]	*RNFL thickness* Global, most sensitive 88 µm, best balanced 76 µm: 100.0, 91.3 Temporal, most sensitive 59 µm, best balanced 49 µm: 100.0, 87.0 Superior, most sensitive 115 µm, best balanced 95 µm: 100.0, 87.0 Nasal, most sensitive 111 µm, best balanced 54 µm: 100.0, 78.3 Inferior, most sensitive 117 µm, best balanced 99 µm: 100.0, 87.0	*RNFL thickness* Global, most sensitive 88 µm, best balanced 76 µm: 55.8, 76.7 Temporal, most sensitive 59 µm, best balanced 49 µm: 60.5, 76.7 Superior, most sensitive 115 µm, best balanced 95 µm: 41.9, 81.4 Nasal, most sensitive 111 µm, best balanced 54 µm: 2.3, 72.1 Inferior, most sensitive 117 µm, best balanced 99 µm: 51.2, 79.1	*RNFL thickness* Global, most sensitive 88 µm, best balanced 76 µm: 54.8, 67.7 Temporal, most sensitive 59 µm, best balanced 49 µm: 57.5, 66.7 Superior, most sensitive 115 µm, best balanced 95 µm: 47.9, 71.4 Nasal, most sensitive 111 µm, best balanced 54 µm: 35.4, 60.0 Inferior, most sensitive 117 µm, best balanced 99 µm: 52.3, 69.0	*RNFL thickness* Global, most sensitive 88 µm, best balanced 76 µm: 100.0, 94.3 Temporal, most sensitive 59 µm, best balanced 49 µm: 100.0, 91.7 Superior, most sensitive 115 µm, best balanced 95 µm: 100.0, 92.1 Nasal, most sensitive 111 µm, best balanced 54 µm: 100.0, 86.1 Inferior, most sensitive 117 µm, best balanced 99 µm: 100.0, 91.9	*RNFL thickness* Global: 0.86 Temporal: 0.82 Superior: 0.86 Nasal: 0.77 Inferior: 0.87

Abbreviations: AUC, area under the curve; CI, confidence interval; GCL-IPL, ganglion cell-inner plexiform layer; NPV, negative predictive value; PPV, positive predictive value; RNFL, retinal nerve fiber layer; SN, sensitivity; SP, specificity.

DISCUSSION

We systematically reviewed the diagnostic accuracy and prognostic value of retinal OCT to detect and monitor VA and VF loss in children with a brain tumour. Studies with VA and or VF as reference standard and retinal OCT parameters (RNFL thickness and GCL-IPL thickness) as index test were included in our review. Based on the five included diagnostic studies, we found sensitivity and specificity for average RNFL thickness measurement in children with OPG, ranging from 60.0 to 100.0% and 76.6 to 100%, respectively. Area under the curve for GCL-IPL thickness measurement ranged from 0.91 to 0.98 for centre and inner location, respectively. These findings are in line with the results of a recent review by Banc and associates, reporting that retinal OCT may be a useful instrument in the screening and follow-up of children with OPG.[15] However, the review by Banc and associates did not report on diagnostic accuracy estimates or predictive outcome measures, nor did they evaluate the possible risk of bias of the included studies.

Although our search strategy was designed to identify both diagnostic and prognostic studies on the value of OCT as tool for the detection of VA or VF loss, no prognostic studies were found. To comprehend the relationship between structural retinal changes and functional visual decline in children with a brain tumour, prognostic studies are needed. Understanding this relationship is essential for the use of OCT in addition to standard ophthalmological examination. In adult patients with a brain tumour, several studies support the use of OCT in the early detection and monitoring of VA and VF loss due to chiasmal compression by different types of brain tumours, such as pituitary adenoma, craniopharyngioma and meningioma.[37-40] However, some of these studies also mentioned that functional deficits (e.g. VF defects) from acute or rapidly progressive visual pathway compression typically occur before structural damage on OCT can be established.[37-40]

Performing an accurate and reliable ophthalmological examination is imperative as visual decline represents an indication of disease progression and needs consideration for further treatment in children with a brain tumour located along the visual pathway. Unfortunately, VA and VF assessment is often challenging in young children because of limitations in cooperation and concentration; especially in part of the children with NF1-related OPG due to associated cognitive and behavioural problems.[41] Retinal OCT is currently already widely applied for the detection and monitoring of various (ocular) conditions affecting the visual pathway. Due to the high imaging speed of modern spectral-domain table-top and handheld OCT devices, this examination can also be performed in young children with limited cooperation.[42] In addition, recent studies

showed adequate repeatability and reproducibility indices for the use of a table-top and handheld OCT devices by a well-trained investigator in these patients.[43-47]

Although the use of retinal OCT in children with OPG seems relevant and promising, there are some aspects which need to be considered. One aspect is that normative reference values for RNFL and macular thicknesses for the young population are not incorporated in present-day OCT devices. This means that the results of OCT examination are not automatically compared with values of normal age-matched individuals, as is the case in the adult population. For the interpretation of the OCT results, one needs existing normative databases for the paediatric population[48] or compare consecutive OCT examinations. Another aspect to consider is the possible necessity to perform handheld OCT under general anaesthesia in young children. Three of five authors of studies included in this review reported on the use of handheld OCT in children, with two studies performing handheld OCT in children under general anaesthesia. A disadvantage of incorporating this technique in regular ophthalmological care for young children is that the HH-OCT device is not widely available in (neuro)ophthalmic departments and the application of the device requires specific training and expertise of the operator. Lastly, purchasing the device is expensive, making it less suitable for developing countries.

A possible confounding factor for the use of retinal thickness measurements in children with a brain tumour is the presence of increased intracranial pressure. More than half of the children with a brain tumour present with signs and symptoms of increased intracranial pressure.[49] Eleftheriou and associates found a significantly reduced GCL thickness in adults with normal pressure hydrocephalus compared to healthy individuals (71 µm vs. 79.5 µm, $P = .001$).[50] Another study by Swanson and associates investigated the potential of OCT to detect increased intracranial pressure in children. In their study, intracranial pressure was correlated with maximal RNFL thickness ($r = 0.60$, $P \leq .001$), maximal retinal thickness ($r = 0.53$, $P \leq .001$) and maximal anterior retinal projection ($r = 0.53$, $P = .003$).[51] The severity and duration of increased intracranial pressure might affect retinal OCT results. Therefore, studies with more precise and earlier assessment of the retinal layers with OCT in larger groups of children with increased intracranial pressure are needed to gain further insight into the relationship between the intracranial pressure, retinal layers and visual function.

The findings of this review should be interpreted in light of several limitations. First, all included studies investigated the diagnostic accuracy of retinal OCT to detect VA or VF loss in children with typical OPG, originating directly from the structures of the optic pathway. Therefore, it is not suitable to extrapolate the results of this review to other types of childhood brain tumours. Secondly, included studies demonstrated consider-

able heterogeneity in visual function testing methods, scanning protocols and used cut off values for the visual outcomes in the included studies. Not all studies evaluating OCT in children with a brain tumour routinely acquired and or described baseline and follow-up values of VA, VF and OCT parameters. Although we contacted authors of the included studies, additional data was not always provided. Therefore, we had to exclude a number of studies because we had insufficient data to calculate sensitivity and specificity. Thirdly, most of the included studies had a high risk of bias. The main issues found in assessing the risk of bias were regarding the index test and flow and timing domains, i.e. by not using prespecified thresholds for the index test, using different reference standards for patients without mentioning this in the method section and or loss to follow-up of patients. Besides, the studies had relatively low sample sizes, which may lower the methodological quality of included studies. Moreover, inconsistency of the reported data prevented us from pooling all results in a meta-analysis. The included cross-sectional and longitudinal studies provided some insights into the relationship between structural changes and functional visual decline in paediatric patients with OPG. However, investigating this relationship in adequately powered studies including children with other types of brain tumours besides OPG with and without increased intracranial pressure, is highly needed to provide consistent data regarding retinal OCT and to introduce OCT as objective imaging device for the evaluation of the visual status of children with a brain tumour at diagnosis as well as during follow up.

CONCLUSION

The literature regarding the diagnostic accuracy and prognostic value of retinal OCT parameters to detect VA or VF loss in children with a brain tumour is scarce. The reviewed literature reveals a relatively high risk of bias. Therefore, we cannot draw any solid conclusions regarding the diagnostic nor the prognostic abilities of retinal OCT to detect VA or VF loss in children with a brain tumour. Well designed, adequately powered studies with prospective longitudinal ophthalmological follow-up and standardized protocols should determine which role is reserved for retinal OCT in the ophthalmological screening and follow-up of children with a brain tumour.

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SUPPLEMENTARY DATA

S1 File. Search strategies for electronic databases.

Search strategy used for PubMed

(glioblastoma*[tiab] OR glioma*[tiab] OR optic nerve glioma*[tiab] OR optic pathway glioma*[tiab] OR glioblastoma multiforme[tiab] OR astrocytoma*[tiab] OR craniopharyngioma*[tiab] OR germ cell tumor*[tiab] OR germ cell tumour*[tiab] OR pineal tumor*[tiab] OR pineal tumour*[tiab] OR medulloblastoma*[tiab] OR ependymoma*[tiab] OR atypical teratoid rhabdoid tumor*[tiab] OR atypical teratoid rhabdoid tumour*[tiab] OR ATRT[tiab] OR DIPG[tiab] OR diffuse intrinsic pontine glioma*[tiab] OR oligodendrogli*[tiab] OR choroid plexus tumor*[tiab] OR choroid plexus tumour*[tiab] OR choroid plexus papilloma*[tiab] OR choroid plexus carcinoma*[tiab] OR PNET[tiab] OR primitive neuroectodermal tumor*[tiab] OR primitive neuroectodermal tumour*[tiab] OR "Glioma"[Mesh] OR "Glioma, Subependymal"[Mesh] OR "Optic Nerve Glioma"[Mesh] OR "Astrocytoma"[Mesh] OR "Medulloblastoma"[Mesh] OR "Ependymoma"[Mesh] OR "Neoplasms, Germ Cell and Embryonal"[Mesh] OR optic chiasm*[tiab] OR optic compression*[tiab] OR chiasm compression*[tiab] OR chiasmal compression*[tiab] OR optic tract*[tiab] OR visual pathway*[tiab] OR visual tract*[tiab] OR "Optic Chiasm"[Mesh] OR brain tumor*[tiab] OR brain tumour*[tiab] OR brain neoplasm*[tiab] OR "Brain Neoplasms"[Mesh]) AND (optical coherence tomography[tiab] OR optic coherence tomography[tiab] OR OCT[tiab] OR ganglion cell layer-inner plexiform layer[tiab] OR ganglion cell layer[tiab] OR inner plexiform layer [tiab] OR retinal nerve fiber layer[tiab] OR "Tomography, Optical Coherence"[Mesh])

Search strategy used for Embase

(('brain'/exp OR brain) AND tumor*:ti,ab,kw OR (('brain'/exp OR brain) AND tumour*:ti,ab,kw) OR (brain AND neoplasm*:ti,ab,kw) OR 'brain tumor'/exp OR optic chiasm*:ti,ab,kw OR optic compression*:ti,ab,kw OR chiasm compression*:ti,ab,kw OR chiasmal compression*:ti,ab,kw OR optic trac*:ti,ab,kw OR visual pathway*:ti,ab,kw OR visual tract*:ti,ab,kw OR 'optic chiasm'/exp OR glioblastoma*:ti,ab,kw OR glioma*:ti,ab,kw OR (optic AND nerve AND glioma*:ti,ab,kw) OR (optic AND pathway AND glioma*:ti,ab,kw) OR (glioblastoma AND multiforme:ti,ab,kw) OR astrocytoma*:ti,ab,kw OR craniopharyngioma*:ti,ab,kw OR (germ AND cell AND tumor*:ti,ab,kw) OR (germ AND cell AND tumour*:ti,ab,kw) OR (pineal AND tumor*:ti,ab,kw) OR (pineal AND tumour*:ti,ab,kw) OR medulloblastoma*:ti,ab,kw OR ependymoma*:ti,ab,kw OR (atypical AND teratoid AND rhabdoid AND tumor*:ti,ab,kw) OR (atypical AND teratoid AND rhabdoid AND tumour*:ti,ab,kw) OR atrt:ti,ab,kw OR dipg:ti,ab,kw OR (diffuse AND intrinsic AND pontine AND glioma*:ti,ab,kw) OR oligodendrogli*:ti,ab,kw OR (choroid AND

plexus AND tumor*:ti,ab,kw) OR (choroid AND plexus AND tumour*:ti,ab,kw) OR (choroid AND plexus AND carcinoma*:ti,ab,kw) OR (choroid AND plexus AND papilloma*:ti,ab,kw) OR pnet:ti,ab,kw OR (primitive AND neuroectodermal AND tumor*:ti,ab,kw) OR (primitive AND neuroectodermal AND tumour*:ti,ab,kw) OR 'central nervous system tumor'/exp OR 'glioma'/exp OR 'optic nerve glioma'/exp OR 'astrocytoma'/exp OR 'medulloblastoma'/exp OR 'ependymoma'/exp) AND (('optical'/exp OR optical) AND ('coherence'/exp OR coherence) AND tomography:ti,ab,kw OR (optic AND coherence AND tomography:ti,ab,kw) OR oct:ti,ab,kw OR (ganglion AND cell AND 'layer inner' AND plexiform AND layer:ti,ab,kw) OR (ganglion AND cell AND layer:ti,ab,kw) OR (inner AND plexiform AND layer:ti,ab,kw) OR (retinal AND nerve AND fiber AND layer:ti,ab,kw) OR 'optical coherence tomography'/exp)

Search strategy used for Cochrane Library

(glioblastoma OR glioma OR optic pathway glioma OR glioblastoma multiforme OR astrocytoma OR craniopharyngioma OR germ cell tumour OR germ cell tumor OR pineal tumor OR pineal tumour OR medulloblastoma OR ependymoma OR atypical teratoid rhabdoid tumor OR atypical teratoid rhabdoid tumour OR ATRT OR DIPG OR diffuse intrinsic pontine glioma OR oligodendroglioma OR choroid plexus tumor OR choroid plexus tumour OR choroid plexus papilloma OR PNET OR primitive neuroectodermal tumor OR primitive neuroectodermal tumour OR glioma [MeSH] OR optic nerve glioma [MeSH] OR astrocytoma [MeSH] OR medulloblastoma [MeSH] OR ependymoma [MeSH] OR brain neoplasms [MeSH] OR optic chiasm OR optic compression OR chiasm compression OR chiasmal compression OR optic tract OR visual tract OR visual pathway OR optic chiasm [MeSH] OR brain tumour OR brain tumor OR brain neoplasm) AND (optical coherence tomography OR optic coherence tomography OR rnfl OR gcl OR retinal nerve fiber layer OR ganglion cell layer OR inner plexiform layer OR [Tomography, Optical Coherence] OR OCT)

S1 Table. QUIPS TOOL

1. Patient selection	
Was a consecutive or random sample of patients enrolled?	YES: if a study explicitly stated that they enrolled all consecutive patients, a random sample of eligible patients or patients within a certain time frame. NO: if a different selection procedure was used to include patients. UNCLEAR: if the patient selection procedure was unclear or not reported.
Was a case-control design avoided?	YES: if a study explicitly stated that all patients were included from the same group. NO: if a different selection procedure was used to include patients. UNCLEAR: if the patient selection procedure was unclear or not reported.
Did the study avoid inappropriate exclusions?	YES: if there was no clear selection for including a high proportion of eligible patients. NO: if there were inappropriate exclusions for a high proportion of eligible patients. UNCLEAR: if no exclusion criteria were reported.
Could the selection of patients have introduced bias?	HIGH: if one or more signalling questions were answered with NO. LOW: if all signalling questions were answered with YES. UNCLEAR: in all other instances.
Are there concerns that the included patients do not match the review question?	YES: if the diagnostic accuracy and or prognostic value of OCT was assessed in a case-control design, or in a highly selected group of patients. NO: in all other instances. UNCLEAR: if there was no description of the included patients.
2. Index test	
Were the index test results interpreted without knowledge of the results of the reference standard?	YES: if the index test is always conducted and interpreted prior to the results of the reference standard. NO: if the index test results were interpreted with knowledge of the results of the reference standard. UNCLEAR: if blinding was unclear or not reported.
If a threshold was used, was it pre-specified?	YES: if the threshold used was stated in the methods section. NO: if the threshold used was not defined before gaining study results; and adapted to optimize sensitivity and or specificity of study results. UNCLEAR: if it was unclear or not reported how the threshold was selected. NA: if no threshold was used.
Could the conduct or interpretation of the index test have introduced bias?	HIGH: if one or more signalling questions were answered with NO. LOW: if all signalling questions were answered with YES. UNCLEAR: in all other instances.
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	YES: if thresholds were adapted based on study results and or if the index test results were interpreted unblinded from the reference test study results. NO: if thresholds were prespecified before receiving study results and if authors were blinded for reference tests results when interpreting the index test results. UNCLEAR: in all other instances.
3. Reference standard	
Is the reference standard likely to correctly classify the target condition?	In this systematic review, the reference standard should be VA and/or VF to correctly classify the visual function.

Were the reference standard results interpreted without knowledge of the results of the index test?	YES: if the reference standard results were interpreted without knowledge of or obtained before the results of the index test. NO: if the reference standard results were interpreted with knowledge of the results of the index test. UNCLEAR: if blinding was unclear or not reported.
Could the reference standard, its conduct, or its interpretation have introduced bias?	HIGH: if one or more signalling questions were answered with NO. LOW: if all signalling questions were answered with YES. UNCLEAR: in all other instances.
Are there concerns that the target condition as defined by the reference standard does not match the review question?	YES: if VA and or VF were not used as the reference standard(s). NO: if VA and or VF were used as reference standard. UNCLEAR: if it was unclear or not reported which reference standard was used.
4. Flow and timing	
Was there an appropriate interval between index test and reference standard?	YES: if the time interval between the index test and reference standard was ≤ 2 weeks. NO: if the time interval between the index test and reference standard was more than two weeks. UNCLEAR: if the time interval between index test and reference standard was not reported or unclear.
Did all patients receive the same reference standard?	YES: if all patients received the same reference standard, or if different reference standards were used depending on the age of patients if this was specified in the methods section. NO: if not all patients received the same reference standard without clarifying for this in the methods section. UNCLEAR: if the reference standards used were not reported for all included patients.
Were all patients included in the analysis?	YES: if all patients were included in the analyses. NO: if not all patients who were recruited into the study were included in the analyses. UNCLEAR: if it was unclear or not reported.
Could the patient flow have introduced bias?	HIGH: if one or more signalling questions were answered with NO. LOW: if all signalling questions were answered with YES. UNCLEAR: in all other instances.

Abbreviations: OCT, optical coherence tomography; VA, visual acuity; VF, visual field.
The QUADAS-2 tool is adapted from
https://www.bristol.ac.uk/medialibrary/sites/quadas/migrated/documents/quadas2.pdf.
The criteria for risk of bias assessment have been adjusted in line with this review.

S2 Table. QUIPS TOOL

1. Study participation	**Goal: To judge the risk of selection bias (likelihood that relationship between PF and outcome is different for participants and eligible non-participants)**
Source of target population	The source population is adequately described, including cases and controls.
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias.
Recruitment period	Period of recruitment is adequately described.
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described.
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described.
Adequate study participation	> 90% of eligible patients do participate in the study.
Baseline characteristics	The baseline study sample is adequately described for tumour type, age, gender and the presence of NF1 or not.
Study participation summary	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.
2. Study attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between PF and outcome are different for completing and non-completing participants)**
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is > 90%.
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for tumour type, age, gender and presence of NF1 or not. There are no important differences between these key characteristics and outcomes in participants who completed the study and those who did not.
Study attrition summary	Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome.
3. Prognostic factor measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome)**
Definition of the PF	A clear description of the OCT device and protocol is provided.
Valid and reliable measurement of PF	The type of OCT device and OCT software are adequately described. Continuous OCT measurements or appropriate cut-offs are used for different OCT parameters.
Method and setting of PF measurement	The OCT device used is the same for all study participants, or different devices are used depending on the age of patients which is specified in the methods section.
Proportion of data on PF available for analysis	> 90% of the study sample provided data for OCT measurement.

Method used for missing data	Imputation is used for missing PF data.
PF measurement summary	PF is adequately measured in study participants to sufficiently limit potential bias.
4. Outcome measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF)**
Definition of outcome	Clear cut-offs are defined for loss of visual acuity and visual field.
Valid and reliable measurement of outcome	The method of visual acuity and visual field assessment used is adequately valid and reliable.
Method and setting of outcome measurement	The method and setting of visual acuity and visual field assessment is the same for all study participants, or different methods are used depending on the age of patients which is specified in the methods section.
Outcome measurement summary	Outcome of interest is adequately measured in study participants to sufficiently limit potential bias.
5. Study confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome)**
Important confounders measured	All important confounders, including type of treatment, presence of NF1 or not, tumour location and researcher blinded or not, are measured.
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including frequency and dose chemotherapy or radiation therapy; timing and frequency of surgery).
Valid and reliable measurement of confounders	Measurement of all important confounders is adequately valid and reliable.
Method and setting of confounding Measurement	The method and setting of confounding measurement are the same for all study participants.
Method used for missing data	Imputation is used for missing confounder data.
Appropriate accounting for confounding	Important potential confounders are accounted for in the study design and analysis.
Study confounding summary	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome.
6. Statistical analysis and reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results**
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.
Model development strategy	The strategy for model building is appropriate and is based on a conceptual framework or model. The selected statistical model is adequate for the design of the study.
Reporting of results	There is no selective reporting of results.
Statistical analysis and reporting Summary	The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.

Abbreviations: OCT, optical coherence tomography; NF1, neurofibromatosis type 1; PF: prognostic factor
The QUIPS tool is adapted from https://methods.cochrane.org/sites/methods.cochrane.org.prognosis/files/public/uploads/QUIPS%20tool.pdf.
The criteria for risk of bias assessment have been adjusted in line with this review.

S3 Table. Characteristics of excluded studies.

Study	Reason for exclusion
Abed (2015)[1]	Insufficient data for 2x2 table + comparison between PhNR and the presence or absence of OPG
Avery (2014)[2]	No VA and VF data
Avery (2014)[3]	No VA, VF and OCT parameters data
Avery (2016)[4]	No VA, VF and OCT parameters data
Bialer (2013)[5]	Insufficient data for 2x2 table
Chang (2010)[6]	Insufficient data for 2x2 table + comparison between NF-1 with OPG and NF-1 non-OPG
Estrada (2019)[7]	Insufficient data for 2x2 table + comparison between asymmetric nystagmus with OPG and stable gaze with OPG
Hepokur (2018)[8]	Insufficient data for 2x2 table + comparison between OPG (sporadic or secondary to NF-1) and NF-1 non-OPG
Mediero (2015)[9]	Insufficient data for 2x2 table
Parrozzani (2013)[10]	Insufficient data for 2x2 table + comparison between different visual function tests and the presence or absence of OPG
Sahinoglu-Keskek (2018)[11]	Insufficient data for 2x2 table
Vagge (2020)[12]	Insufficient data for 2x2 table + comparison between different visual function tests and the presence or absence of OPG
Zahavi (2018)[13]	Insufficient data for 2x2 table

Abbreviations: OPG, optic pathway glioma; PhNR, photopic negative response; NF-1, neurofibromatosis type 1; VA, visual acuity; VF, visual field

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S1 Checklist. PRISMA checklist.

Weblink: https://doi.org/10.1371/journal.pone.0261631.s005



CHAPTER 5

Visual impairment in children with a brain tumor: a prospective nationwide multicenter study using standard visual testing and optical coherence tomography (CCISS study)

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BMC Ophthalmol. 2019 doi: 10.1186/s12886-019-1225-8

ABSTRACT

Background

Children with a brain tumor have a high risk of impaired vision. Up to now, visual acuity measurement, visual field testing and orthoptic testing are the most informative diagnostic investigations for the assessment of the visual function. Evaluating vision in children can be challenging given the challenges in cooperation, concentration and age-dependent shifts in visual tests. Since visual loss due to a brain tumor can be progressive and irreversible, we must aim to detect visual impairment as early as possible. Several studies have shown that optical coherence tomography facilitates discovery of nerve fiber damage caused by optic nerve glioma. Consequently, early detection of potential ocular damage will effect treatment decisions and will provide timely referral to visual rehabilitation centers.

Methods/design

The CCISS study is a prospective, observational, multicenter cohort study in the Netherlands. Patients aged 0-18 years with a newly diagnosed brain tumor are invited for inclusion in this study. Follow-up visits are planned at 6, 12, 18 and 24 months. Primary endpoints are visual acuity, visual field and optical coherence tomography parameters (retinal nerve fiber layer thickness and ganglion cell layer - inner plexiform layer thickness). Secondary endpoints include the course of visual function (measured by visual acuity, visual field and optical coherence tomography at different follow-up visits), course of the disease and types of treatment.

Discussion

The CCISS study will heighten the awareness of visual impairment in different types of brain tumors in children. This study will show whether optical coherence tomography leads to earlier detection of visual impairment compared to standard ophthalmological testing (i.e. visual acuity, visual field testing) in children with a brain tumor. Furthermore, the systematic approach of ophthalmological follow-up in this study will give us insight in the longitudinal relation between the course of visual function, course of the disease and types of treatment in children with a brain tumor.

Trial registration

The CCISS study is prospectively registered in the Netherlands Trial Register (NTR) since April 2019. Identifier: NL7697.

BACKGROUND

Brain tumors are the second most common malignancies in children with an age-standardized incidence of 4 / 100.000.[1,2] Due to improvements in diagnostics and treatment, the overall survival rate of children with a brain tumor has improved.[3,4] However, survivors of a brain tumor are at risk for severe late effects of the disease and its treatment.[5] Visual impairment is one of these severe late sequelae of a pediatric brain tumor.[6,7] It is reported that the harmful influence of the disease and/or its treatment on visual functioning has great impact on the general psychomotor development, school participation and societal participation later in life.[7,8]

Brain tumors can cause visual impairment by affecting both the afferent and efferent visual pathway. Important predictors for visual impairment are tumor location and elevated intracranial pressure (ICP).[9,10] Compression of the visual pathway by the tumor may lead to decreased visual acuity (VA), visual field (VF) loss and ocular motility deficits.[6,7,11] Furthermore, obstructive hydrocephalus, mass effect of the brain tumor, brain edema and leptomeningeal involvement by the tumor can cause elevated ICP. Elevated ICP can eventually lead to papilledema and optic disc atrophy, causing visual loss as well.[12] In addition, visual impairment can also be the consequence of different therapies such as surgery, radiation and chemotherapy.[13] Surgical resection of the brain tumor can lead to visual impairment via direct surgical trauma of the optic pathway or via perioperative visual loss. Perioperative visual loss can be the result of abrupt decrease in ICP or interruption of the vascular supply of visual structures.[14,15] Furthermore, radiation can lead to radiation-induced optic neuropathy and/or radiation necrosis of the visual system.[16-18] Finally, different types of chemotherapy can cause optic neuritis, optic neuropathy, papilledema, maculopathy and cataracts.[19,20] Early detection of visual impairment is crucial because visual loss due to a brain tumor or its treatment is often irreversible.[21] In addition, the selection of the most accurate diagnostic testing methods for monitoring visual function per age and type of brain tumor is still inconsistent. Currently, each center uses its own schedule for checkups since there is no international standardization of vision testing for this patient group. Standardization of diagnostic testing methods will optimize earlier detection of changes in visual function, initiation of early treatment to preserve visual function and provide timely referral to visual rehabilitation centers to improve coping with aspects of development in daily life.[22]

Testing of VA is most commonly used as an ophthalmological endpoint in children with a brain tumor. Other frequently used ophthalmological testing methods include VF examination, funduscopy, color and contrast vision and neurophysiological assessment with visual evoked potentials. However, these tests are often not possible in (young)

children because of limitations in cooperation and communication or the tests are too burdensome to perform repeatedly.[7,23-25] Several studies have shown promising results for retinal optical coherence tomography (OCT) as an objective and consistent method for ophthalmological follow up in children with optic pathway glioma or craniopharyngioma.[26-30] Optical coherence tomography makes use of infrared light waves to measure the thickness of separate retinal layers.[31,32] The relation between an abnormal retinal nerve fiber layer (RNFL) thickness and macular ganglion cell layer – inner plexiform layer (GCL-IPL) thickness on one side and decline in VA and VF for children with optic pathway glioma (OPG) on the other side has already been established.[29,33,34] However, studies evaluating the relevance of VA testing, VF testing and OCT for monitoring visual function in different subgroups of childhood brain tumors at different time points of follow-up are not available yet.

The results of our CCISS study: "Child Central nervous tumors InSight in Sight" will provide information on the development of the visual function in children with different types of brain tumors in the Netherlands. The aim of this study is to investigate whether OCT leads to earlier detection of visual impairment compared to standard ophthalmological testing (VA, VF) in children with a brain tumor. Furthermore, this study will provide information about the longitudinal relation between the course of visual function, course of the disease and types of treatment in children with a brain tumor.

METHODS/DESIGN

Study objectives

The primary objective of the study is to investigate whether changes in OCT parameters (thickness of RNFL and GCL-IPL) lead to earlier detection of visual impairment compared to standard ophthalmological testing (VA, VF testing) in children with a brain tumor. Secondary objectives in this study focus on the longitudinal relation between the course of visual function, course of disease and types of treatment in children with a brain tumor.

Study design and setting

We will perform a quantitative prospective, observational, national cohort study in the Netherlands. This multicenter study is embedded in the University Medical Center Utrecht and will be carried out at Amsterdam University Medical Center, Erasmus Medical Center Rotterdam, Princess Máxima Center for Pediatric Oncology Utrecht, University Medical Center Groningen and University Medical Center Utrecht. The Princess Máxima Center for Pediatric Oncology Utrecht is recently opened as main pediatric oncology center in The Netherlands and therefore the largest cohort of patients will be included

here. Selection, invitation and inclusion of patients and performing of ophthalmological tests can take place in all of the abovementioned study sites. Outcomes will be measured at baseline and after six, 12, 18 and 24 months from baseline. Baseline measurement will take place within 4 weeks after the patient is diagnosed with a brain tumor. Allowance of variation around follow-up measurements will be 4 weeks. Depending on tumor type and ophthalmological findings, additional ophthalmological measurements may be necessary and will be performed in the context of patient care.

Study population

Children, aged 0–18 years old, who are newly diagnosed with a brain tumor in the Netherlands between May 15th 2019 and May 15th 2021 are eligible for participation in the study.

Recruitment and informed consent procedure

The pediatric oncologist, neurosurgeon or ophthalmologist from the cooperating centers will select patients for invitation. Oral and written explanation will be provided about the purpose of the study and information on any risks and potential discomfort that could be experienced during the study. Written informed consent will be obtained from the parents or guardians of each patient and of the patients older than 12 years of age themselves. Study withdrawal is possible at any moment without providing the reason.

Study procedures

Standard ophthalmological tests

Visual function of the patients will be examined by age-adapted standard ophthalmological tests and OCT. Standard ophthalmological assessment includes orthoptic evaluation, VA, fundus examination and VF testing. We schedule a total of four follow-up visits at 6, 12, 18, and 24 months after inclusion (see **Table 1**).

Orthoptic examination includes inspection/observation of the eyes, eye position tests, ocular motility and convergence, relative afferent pupillary defect (RAPD), color vision test, stereopsis and VA. Visual acuity testing will be performed for each eye separately (monocular VA). Binocular VA testing will be performed if monocular VA testing fails, for example if the patient is not able to focus and concentrate consistently during testing. Type of VA test will be chosen based on the child's age, cognitive level and ability to cooperate.[23,35] Teller acuity cards (TAC) will be used for infants and preverbal toddlers. If possible, Kay Pictures, E-charts, Snellen or numeral charts will be chosen for patients aged 2–3 years old, 3–5 years old and 6 years old or older, respectively.

Table 1. Examination schedule

Assessment	Baseline	6 months	12 months	18 months	24 months
Check eligibility	x				
Informed consent	x				
Demographic data	x				
Check treatment plan	x	x	x	x	x
MRI	x	x	x	x	x
Ophthalmological assessment:					
· Orthoptic examination	x	x	x	x	x
· Visual acuity	x	x	x	x	x
· Refraction	(x)[a]	(x)[a]	(x)[a]	(x)[a]	(x)[a]
· Slit lamp	(x)[a]	(x)[a]	(x)[a]	(x)[a]	(x)[a]
· Funduscopy	x	x	x	x	x
Visual fields	x	x	x	x	x
Optical Coherence Tomography	x	x	x	x	x
Adverse events	x	X	x	x	x

[a]If there is a clinical indication

Funduscopy will be performed to assess the optic disc for the presence of swelling. Presence of papilledema will be considered if there is disc elevation, retinal vessel obscuration or blurred disc margin. The optic disc is graded according to the modified Frisén Scale. The modified Frisén Scale characterizes disc swelling as Grades 0-5, indicating increasing severity of optic disc edema with Grade 0: normal optic disc, and Grade 5: severe degree of edema.[36] Optic nerve head pallor will also be noted.

Visual field will be tested according to age-appropriate methods using either the Behavioral Visual Field (BEFIE) Screening test[37], the Humphrey Visual Field Analyzer (HFA) (SITA 24–2 FAST algorithm)[38], the semiautomatic-static Peritest[39] or Goldmann kinetic perimetry.[40] Patient age and cooperation and availability of perimetry instruments per study site determines VF testing method. Most likely a BEFIE test will be performed for children aged 0–5 years. Children old enough (between 5 and 6 years) – 18 years will complete a HFA 24–2 SITA-FAST test, a non-automated static peritest or Goldmann perimetry[37,41,42]. Quality of each perimetry test will be assessed using the Examiner Based Assessment of Reliability (EBAR).[42]

Optical coherence tomography

Measurements of circumpapillary RNFL thickness and macular GCL-ILP thickness will be performed in all participants using OCT. Children old enough (aged 5–18 years old) and with ability to cooperate (sitting upright and being able to focus for at least 5 min) will be examined with a table-top spectral domain OCT scan (SD Cirrus OCT; Carl Zeiss Meditec, Dublin, CA) using Optic Disc Cube 200 × 200 cube and Macular Cube

200 × 200 protocols (software version 7.0.1.290). For all young patients (between 0 and 5 years old) a handheld OCT-scan (Bioptigen, Research Triangle Park, North Carolina, USA) will be performed under general anesthesia directly after a scheduled MRI-scan.[43] Thirty minutes before undergoing MRI, all patients will receive mydriatic eye drops (0.5% tropicamide and 2.5% phenylephrine). Once optimal image quality is achieved with handheld OCT scanning, a 12 × 12-mm image will be acquired with 600 A-scans per 80 B-scans. Working distance between the handheld OCT probe and the cornea will be based on the child's axial length and adjusted according to the Pediatric Calculation Table (Bioptigen) adapted from previous recommendations.[44]

An overview of age based ophthalmological assessments for study purpose is given in **Table 2**.

Table 2. Overview of age based ophthalmological assessments for study purpose

Primary outcome measures	Ophthalmological testing methods			
	0.5-2 years	2-3 years	3-5 years	≥ 6 years
Visual acuity	TAC	KP	E- charts	Numeral/Snellen charts
Visual fields	BEFIE	BEFIE	BEFIE	Peritest, HFA 24-2 SITA-FAST, Goldmann Perimetry
Thickness of retinal layers (RNFL, GCL-IPL)	Handheld OCT	Handheld OCT	Handheld OCT	Table-top OCT

Abbreviations: BEFIE, Behavioral Visual Field Screening test; GCL-IPL, ganglion cell layer – inner plexiform layer; HFA, Humphrey Visual Field Analyzer; KP, Kay Pictures; OCT, Optical Coherence Tomography; RNFL, retinal nerve fiber layer; TAC, Teller Acuity Cards

Outcomes

Baseline characteristics

Baseline variables include age, gender, medical and ophthalmological history, neurofibromatosis 1 (yes/no), brain tumor type (histology if available), MRI tumor location, tumor size and presence/absence of hydrocephalus and/or metastases.

Primary outcome measures

Primary outcome measures are visual acuity, visual field and changes in OCT parameters (RNFL thickness and GCL-ILP thickness).

Visual acuity improves with age, most dramatically in the first 24 months of life, followed by a consistent phase of slower improvement continuing up to 72 months of age and likely beyond. We therefore use age-specific VA norms for the definition of normal vision.[35,45] Clinically relevant change in VA will be defined as a difference of 0.2 logarithm

of the minimal angle of resolution (logMAR) VA or more compared to the VA at baseline visit for each eye.[29]

Visual field size/area and sensitivity of normal VF increases with age. Visual field development occurs predominantly in the temporal and inferotemporal field for children between 5 and 12 years.[41] Results of the BEFIE test will be categorized as 'normal' when the peripheral visual field (PVF) extended ≥40 degrees nasally and ≥ 70 degrees temporally, corresponding to the maximum measurable VF with the semiautomatic-static Peritest method.[37] Age-dependent pathological limits for PVF are available for patients under five years of age.[46] An abnormal PVF will be subclassified into symmetric (concentric) PVF defects and asymmetric or homonymous PVF defects. Further subclassification of asymmetric or homonymous PFV defects is made in the article of Koenraads.[37] Visual field loss using HFA24–2 SITA-FAST will be defined as three or more contiguous points reaching significance ($P < 0.05$). Humphrey VF tests will be included if false-positive errors, false negative errors and fixation losses will be less than 20%. Goldmann perimetry will be performed using V-4-E and I-4-E isopters. VF loss using Goldmann perimetry will be defined as any constriction greater than 10 degrees across a minimum of 3 contiguous 15 degree vectors.[29]

Changes in OCT parameters will be determined by measuring RNFL thickness and GCL-ILP thickness at different time points. To account for differences between patient specific circumpapillary RNFL thickness and macular GCL-IPL thickness values at study entry, OCT devices and OCT segmentation algorithms, change in circumpapillary RNFL thickness and macular GCL-IPL thickness will be calculated as a percent change from baseline. A change in circumpapillary RNFL thickness and/or macular GCL-ILP thickness of ≥10% from baseline will be chosen based on previously published data.[29,34,47,48]

Secondary outcome measures

Secondary outcome measures include the course of visual function, course of disease and types of treatment. Visual function will be measured by the above-mentioned primary outcome measures in a follow-up period of 2 years. Disease status will be determined by MRI including tumor size, tumor location, hydrocephalus score and presence or absence of metastases. Optic pathway gliomas will be classified using the modified Dodge classification.[49] Treatment characteristics will include the following types of treatment: 1) neurosurgery; 2) systemic therapy (chemotherapy and/ or targeted therapy; and 3) radiotherapy. Neurosurgical procedures will be defined by biopsy, tumor resection (partial, near total or total) and neurosurgical procedures in patients presenting with hydrocephalus (e.g. external ventricular drain (EVD), endoscopic third ventriculostomy (ETV) and/or ventriculperitoneal (VP) shunt). Systemic therapy will be defined by type

and dose of drug and duration of treatment. Radiotherapy will be defined by local/craniospinal and total dose in Gray (Gy).

Adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the ophthalmological tests. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded if they occur within 24 h after the ophthalmological examination.

Statistical analysis

All baseline variables will be summarized as the distribution of frequency, absolute and percentage. For all baseline variables, synthesis tables containing mean, standard deviation, maximum and minimum will be produced. Data on the outcomes of VA testing, VF and OCT are continues variables. The visual function at diagnosis of a childhood brain tumor measured with VA and VF testing will be reported for tumor subgroups. Data which is missing completely at random (MCAR), will be handled with multiple imputation. With 10 imputations, pooled estimates will be reported. As a sensitivity analysis, a complete case analyses will be presented.

The predictive value of OCT will be investigated by estimating two logistic regression models, separate for VA and VF. The outcome variables are the presence/absence of VA loss and VF loss. Since OCT will be performed at different time points, a mixed model will be carried out to study the association between OCT and the outcome, taking the repeated measurement design of the study into account.

The longitudinal relation between the course of visual function, course of disease and types of treatment will be assessed with linear mixed models. Confounding factors could possibly be medical and ophthalmological history, presence of neurofibromatosis, type of tumor, tumor size, tumor location, metastasis and/or the presence of hydrocephalus.

Statistical analysis will be performed with the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA), version 25.0.0.2.

Sample size

The incidence of a childhood brain tumor in the Netherlands is about 120 per year.[50] This observational study aims to include a nationwide cohort children diagnosed with a brain tumor between May 15th 2019 and May 15th 2021. We estimate a participation rate of 70% since no age-limits and/or barriers like extra burden for the child and/or language difficulties are expected ($N = 168$). We expect 70% of those children to be at

risk of developing visual impairment. Thirty percent of those 168 ($N = 50$) children do not have a risk of developing visual impairment. In logistic regression analysis, 1 variable per 10 patients with the outcome can be included, therefore we expect to be able to correct for 4 confounding factors.

Data management

Personal data will be handled confidentially and according to Good Clinical Practice (GCP) guidelines. The handling of personal data will comply with the General Data Protection Regulation. Patient data will be collected in the certified electronic data capture tool "Castor". Personal patient information (e.g. name and date of birth) will be stored in the participating center separately from the research data. A subject identification code list will be used to link the research data to personal patient information. The subject identification code list will be safeguarded by the coordinating researcher per participating center. All data and documents will be archived by the members of the research team for 15 years.

DISCUSSION

Numerous visual problems have been reported in children with a brain tumor. However, the most appropriate ophthalmological testing methods for monitoring the visual function in this patient group are still unknown. Accurate testing of visual function and timely detection of visual problems will lead to improved patient care and improved quality of life for children diagnosed with a brain tumor. The primary aim of the CCISS study is to assess whether OCT leads to earlier detection of visual decline compared to VA and VF testing in children with a brain tumor. Optical coherence tomography can also be successfully performed in young and non-cooperative children by using a handheld OCT equipment, whereas VA and VF testing are less reliable since they require patient's collaboration. More reliable outcome data for vision can be supportive to improve upcoming treatment decisions. Furthermore, we will collect high quality data on the longitudinal relation between the course of visual function, disease status and type of treatment in children with a brain tumor at standardized follow-up moments.

STUDY STATUS

The final protocol version is 2.0 and date April 2019. This study is currently ongoing. Recruitment of patients has started on 15 May 2019 and we expect the recruitment to be complete by 15 May 2021.

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CHAPTER 6

Ophthalmological findings in youths with a newly diagnosed brain tumor

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JAMA Ophthalmol. 2022 doi: 10.1001/jamaophthalmol.2022.3628

ABSTRACT

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.

INTRODUCTION

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.

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 classi-

fied 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.

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%]).

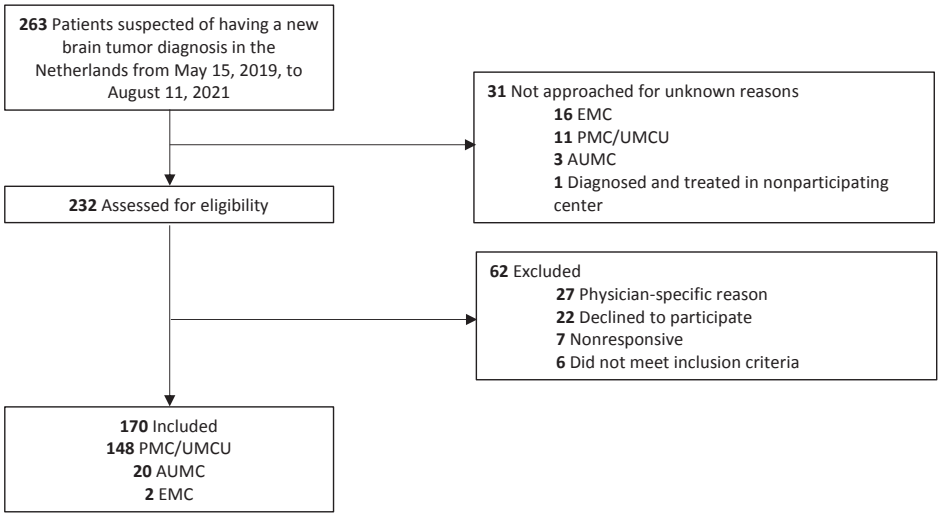


Fig. Patient flowchart.
Abbreviations: AUMC, Amsterdam University Medical Center; EMC, Erasmus Medical Center; PMC, Princess Máxima Center for Pediatric Oncology; UMCU, University Medical Center Utrecht.
Patients were aged 0 to 18 years.

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.

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)
> 5-10	39 (22.9)
> 10- 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 histology	
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)
Without histology[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 / optic chiasm	21 (12.4)
Pineal gland[e]	10 (5.9)
Infratentorial	
All	82 (48.2)
Cerebellum / fourth ventricle	69 (40.6)
Brainstem / 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)

Table 1. Clinicopathological and radiological characteristics (*continued*)

Characteristic	Patients (N = 170)[a]
No information	5 (2.9)
Relation with optic pathways	
Any	51 (30.0)
Mass effect of the tumor on optic pathways	30 (17.6)
No relation 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)
Modified Dodge classification[g]	
1a. Single optic nerve	1 (0.6)
1b. Bilateral optic nerve	0
1c. Cisternal segment optic nerve	3 (1.8)
2a. Central chiasmatic	1 (0.6)
2b. Asymmetric chiasmatic	4 (2.4)
3. Optic tracts	7 (4.1)
3b. Asymmetric tracts	5 (2.9)
4. Diffuse posterior tracts	0
4b. 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)
CT only	4 (2.4)
RT only	0
Neurosurgery + CT	16 (9.4)
Neurosurgery + RT	10 (5.9)
CT + RT	1 (0.6)
Neurosurgery + CT + RT	40 (23.5)

Abbreviations: ATRT, atypical teratoid rhabdoid tumor; CT, chemotherapy; RT, radiotherapy, WHO, World Health Organization.

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

[b]Diagnosis of neurofibromatosis type I is 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); 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); serum/cerebrospinal fluid suspicion of germ cell tumor (n = 5).

[e]Two patients with bifocal germinoma localized in the pineal gland and pituitary gland are classified as 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.

Table 2. Pre-diagnostic symptoms among youths with a brain tumor according to tumor location

		Supratentorial		
	All	**Cerebral hemispheres**	**Midline**	**Infratentorial**
No. (%)	170 (100.0)	35 (20.6)	53 (31.2)	82 (48.2)
Prediagnostic symptomatic interval, median (range), d[a]	61 (0 - 1826)	45.5 (1 - 1461)	91 (0 - 1826)	61 (1 - 1461)
WHO grade I	83.5 (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	30.5 (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)
Behavioural 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 conciousness	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)

Table 2. Pre-diagnostic symptoms among youths with a brain tumor according to tumor location (*continued*)

	All	Supratentorial		Infratentorial
		Cerebral hemispheres	Midline	
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); 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); red eyes (n = 1).

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 present 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 3. Ophthalmological findings among youths with a newly diagnosed brain tumor displayed based on tumor location and timing of ophthalmological examination

		Eyes						
			Supratentorial tumors					
	Patients	Total	Cerebral hemispheres (n = 70)		Midline (n = 106)		Infratentorial tumors (n = 164)	
Findings	(N=170)	(N=340)	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 – 0.2)	0.0 (-0.1 – 1.7)	0.0 (-0.2 – 3.0)	0.1 (-0.1 – 3.0)	0.0 (-0.2 – 0.3)	0.0 (-0.1 – 1.7)
Median (range), Snellen fraction	NA	NA	20/200 (20/16 – 20/32)	20/200 (20/16 – 20/1000)	20/20 (20/12.5 – LP-)	20/25 (20/16 – LP-)	20/20 (20/12.5 – 20/40)	20.20 (20/16 – 20/1000)
Best eye								
Median (range), logMAR	NA	NA	0.0 (-0.1 – 0.1)	0.0 (-0.1 – 0.4)	0.0 (-0.2 – 1.1)	0.1 (-0.1 – 2.0)	0.0 (-0.2 – 0.2)	0.0 (-0.1 – 1.0)
Median (range), Snellen fraction	NA	NA	20/200 (20/16 – 20/25)	20/20 (20/16 – 20/50)	20/20 (20/12.5 – 20/250)	20/25 (20/16 – 20/2000)	20/20 (20/12.5 – 20/32)	20/20 (20/16 – 20/200)

Table 3. Ophthalmological findings among youths with a newly diagnosed brain tumor displayed based on tumor location and timing of ophthalmological examination (*continued*)

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
Worst eye								
Median (range), LogMAR	NA	NA	0.0 (-0.1 – 0.2)	0.0 (-0.1 – 1.7)	0.1 (-0.1 – 3.0)	0.2 (-0.1 – 3.0)	0.0 (-0.1 – 0.3)	0.1 (-0.1 – 1.7)
Median (range), Snellen fraction	NA	NA	20/200 (20/16 – 20/32)	20/20 (20/16 – 20/1000)	20/25 (20/16 – LP-)	20/32 (20/16 – LP-)	20/20 (20/16 – 20/40)	20/25 (20/16 – 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 – 1.5)	0.4 (0.0 – 0.5)	0.4 (0.0 – 1.1)	0.7	0.2 (-0.1 – 1.4)
Median (range), Snellen fraction	NA	NA	NA	20/80 (20/25 – 20/630)	20/50 (20/20 – 20/63)	20/50 (20/20 – 20/250)	20/100	20/32 (20/16 – 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 responses, 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
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]	
Slit-lamp 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)

Table 3. Ophthalmological findings among youths with a newly diagnosed brain tumor displayed 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
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 I	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 II	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 III	21 (12.8)	38 (11.6)	4 (16.7)	0	4 (5.6)	2 (5.9)	16 (23.5)	12 (12.8)
Grade IV	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 V	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)

Table 3. Ophthalmological findings among youths with a newly diagnosed brain tumor displayed based on tumor location and timing of ophthalmological examination (*continued*)

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
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)
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

Table 3. Ophthalmological findings among youths with a newly diagnosed brain tumor displayed based on tumor location and timing of ophthalmological examination (*continued*)

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
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]	

Abbreviations: BCVA, best-corrected visual acuity; BEFIE, Behavioral Visual Field; HFA, Humphrey Visual Field Analyzer; LogMAR, logarithm of minimal angle of resolution scale; LP-, no light perception; NA, not applicable; RAPD, relative afferent pupillary defect.

[a]Ptosis was caused by tumor location and/or cranial nerve palsies (e.g. third nerve palsy), not by post-operative 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).

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.

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.

ADDITIONAL CONTRIBUTIONS

The following persons from the Department of Ophthalmology, University Medical Center Utrecht, assisted with data collection: Ozlem Engin, MD; Willemien de Bruijn, MD; Denise C.P. van der Linden; Pascale E.Q. Cooijmans; Sacha Stramrood-van Buitenen; Meike P. Veenman-Cornielje; Aicha Belhaj; Irem Bozkir; Dagmar Gultzau; Yvonne G.M. Burgers; and Melanie Edelijn. These individuals did not receive compensation outside their salary.

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CHAPTER 7

Diagnostic accuracy of retinal optical coherence tomography in children with a newly diagnosed brain tumour

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Adapted version accepted for publication in Acta Ophthalmologica

ABSTRACT

Purpose

To estimate the diagnostic accuracy of circumpapillary retinal nerve fibre layer (RNFL) thickness and macular ganglion cell layer-inner plexiform layer (GCL-IPL) thickness measurements to discriminate an abnormal visual function (i.e. abnormal age-based visual acuity and/or visual field defect) in children with a newly diagnosed brain tumour.

Methods

This cross-sectional analysis of a prospective longitudinal nationwide cohort study was conducted at 4 hospitals in the Netherlands, including the national referral centre for paediatric oncology. Patients aged 0-18 years with a newly diagnosed brain tumour and reliable visual acuity and/or visual field examination and optical coherence tomography were included. Diagnostic accuracy was evaluated with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Results

Of 115 patients included in the study (67 [58.3%] male; median age 10.6 years [range, 0.2-17.8 years]), reliable RNFL thickness and GCL-IPL thickness measurements were available in 92 patients (80.0%) and 84 patients (73.0%), respectively. The sensitivity for detecting an abnormal visual function was 74.5% for average RNFL thickness and 41.7% for average GCL-IPL thickness at a specificity of 44.5% and 82.9%, respectively. The PPV and NPV were 33.0% and 82.6% for the average RNFL thickness and 57.1% and 82.2% for the average GCL-IPL thickness.

Conclusion

Seven and four out of ten patients with an abnormal visual function were discriminated correctly using average RNFL thickness and average GCL-IPL thickness measurements, respectively. The relative high NPVs signified that patients with normal average RNFL thickness and average GCL-IPL thickness measurements had a relative high certainty of a normal visual function.

INTRODUCTION

Visual sequelae are a common adverse effect in childhood brain tumour survivors.[1–3] The prevalence of visual sequelae reported in the literature ranges between 15% - 67% and depends on the subtype and location of the brain tumour, the presence of increased intracranial pressure and the given treatment modality.[2–5]

Ophthalmological surveillance at diagnosis and during follow-up in children with a braintumour is of great importance for early detection of vision loss and to provide treatment to potentially preserve visual function. In particular, in children with an optic pathway glioma (OPG), treatment is often only initiated once new or progressive vision loss has been identified. However, accurate measurement of visual function (i.e. visual acuity [VA] and visual field [VF]) can be challenging in children with a brain tumour. Impaired neurologic status, fatigue and young age are issues that can limit cooperation and thereby reduce the reliability of standard ophthalmological testing methods.[6] The inability to reliably assess the visual function puts these children at increased risk to develop significant and permanent vision loss before treatment has been initiated. Therefore, a reliable non-behavioural ophthalmological testing method, independent of a child's cooperation, might provide more objective opportunities to estimate the visual function in all children with a newly diagnosed brain tumour.

A promising non-behavioural objective testing method for ophthalmological surveillance is spectral-domain optical coherence tomography (OCT). OCT is a non-invasive imaging modality that applies low-coherence interferometry to measure the thickness of separate retinal layers.[7,8] A spectral-domain handheld OCT device could be used to image the retinal layers in young and/or non-cooperative children with a variety of conditions.[9,10] In the past decade, several investigators have described that a decrease in visual function (i.e. decreased VA and VF defects) is associated with thinning of the circumpapillary retinal nerve fibre layer (RNFL) and macular ganglion cell layer – inner plexiform layer (GCL-IPL) in children with an OPG.[9–13] In a recent systematic review, we found that studies evaluating the diagnostic accuracy of circumpapillary RNFL thickness and macular GCL-IPL thickness measurements for estimating the visual function (VA and VF) in different subtypes of brain tumours in children are lacking.[14] Therefore, we aim to prospectively investigate the diagnostic accuracy of circumpapillary RNFL thickness and macular GCL-IPL thickness measurements to discriminate an abnormal visual function in children recently diagnosed with a brain tumour.

METHODS

Study design and patients

For this cross-sectional study, data was obtained from a prospective longitudinal nationwide cohort study investigating visual impairment in children newly diagnosed with a brain tumour in the Netherlands (Dutch Trial Register, identifier: NL7697)[15]. The study was conducted in compliance with the Helsinki principles and was approved by the Medical Ethical Committee Utrecht as part of the CCISS study (identifier: 19-106/M). After full explanation of the nature of the study, written informed consent was obtained from all parents or legal guardian(s) of children < 16 years of age and from children aged 12-18 years. Consecutive children, aged 0-18 years, with a newly diagnosed brain tumour between May 15, 2019, and August 11, 2021, were eligible for inclusion in this study. Inclusion of children and the ophthalmological examination took place at the Princess Máxima Centre for Paediatric Oncology Utrecht, University Medical Centre Utrecht, Amsterdam University Medical Centre and Erasmus Medical Centre Rotterdam. In some children the ophthalmological examination took place at the University Medical Centre Groningen prior to proton therapy. All children underwent a comprehensive ophthalmological examination including orthoptic examination, VA, fundus examination, VF examination, and OCT within four weeks from brain tumour diagnosis. Children without reliable OCT and/or VA or VF examination at diagnosis were excluded in this cross-sectional study. Data were captured using electronic case report forms.

Clinical and radiological characteristics

Clinical characteristics were collected from electronic health records using a standardized format that included age at brain tumour diagnosis, sex, medical history (including diagnosis of neurofibromatosis type 1) and tumour histology. Histopathological data were obtained from the original pathology reports and included tumour staging according to the World Health Organization classification.[16] Diagnostic MRIs were assessed independently by two medical reviewers, blinded to the patient's clinical status, to obtain the location of the brain tumour, the presence and degree of hydrocephalus and involvement of the optic pathway. Discrepancies between reviewers were discussed with an experienced neuro-radiologist. The presence and extent of hydrocephalus was described following the classification of Traunwieser et al. and was restricted to 3 grades: minor hydrocephalus (enlarged ventricles only), moderate hydrocephalus (enlarged ventricles and additional periventricular fluid accumulation), and severe hydrocephalus (enlarged ventricles, periventricular fluid accumulation and additional flattened cerebral sulci at the vertex).[17] Based on the location, brain tumours were classified into three groups: supratentorial cerebral hemisphere tumours, supratentorial midline tumours, and infratentorial tumours. Two particular types of supratentorial midline tumours in

which the optic pathway is often involved have been analysed in more detail, namely OPGs and craniopharyngiomas. Involvement of the optic pathway by OPGs was classified according to the modified Dodge classification. The most posterior tumour location was assigned to OPGs involving multiple regions.[18]

OCT image acquisition, analysis and definitions

Quantitative circumpapillary RNFL thickness and macular GCL-IPL thickness measurements serve as index tests and were obtained within four weeks from diagnosis using either a tabletop OCT (Cirrus HD OCT 5000, Zeiss Meditec AG, Germany or Spectralis SD-OCT, Heidelberg Engineering, Heidelberg, Germany) or handheld OCT (Bioptigen, Research Triangle Park, North Carolina, USA). Clinical information and reference standard results were not available to the assessors of the index tests.

In children old enough to cooperate and who were evaluated at the University Medical Centre Utrecht, circumpapillary RNFL thickness and macular GCL-IPL thickness measurements were acquired with the tabletop Carl Zeiss Cirrus HD OCT 5000 (Carl Zeiss Meditec AG). Circumpapillary RNFL measurements including average and quadrant-specific (i.e. superior, nasal, inferior and temporal) thicknesses were automatically calculated using the Optic Disc Cube 200 x 200 protocol. Macular GCL-IPL measurements including average, minimum and sector-specific (i.e. average, minimum, supero-temporal, superior, supero-nasal, infero-nasal, inferior and infero-temporal) thicknesses were automatically calculated using the Macular Cube 200 x 200 protocol. Scans with a signal strength <6 dB were discarded. In children who were evaluated at the Amsterdam University Medical Centre or Erasmus Medical Centre Rotterdam, circumpapillary RNFL thickness measurements were acquired with the tabletop Spectralis SD-OCT (Heidelberg Engineering GmbH) in high-speed mode using the eye tracking feature to accurately center a 3.5 mm circle over the optic nerve head. Average and quadrant-specific (i.e. superior, nasal, inferior and temporal) RNFL thicknesses were automatically recorded. Scans with a signal strength <20 dB were discarded. The Spectralis SD-OCT device used in this study does not segment the GCL-IPL and therefore GCL-IPL thickness measurements were not available for children evaluated with the Spectralis SD-OCT. All OCT scans were reviewed for centration or segmentation errors and image artefacts by two examiners (M.A.N., S.M.I.). RNFL thickness and GCL-IPL thickness measurements were considered abnormal when they fall outside the age-based 95% confidence interval (CI) for RNFL thickness or GCL-IPL thickness for the particular OCT device.[19,20]

In young children who were not able to cooperate with tabletop OCT imaging and who were evaluated at the University Medical Centre Utrecht, handheld OCT imaging (Bioptigen, Research Triangle Park, North Carolina, USA) was performed during sedation

after children had undergone MRI as part of their routine clinical care. Children received mydriatic eye drops (0.5% tropicamide and 2.5% phenylephrine hydrochloride) before undergoing MRI. The handheld OCT was performed during slight prolongation of continuous infusion of propofol to maintain adequate sedation. The examiner was positioned at the head of the bed, and eyelids were moved away from the pupil by the examiner's fingers. The handheld OCT lens was held between the index finger and thumb and was placed over the patient's eye. Movement of the handheld OCT probe was minimized by placing the other fingers against the forehead of the patient. According to previous recommendations, the working distance between the handheld OCT probe and the cornea was adjusted based on the child's axial length.[21] Volumetric OCT images were acquired using a 10 mm x 10 mm horizontal raster scan protocol (600 A-scans x 80 B-scan). According to a previous study protocol [22], images were converted using an ImageJ script into a format that could be imported into Copernicus SR Analysis software (Optopol Technology, Zaiwercie, Poland). Circumpapillary RNFL thickness measurements including average and quadrant-specific (i.e. superior, nasal, inferior and temporal) thicknesses were assessed at 6º radii from the optic disc center. The computer software algorithm used for the automatic segmentation of the handheld OCT scans does not calculate the GCL-IPL thickness and therefore these measurements were not available in children imaged with the handheld OCT. The handheld OCT delivers information on the continuous RNFL thickness measurements. Age-based 95% CIs are not yet available for this particular OCT device, so diagnostic accuracy could not be calculated.

VA and VF outcomes and definitions

All children underwent a VA and/or VF examination within 4 weeks from brain tumour diagnosis which serve as reference standard for the visual function. Clinical information (i.e. tumour type and location) and index test results were partial available to the assessors of the reference standard. Best-corrected visual acuity (BCVA) was measured for each eye separately (monocular VA) using age-appropriate tests (e.g., Teller Acuity Cards, Cardiff Acuity Test, Kay Pictures, E-charts, numeral or Snellen Chart). Binocular VA was measured when monocular VA measurement failed. BCVA was converted to the logarithm of the minimum angle of resolution (logMAR) for statistical purposes. The VF was measured by using age-appropriate tests including the Behavioural Visual Field (BEFIE) Screening test [23], the semiautomatic-static Peritest [24], Goldmann kinetic perimetry [25] or the Humphrey Visual Field Analyzer (HFA) (SITA 24–2 FAST algorithm) [26]. Assessment of the VF was performed blinded by two individual graders (G.L.P. and M.A.N.) to avoid misclassification. Both the presence and type of VF defects were scored according to predefined definitions. Results of the BEFIE test were categorized as normal when the peripheral visual field (PVF) extended ≥40 degrees nasally and ≥ 70 degrees temporally, or according to age-specific PVF limits in patients under five years of age. PVF defects

were further classified into symmetric (concentric) and asymmetric or homonymous defects.[23] Results of the HFA 24–2 SITA-FAST or semiautomatic-static Peritest were defined as abnormal when three or more contiguous points reached significance ($P < 0.05$). Results of Goldmann perimetry were classified as abnormal when there was a constriction greater than 10 degrees across a minimum of 3 contiguous 15° vectors. Humphrey 24-2 SITA-FAST tests were excluded when false-positive errors, false negative errors and fixation losses were greater or equal to 20%.[12,27] Discrepancies between graders were resolved by discussion between them. Patients with unreliable VA and VF measurements were excluded from further analysis. An abnormal visual function was defined as VA ≥ 0.2 logMAR below normal age-based norms and/or a VF defect.

Outcome measures and statistical analysis

All patients with reliable VA and/or VF examination and OCT were included in the analysis. Baseline characteristics and continuous circumpapillary RNFL thickness and macular GCL-IPL thickness measurements (microns) obtained both by tabletop OCT and handheld OCT were summarized using standard descriptive statistics (e.g. median and range for non-parametric distributed variables and number and percentage for categorical variables).

A patient was considered screen positive if there was an abnormal visual function (i.e. abnormal age-based VA measurement and/or VF defect) at the specified age-based cut-off level for the two index tests (i.e. circumpapillary RNFL thickness [average, superior, nasal, inferior or temporal thickness] and macular GCL-IPL thickness [average, minimum, supero-temporal, superior, supero-nasal, infero-nasal, inferior and infero-temporal thickness]). Diagnostic accuracy for the tabletop OCT devices is reported as sensitivity (proportion of patients with a true positive index test result [i.e. abnormal RNFL thickness or GCL-ILP thickness measurement] that have an abnormal visual function [i.e. abnormal age-based VA and/or VF defect]), specificity (proportion of patients with a true negative index test result [i.e. normal RNFL or GCL-ILP thickness measurement] that have a normal visual function [i.e. normal age-based VA and VF examination]), positive predictive value (PPV) (proportion of patients with a true positive index test result divided by the group of patients with a true positive and false positive index test result) and negative predictive value (NPV) (proportion of patients with a true negative index test result divided by the group of patients with a true negative and false negative index test result). Diagnostic accuracy was estimated for the total group of patients and for particular tumour subgroups in which the optic pathway is involved (i.e. OPGs and craniopharyngiomas). Results were reported according to the standards for reporting of diagnostic accuracy (STARD).[28] The collected data were analysed using Statistical Package for the Social Sciences (version 26.0.0.1, SPSS Inc., Chicago IL).

RESULTS

Patient population

A total of 230 eyes of 115 patients with a newly diagnosed brain tumour were included (**Fig 1** and **Fig 2**). Fifty-five of the initial 170 patients [32.4%] of our CCISS cohort were excluded because OCT imaging was not performed at diagnosis (N=42 [24.6%]; logistical reasons [N=32, 18.8%], inability of the patient to cooperate with testing [N=6, 3.5%] or poor clinical condition of the patient [N=4, 2.4%]), OCT imaging was unreliable (N=8 [4.7%]) or no reference standard (i.e. VA or VF examination) was performed at diagnosis (N=5 2.9%]).

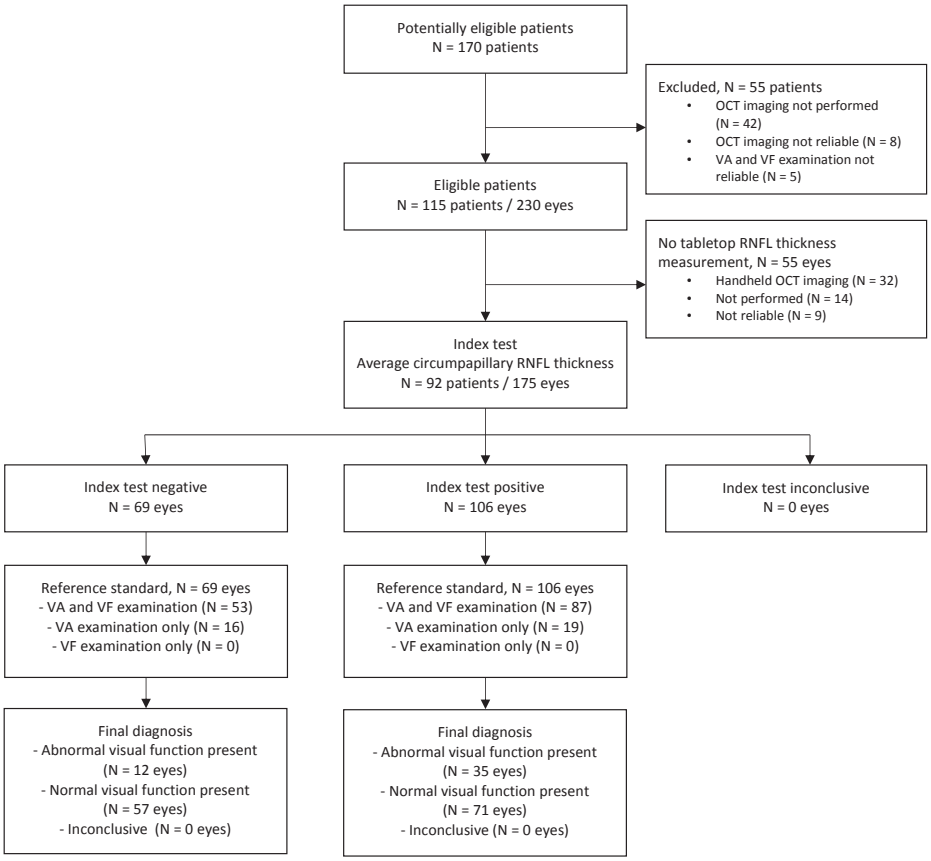


Fig 1. Study flow for average circumpapillary retinal nerve fiber layer thickness measurements. Flow-chart according to standards for reporting diagnostic accuracy.
Abbreviations: OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; VA, visual acuity; VF, visual field.

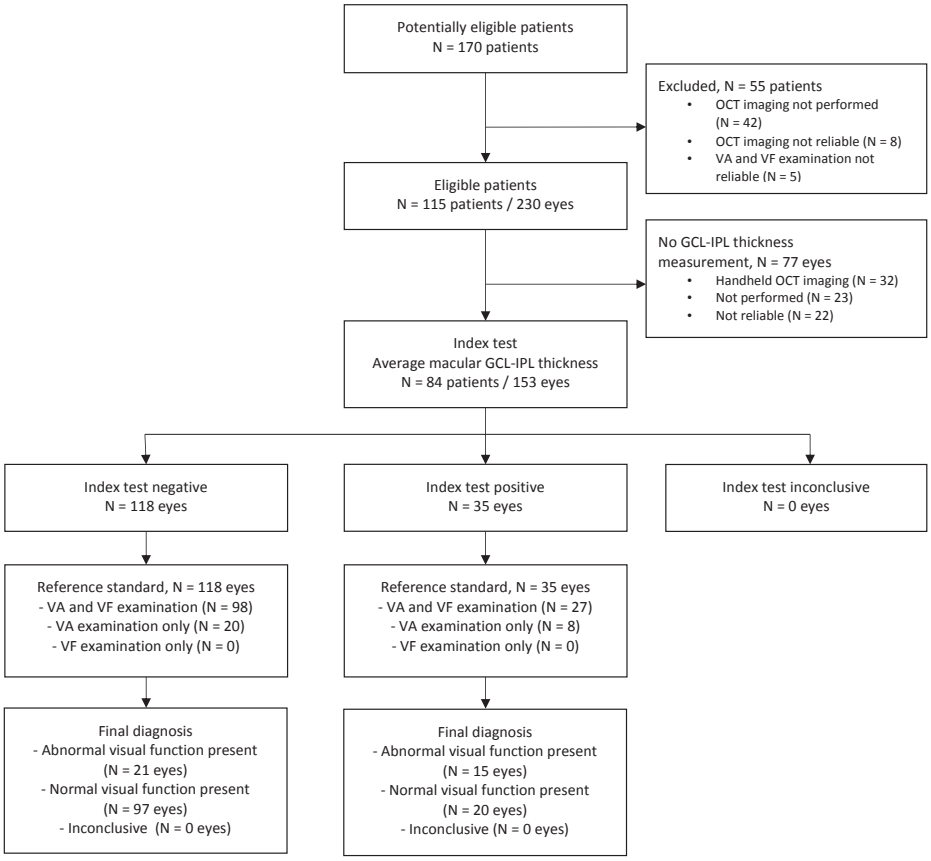


Fig 2. Study flow for average macular ganglion cell layer – inner plexiform layer thickness measurements. Flow-chart according to standards for reporting diagnostic accuracy.
Abbreviations: GCL-IPL, ganglion cell layer – inner plexiform layer; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; VA, visual acuity; VF, visual field.

Table 1 provides an overview of the baseline characteristics. The median age was 10.6 years (range, 0.2 – 17.8 years), 67 of 115 (58.3%) were male. The tumour was located infratentorial in 58 (50.4%) patients, in the supratentorial midline in 33 (28.7%) patients and in the cerebral hemispheres in 24 (20.9%) patients. Nine (27.3%) and 11 (33.3%) patients with a supratentorial midline tumour were diagnosed with an OPG (bilateral, N=6 [66.7%]; unilateral, N=3 [33.3%]) and 11 (33.3%) and craniopharyngioma, respectively.

Results of VA testing and VF examination

Both VA and VF examination were performed in 91 of all 115 included patients (79.1%); in 24 of 115 patients (20.9%) only VA examination was performed. Of the total of 115 patients, 52 eyes of 31 patients (27.0%) had an abnormal visual function (i.e. abnormal age-based VA and/or VF defect). Twelve eyes of 10 patients (8.7%) presented with an

abnormal age-based VA only, 27 eyes of 18 patients (15.7%) with a VF defect only, and 13 eyes of 9 patients (7.8%) with both an abnormal age-based VA and VF defect.

Table 1. Baseline patient characteristics

Characteristic	Total (N = 115)
Age at diagnosis, years	
Median [range]	10.6 [0.2 – 17.8]
0-5	24 (20.9)
> 5-10	30 (26.1)
> 10- 15	42 (36.5)
> 15	19 (16.5)
Male sex	67 (58.3)
Neurofibromatosis type 1[a]	4 (3.5)
Tumour histology	
Low-grade glioma	54 (47.0)
High-grade glioma	15 (13.0)
Medulloblastoma	8 (7.0)
Craniopharyngioma	8 (7.0)
Ependymoma	6 (5.2)
Germ cell tumour	7 (6.1)
Other[b]	8 (7.0)
Without histology[c]	9 (7.5)
Tumour location	
Supratentorial	57 (49.6)
Cerebral hemispheres	24 (20.9)
Midline	33 (28.7)
Thalamus	5
Pituitary gland	11
Optic pathways and/or optic chiasm	9
Pineal gland[d]	8
Infratentorial	58 (50.4)
Optic pathway involvement by optic pathway gliomas	9 (7.8)
Modified Dodge classification[e]	
1a. Single optic nerve	0
1b. Bilateral optic nerve	0
1c. Cisternal segment optic nerve	2 (1.7)
2a. Central chiasmatic	1 (0.9)
2b. Asymmetric chiasmatic	1 (0.9)
3. Optic tracts	1 (0.9)
3b. Asymmetric tracts	4 (3.5)

Table 1. Baseline patient characteristics (*continued*)

Characteristic	Total (N = 115)
4. Diffuse posterior tracts	0
4b. Asymmetric posterior tracts	0
Hydrocephalus at diagnosis[f]	
None	32 (27.8)
Minor	12 (10.4)
Moderate	52 (45.2)
Severe	15 (13.0)
No information	4 (3.5)

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

[a]Diagnosis of neurofibromatosis type I is based on genetic testing.

[b]Atypical teratoid rhabdoid tumour (N = 2); meningioma (N = 1); pineoblastoma (N = 1); plexus tumour (N = 2); dysembryoplastic neuroepithelial tumour (N = 1); hemangioblastoma (N = 1).

[c]Radiological suspicion of optic pathway glioma (N = 3); radiological suspicion of non-optic pathway low-grade glioma (N = 1); serum/cerebrospinal fluid markers of germ cell tumour (N = 5).

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

[e]Optic pathway gliomas were classified according to the modified Dodge classification of Taylor et al., Br J Radiol, 2008. The most posterior tumour location was assigned to OPGs involving multiple regions.

[f]Hydrocephalus was classified according to the classification of Traunwieser et al., Neuro-Oncology Adv, 2020.

Characteristics of tabletop circumpapillary RNFL thickness measurements

In total, tabletop circumpapillary RNFL thickness measurements were available for 175 eyes of 92 patients (**Fig 1**). Fifty-five of 230 eyes (23.9%) of the baseline cohort had to be excluded from RNFL thickness measurements analyses as RNFL thickness measurements were performed with the handheld OCT device (N=32 [13.9%]), were not performed (N=14 [6.1%]) or were unreliable (N=9 [3.9%]). **Table 2** demonstrates the results of the continuous tabletop circumpapillary RNFL thickness measurements (i.e. average, superior, nasal, inferior and temporal thickness) for eyes with a normal visual function (N=128 eyes [73.1%]; median average circumpapillary RNFL thickness, 105 microns [range, 82 - 329 microns]) and eyes with an abnormal visual function (N=47 eyes [26.9%]; median average circumpapillary RNFL thickness, 204 microns [range, 59-605 microns]). For the subgroup of children with an OPG (N=13 eyes [7.4%]), eyes with a normal visual (N=8 eyes [61.5%]) function showed greater average circumpapillary RNFL thickness (median, 105 microns [range, 82-329 microns]) compared to eyes with an abnormal visual function (N=5 eyes [38.5%]; median, 82 microns [range, 59-145 microns]). In the subgroup of children with craniopharyngioma (N=22 eyes [12.6%]), the average circumpapillary RNFL thickness was lower in eyes with a normal visual function (N=12 eyes [54.5%]; median, 104 microns [range, 88-258 microns]) compared to eyes with an abnormal visual function (N=10 eyes [45.5%]; median, 111 microns [range, 83-282 microns]).

Characteristics of handheld circumpapillary RNFL thickness measurements

In total, 26 eyes of 16 patients were available for handheld circumpapillary RNFL thickness measurements at brain tumour diagnosis (i.e. average, superior, nasal, inferior and temporal thickness) (**Table 2**). Six of 32 eyes (18.8%) of the total cohort of handheld circumpapillary RNFL OCT measurements were excluded due to unreliable measurements due to severe papilledema (N=3 [50.0%]) or insufficient image quality (N=3 [50.0%]). The median average circumpapillary RNFL thickness was 117 microns (range 86-209 microns). Subgroup analyses were not performed due to a small sample size.

Diagnostic accuracy of tabletop circumpapillary RNFL thickness measurements

The diagnostic accuracy of tabletop circumpapillary RNFL thickness measurements (i.e. average, superior, nasal, inferior and temporal thickness) in detecting an abnormal visual function at the age-based cut-off levels is summarized in **Table 3**. In the total group of eyes (N= 175), 35 of 47 eyes (74.5%) with an abnormal visual function had an abnormal average circumpapillary RNFL thickness measurement (true positives). Fifty-seven of 128 eyes (44.5%) had a normal visual function and a normal average circumpapillary RNFL thickness measurement (true negatives). Therefore, the average circumpapillary RNFL thickness had a sensitivity of 74.5% at a specificity of 44.5%. The PPV and NPV of the average circumpapillary RNFL thickness for an abnormal visual function are 33.0% and 82.6%, respectively. For the subgroup of patients with an OPG (N=13 eyes [7.4%]), 4 of 5 eyes (80.0%) with an abnormal visual function had an abnormal average circumpapillary RNFL thickness measurement. Six of 8 eyes (75.0%) had a normal visual function and a normal average circumpapillary RNFL thickness measurement. Corresponding numbers for the sensitivity, specificity, PPV and NPV were 80.0%, 75.0%, 66.7% and 85.7%, respectively (**S1 Table**). For the subgroup of patients with craniopharyngioma (N=22 eyes [12.6%]), 4 of 10 eyes (40.0%) with an abnormal visual function had an abnormal average circumpapillary RNFL thickness measurement. Nine of 12 eyes (75.0%) had a normal visual function and a normal average circumpapillary RNFL thickness measurement. Sensitivity, specificity, PPV and NPV for average circumpapillary RNFL thickness measurement in this patient group were 40.0%, 75.0%, 57.1% and 60.0%, respectively (**S2 Table**).

Characteristics of macular GCL-IPL thickness measurements

In total, GCL-IPL thickness measurements were available for 153 eyes of 84 patients (**Fig 2**). Seventy-seven eyes (33.5%) of the baseline cohort were excluded from GCL-IPL thickness measurements analyses because handheld OCT was performed (N=32 [13.9%]), GCL-IPL thickness measurements were unreliable (N=23 [10%]) or not performed (N=22

Table 2. Characteristics of circumpapillary retinal nerve fibre layer thickness measurements in children with a normal and abnormal visual function

	Normal visual function				Abnormal visual function		
	Total	**Total**	**OPG**	**Craniopharyngioma**	**Total**	**OPG**	**Craniopharyngioma**
Tabletop OCT	(N = 175)	(N = 128)	(N = 8)	(N = 12)	(N = 47)	(N = 5)	(N = 10)
RNFL thickness, median (range), µm							
Average	123.5 (59 – 605)	118 (77 – 498)	105 (82 – 329)	104 (88 – 258)	204 (59 – 605)	82 (59 – 145)	110.5 (83 – 282)
Superior	163.5 (81 – 693)	152 (83 – 639)	144.5 (103 – 377)	131 (107 – 352)	264 (81 – 693)	106 (81 – 212)	131 (107 – 347)
Nasal	98.5 (49 – 545)	91 (49 – 514)	68.5 (56 – 323)	78 (58 – 180)	156 (51 – 545)	72 (51 – 86)	99 (56 – 350)
Inferior	159.0 (48 – 815)	152 (77 – 680)	131.5 (108 – 429)	124 (106 – 380)	245 (48 – 815)	114 (48 – 198)	157 (105 – 344)
Temporal	81.5 (37 – 608)[a]	78 (42 – 442)[a]	69.5 (44 – 190)	76 (61 – 121)[a]	94 (37 – 608)	57 (37 – 83)	48 (41 – 94)
Handheld OCT	(n = 26)	(n = 25)	(n = 1)	(n = 0)	(n = 1)	(n = 0)	(n = 0)
RNFL thickness, median (range), µm							
Average	117 (86 – 209)	116 (86 – 209)	130	NA	187	NA	NA
Superior	130 (101 – 280)	128 (101 – 280)	132	NA	185	NA	NA
Nasal	95.5 (85 – 232)	95 (58 – 232)	114	NA	185	NA	NA
Inferior	136 (83 – 227)	133 (83 – 227)	171	NA	226	NA	NA
Temporal	71.5 (50 -100)	71 (50 – 97)	51	NA	100	NA	NA

Abbreviations: NA, not applicable; OCT, optical coherence tomography; OPG, optic pathway glioma; RNFL, retinal nerve fibre layer.
Data are presented as median (range).
[a]Measurement of the temporal retinal nerve fibre layer thickness is missing for one eye.

Table 3. Diagnostic accuracy of tabletop circumpapillary retinal nerve fibre layer thickness

Location	Abnormal visual function (n/N)	Abnormal RNFL thickness (n/N)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Tabletop OCT (N = 175)						
Average[a]	47/175	106/175	74.5	44.5	33.0	82.6
Superior[b]	47/175	98/175	76.6	51.6	36.7	85.7
Nasal[c]	47/175	97/175	68.1	49.2	33.0	80.8
Inferior[d]	47/175	105/175	70.2	43.8	31.4	80.0
Temporal[e,f]	47/174	93/174	80.9	56.7	40.9	88.9

Abbreviations: NPV, negative predictive value; OCT, optical coherence tomography; PPV, positive predictive value; OCT, optical coherence tomography; RNFL, retinal nerve fibre layer.
[a]35/47 eyes (74.5%) with an abnormal visual function had an abnormal average circumpapillary RNFL thickness; 57/128 eyes (44.5%) had a normal visual function and a normal average circumpapillary RNFL thickness.
[b]36/47 eyes (76.6%) with an abnormal visual function had an abnormal superior circumpapillary RNFL thickness; 66/128 eyes (51.6%) had a normal visual function and a normal superior circumpapillary RNFL thickness.
[c]32/47 eyes (68.1%) with an abnormal visual function had an abnormal nasal circumpapillary RNFL thickness; 63/128 eyes (49.2%) had a normal visual function and a normal nasal circumpapillary RNFL thickness.
[d]33/47 eyes (70.2%) with an abnormal visual function had an abnormal inferior circumpapillary RNFL thickness; 56/128 eyes (43.8%) had a normal visual function and a normal inferior circumpapillary RNFL thickness.
[e]Diagnostic accuracy of the temporal retinal nerve fibre layer thickness is missing for one eye.
[f]38/47 eyes (80.9%) with an abnormal visual function had an abnormal temporal circumpapillary RNFL thickness; 72/127eyes (56.7%) had a normal visual function and a normal temporal circumpapillary RNFL thickness.

[9.6%]). **Table 4** shows the results of the continuous GCL-IPL thickness measurements (i.e. average, minimum, supero-temporal, superior, supero-nasal, infero-nasal, inferior and infero-temporal thickness) for eyes with a normal visual function (N=117 eyes [76.5%]; median average macular GCL-IPL thickness, 84 microns [range, 57-100 microns]) and eyes with an abnormal visual function (N=36 eyes [23.5%]; median average macular GCL-IPL thickness, 78 microns [range, 54-94 microns]). For the subgroup of children with an OPG (N=15 eyes), eyes with a normal visual function showed greater average macular GCL-IPL thickness (median, 76 microns [range, 61-87 microns]) compared to eyes with an abnormal visual function (median, 62 microns [range, 54-71 microns]). Also, in children with a craniopharyngioma the average macular GCL-IPL thickness was greater in eyes with a normal visual function (median, 85 microns [range, 57-96 microns]) compared to eyes with an abnormal visual function (median, 72 microns [range, 64-80 microns]).

Diagnostic accuracy of macular GCL-IPL thickness measurements

The diagnostic accuracy of macular GCL-IPL thickness measurements (i.e. average, minimum, supero-temporal, superior, supero-nasal, infero-nasal, inferior and infero-temporal thickness) in detecting an abnormal visual function at the age-based cut-off levels is summarized in **Table 5**. In the total group of eyes (N= 153), 15 of 36 eyes (41.7%) with an abnormal visual function had an abnormal average macular GCL-IPL thickness

Table 4. Characteristics of ganglion cell layer-inner plexiform layer thickness measurements in children with a normal and abnormal visual function

	Normal visual function				Abnormal visual function		
	Total	**Total**	**OPG**	**Craniopharyngioma**	**Total**	**OPG**	**Craniopharyngioma**
Tabletop OCT	(N = 153)	(N = 117)	(N = 9)	(N = 15)	(N = 36)	(N = 6)	(N = 10)
GCL-IPL thickness, median (range), µm							
Average	84 (54 – 100)	84 (57 – 100)	76 (61 – 87)	85 (57 – 96)	78 (54 – 94)	62 (54 – 71)	72 (64 – 80)
Minimum[a]	81 (45 – 97)[a]	82 (47 – 97)	71 (54 – 85)	83 (47 – 93)	69.5 (45 – 91)[a]	51 (45 – 57)	65 (58 – 80)
Supero-Temporal	83 (58 – 96)	84 (58 – 96)	80 (66 – 86)	86 (68 – 94)	79.5 (58 – 92)	62 (58 – 90)	74.5 (68 – 81)
Superior	84 (44 – 104)	84 (54 – 104)	78 (64 – 87)	85 (54 – 98)	78 (44 – 98)	57 (44 – 69)	69 (62 – 77)
Supero-Nasal	85 (51 – 105)	86 (54 – 102)	74 (54 – 89)	84 (54 – 98)	80.5 (51 – 105)	57 (51 – 78)	73 (62 – 83)
Infero-Nasal	84 (49 – 105)	85 (52 – 105)	71 (55 – 88)	84 (52 – 99)	79.5 (49 – 95)	57 (49 – 73)	69.5 (59 – 83)
Inferior	82 (51 – 100)	83 (51 – 100)	75 (57 – 93)	82 (51 -94)	76.5 (54 – 93)	60 (54 – 69)	69 (60 – 85)
Infero-Temporal	85 (58 – 101)	86 (58 – 101)	85 (59 – 88)	88 (63 – 96)	85 (59 – 95)	62 (59 – 86)	78 (69 – 89)

Abbreviations: GCL-IPL, ganglion cell layer-inner plexiform layer; OCT, optical coherence tomography; OPG, optic pathway glioma.
Data are presented as median (range).
[a]Measurement of the minimum ganglion cell layer-inner plexiform layer thickness is missing for two eyes.

Table 5. Diagnostic accuracy of ganglion cell layer–inner plexiform layer thickness

Location	Abnormal visual function (n/N)	Abnormal GCL-IPL thickness (n/N)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Tabletop OCT (N = 153)						
Average[a]	36/153	35/153	41.7	82.9	57.1	82.2
Minimum[b,c]	35/152	65/152	61.8	62.4	32.3	84.9
Supero-Temporal[d]	36/153	25/153	38.9	90.6	56.0	82.8
Superior[e]	36/153	34/153	44.4	84.6	47.1	83.2
Supero-Nasal[f]	36/153	42/153	52.8	80.3	45.2	84.7
Infero-Nasal[g]	36/153	35/153	38.9	82.1	40.0	81.4
Inferior[h]	36/153	40/153	41.7	78.6	37.5	81.4
Infero-Temporal[i]	36/153	29/153	38.9	87.2	48.3	82.3

Abbreviations: GCL-IPL, ganglion cell layer-inner plexiform layer; NPV, negative predictive value; OCT, optical coherence tomography; PPV, positive predictive value; OCT, optical coherence tomography.

[a]15/36 eyes (41.7%) with an abnormal visual function had an abnormal average macular GCL-IPL thickness; 97/117 eyes (82.9%) had a normal visual function and a normal average macular GCL-IPL thickness.

[b]Diagnostic accuracy of the minimum ganglion cell layer-inner plexiform layer thickness is missing for two eyes.

[c]21/34 eyes (61.8%) with an abnormal visual function had an abnormal minimum macular GCL-IPL thickness; 73/117 eyes (62.4%) had a normal visual function and a normal minimum macular GCL-IPL thickness.

[d]14/36 eyes (38.9%) with an abnormal visual function had an abnormal supero-temporal macular GCL-IPL thickness; 106/117 eyes (90.6%) had a normal visual function and a normal supero-temporal macular GCL-IPL thickness.

[e]16/36 eyes (44.4%) with an abnormal visual function had an abnormal superior macular GCL-IPL thickness; 99/117 eyes (84.6%) had a normal visual function and a normal superior macular GCL-IPL thickness.

[f]19/36 eyes (52.8%) with an abnormal visual function had an abnormal supero-nasal macular GCL-IPL thickness; 94/117 eyes (80.3%) had a normal visual function and a normal supero-nasal macular GCL-IPL thickness.

[g]14/36 eyes (38.9%) with an abnormal visual function had an abnormal infero-nasal macular GCL-IPL thickness; 96/117 eyes (82.1%) had a normal visual function and a normal infero-nasal macular GCL-IPL thickness.

[h]15/36 eyes (41.7%) with an abnormal visual function had an abnormal inferior macular GCL-IPL thickness; 92/117 eyes (78.6%) had a normal visual function and a normal inferior macular GCL-IPL thickness.

[i]14/36 eyes (38.9%) with an abnormal visual function had an abnormal infero-temporal macular GCL-IPL thickness; 102/117 eyes (87.2%) had a normal visual function and a normal infero-temporal macular GCL-IPL thickness.

measurement (true positives). Ninety-seven of 117 eyes (82.9%) had a normal visual function and a normal average macular GCL-IPL thickness measurement (true negatives). Therefore, the average macular GCL-IPL thickness had a sensitivity of 41.7% at a specificity of 82.9%. The PPV and NPV of the average macular GCL-IPL thickness for an abnormal visual function are 57.1% and 82.2%, respectively. For the subgroup of patients with an OPG (N=15 eyes [9.8%]), 6 of 6 eyes (100.0%) with an abnormal visual function had an abnormal average macular GCL-IPL thickness measurement. Five of 9 eyes (55.6%) had a normal visual function and a normal average macular GCL-IPL thickness measurement. Corresponding numbers for the sensitivity, specificity, PPV and NPV were 100.0%, 55.6%, 60.0% and 100.0%, respectively (**S3 Table**). For the subgroup of patients with craniopharyngioma (N=25 eyes [16.3%]), 7 of 10 eyes (70.0%) with an abnormal visual function had an abnormal average macular GCL-IPL thickness measurement. Twelve of 15 eyes (80.0%) had a normal visual function and a normal average

macular GCL-IPL thickness measurement. Sensitivity, specificity, PPV and NPV for average macular GCL-IPL thickness measurement in this patient group were 70.0%, 80.0%, 70.0% and 80.0%, respectively (**S4 Table**).

DISCUSSION

In this prospective nationwide study in the Netherlands, we investigated the diagnostic accuracy of circumpapillary RNFL thickness and macular GCL-IPL thickness measurements to discriminate an abnormal visual function (i.e. abnormal age-based VA and/or VF defect) in children with a newly diagnosed brain tumour.

The NPVs of the average circumpapillary RNFL thickness (82.6%) and average macular GCL-IPL thickness (82.2%) are relatively high, but the PPVs (respectively 33.0% and 57.1%) are low, showing that the diagnostic capacity of circumpapillary RNFL thickness and macular GCL-IPL thickness measurements is moderate, which is in line with the low to moderate sensitivity and specificity of the thickness measurements. Our findings show that 7 to 8 out of 10 children with an abnormal visual function are discriminated correctly by the average circumpapillary RNFL thickness and 4 out of 10 children with an abnormal visual function are discriminated correctly by the average macular GCLP-IPL thickness. This while 4 out of 10 children and 8 out of 10 with a normal visual function are detected as such with the average circumpapillary RNFL thickness and the average macular GCL-IPL thickness, respectively.

These findings may be particularly important for children who are not able to cooperate with traditional VA and/or VF examination at brain tumour diagnosis, and in whom RNFL thickness and GCL-IPL thickness measurements could provide a certain amount of reassurance that the visual function is normal. However, at this stage, these thickness measurements should only serve as a fast diagnostic screening test in the acute stage which will be followed by a traditional VA and VF examination when the child is feeling more comfortable. Obtaining reliable RNFL thickness and GCL-IPL thickness measurements may be easier than performing a reliable traditional ophthalmological examination in children with a newly diagnosed brain tumour, because OCT imaging is a rapid, non-invasive and objective testing method.[7,8] In young and non-cooperative children, handheld OCT can be performed under sedation.[9,10] Nevertheless, despite the prospective nature of this study and a standardized ophthalmological screening protocol, OCT imaging was not manageable or was not reliable in 29% of the children, mostly due to logistical reasons or a poor clinical condition of the patient.

Our literature review showed that previous studies only assessed the diagnostic accuracy in children diagnosed with OPG.[14] These studies demonstrated higher overall sensitivity, specificity, PPVs and NPVs for average RNFL thickness [9–13] and average GCL-IPL [10] thickness measurements as compared to our subgroup analysis. Possible explanations for these differences could be the larger and homogeneous study groups in previous studies [9–13], the lower prevalence of patients with OPG and an abnormal visual function [9–13], and the use of different criteria to determine an abnormal RNFL thickness and GCL-IPL thickness (e.g. abnormal criteria were based on the lower fifth and lower first percentile of the normal vision in the OPG group [9,10] compared to our study in which we used age-based 95% confidence interval cut off levels of healthy children). Other studies investigated RNFL thickness measurements in children with craniopharyngioma and reported RNFL thinning in children with vision loss [29,30], however these studies did not specifically assess the diagnostic accuracy.

This study also demonstrates that the continuous GCL-IPL thickness (in microns) was greater in children with a normal visual function compared to children with an abnormal visual function, both in the total group of children and in the subgroups of children with an OPG and craniopharyngioma. Although comparing GCL-IPL thickness measurements between groups was not the primary objective of our study, these numbers provide insight into the absolute differences of GCL-IPL thickness seen in daily practice and the potential of GCL-IPL thickness measurements to differentiate between children with a normal visual function and abnormal visual function. A previous study in children with OPGs showed similar results with significantly smaller GCL-IPL thickness in children with an abnormal visual function.[10] In contrast, the continuous RNFL thickness measurements (in microns) were greater in children with an abnormal visual function when compared to children with a normal visual function, except for the subgroup of children with OPG where the opposite was true. A possible explanation may be that the RNFL thickness was relatively more affected by the presence of papilledema compared to the GCL-IPL thickness.[10] Papilledema is a common finding in children with a newly diagnosed brain tumour and can contribute to an abnormal visual function and elevated RNFL thickness.[31–35] Contrary, in children with an OPG, an abnormal visual function is commonly described as associated with optic disc pallor and subsequent RNFL thinning.[10,36,37]

A number of important limitations should be acknowledged when interpreting the data from our study. Although the aim of the study was to assess the diagnostic accuracy of RNFL thickness and GCL-IPL thickness in children with all types of brain tumours, this heterogeneity of tumour subtypes, tumour locations and the various ophthalmological findings may affect the interpretation of the study results. For example, in children with a brain tumour and severe papilledema, RNFL thickness measurements were often unreli-

able due to segmentation errors. We assessed the diagnostic accuracy of RNFL thickness and GCL-IPL thickness measurements in brain tumour subgroups which are frequently associated with an abnormal visual function (i.e. OPGs and craniopharyngiomas). However, these subgroups were relatively small, limiting drawing solid conclusions about the diagnostic accuracy. Next, we only included children who were able to complete standard ophthalmological examination (i.e. VA or VF examination). Although children who are unable to complete standard ophthalmological examination may benefit the most from OCT imaging, this inclusion criterion was necessary for the study to estimate the diagnostic accuracy of the RNFL thickness and GCL-IPL thickness against the outcomes of ophthalmological examination used in daily practice. Also, we had to accept three different OCT devices in the current study, because not all participating study sites had access to the same OCT device. Each OCT device has its own resolution and computer software algorithm to segment the images and measure the RNFL thickness and GCL-IPL thickness. This could potentially lead to differences in continuous RNFL thickness and GCL-IPL thickness measurements between devices. In order to minimalize this device-specific effect, we considered RNFL thickness and GCL-thickness measurements abnormal when they fall outside the age-based 95% confidence interval for the particular OCT device. Regrettably, the GCL-IPL thickness could not be measured with the software of the tabletop Spectralis SD-OCT (Heidelberg Engineering GmbH) and the handheld OCT (Bioptigen), although these devices are used in the minority of the study patients (8.7%). Also, the handheld OCT device was not available in all participating study sites, resulting in a small group of young children (4.1%) without RNFL thickness and GCL-IPL thickness measurements at brain tumour diagnosis. This could have led to an underrepresentation of this particular age group and associated tumour types, such as OPGs. Moreover, age-based cut-off values for abnormal RNFL thickness measurements were lacking for the handheld OCT device (Bioptigen), making it impossible to evaluate the diagnostic accuracy in patients scanned with this device and representing the limitations of handheld OCT in daily practice. Lastly, there is variability in the timing of ophthalmological examination and OCT imaging (i.e. pre- and post-operatively), which could have introduced bias by influencing the RNFL thickness and GCL-IPL thickness measurements. This variability in timing was unavoidable due to a poor clinical condition of some children pre-operatively.

At this moment, we do not recommend using RNFL thickness and GCL-IPL thickness measurements to influence clinical care decision making in children with a newly diagnosed brain tumour, nor should these measurements replace a thorough ophthalmological examination by a paediatric neuro-ophthalmologist. The main reasons for this recommendation are limitations in retinal layer analyses, the lack of a normality database for children in OCT software and the relatively small subgroup analyses in this

study. However, as mentioned before, the relatively high NPVs for the average circumpapillary RNFL thickness and average macular GCL-IPL thickness signify that children with normal thickness measurements at brain tumour diagnosis have a relative high certainty of a normal visual function and as such may be helpful in children who are not cooperative with traditional VA and/or VF examination. The longitudinal data of the CCISS study will be analysed after the completion of the two year follow-up. These data will provide more insight into the structure-function relationship between RNFL thickness and GCL-IPL thickness and the visual function and may clarify the potential role of OCT imaging in the ophthalmological evaluation of children with a brain tumour.

In conclusion, our study demonstrates that circumpapillary average RNFL thickness measurements have a relatively moderate sensitivity and low to moderate specificity in discriminating an abnormal visual function in children with a newly diagnosed brain tumour. Macular average GCL-IPL thickness measurements have a relatively low to moderate sensitivity and high specificity in the detection of an abnormal visual function in the same patient group. The amount of data on retinal OCT in children with a brain tumour is currently still too little to apply in clinical decision making.

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SUPPLEMENTARY DATA

S1 Table. Diagnostic accuracy of tabletop circumpapillary retinal nerve fibre layer thickness in children with optic pathway glioma

Location	Abnormal visual function (n/N)	Abnormal RNFL thickness (n/N)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Tabletop OCT (N = 13)						
Average[a]	5/13	6/13	80.0	75.0	66.7	85.7
Superior[b]	5/13	7/13	80.0	62.5	57.1	83.3
Nasal[c]	5/13	3/13	20.0	75.0	33.3	60.0
Inferior[d]	5/13	6/13	60.0	62.5	50.0	71.4
Temporal[e]	5/13	7/13	40.0	37.5	28.6	50.0

Abbreviations: NPV, negative predictive value; OCT, optical coherence tomography; PPV, positive predictive value; OCT, optical coherence tomography; RNFL, retinal nerve fibre layer.

[a]4/5 eyes (80.0%) with an abnormal visual function had an abnormal average circumpapillary RNFL thickness; 6/8 eyes (75.0%) had a normal visual function and a normal average circumpapillary RNFL thickness.

[b]4/5 eyes (80.0%) with an abnormal visual function had an abnormal superior circumpapillary RNFL thickness; 5/8 eyes (62.5%) had a normal visual function and a normal superior circumpapillary RNFL thickness.

[c]1/5 eyes (20.0%) with an abnormal visual function had an abnormal nasal circumpapillary RNFL thickness; 6/8 eyes (75.0%) had a normal visual function and a normal nasal circumpapillary RNFL thickness.

[d]3/5 eyes (60.0%) with an abnormal visual function had an abnormal inferior circumpapillary RNFL thickness; 5/8 eyes (62.5%) had a normal visual function and a normal inferior circumpapillary RNFL thickness.

[e]2/5 eyes (40.0%) with an abnormal visual function had an abnormal temporal circumpapillary RNFL thickness; 3/8 eyes (37.5%) had a normal visual function and a normal temporal circumpapillary RNFL thickness.

S2 Table. Diagnostic accuracy of tabletop circumpapillary retinal nerve fibre layer thickness in children with craniopharyngioma

Location	Abnormal visual function (n/N)	Abnormal RNFL thickness (n/N)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Tabletop OCT (N = 22)						
Average[a]	10/22	7/22	40.0	75.0	57.1	60.0
Superior[b]	10/22	7/22	40.0	75.0	57.1	60.0
Nasal[c]	10/22	8/22	50.0	75.0	62.5	64.3
Inferior[d]	10/22	7/22	50.0	83.3	71.4	66.7
Temporal[e,f]	10/22	13/22	90.0	63.6	69.2	87.5

Abbreviations: NPV, negative predictive value; OCT, optical coherence tomography; PPV, positive predictive value; OCT, optical coherence tomography; RNFL, retinal nerve fibre layer.

[a]4/10 eyes (40.0%) with an abnormal visual function had an abnormal average circumpapillary RNFL thickness; 9/12 eyes (75.0%) had a normal visual function and a normal average circumpapillary RNFL thickness.

[b]4/10 eyes (40.0%) with an abnormal visual function had an abnormal superior circumpapillary RNFL thickness; 9/12 eyes (75.0%) had a normal visual function and a normal superior circumpapillary RNFL thickness.

[c]5/10 eyes (50.0%) with an abnormal visual function had an abnormal nasal circumpapillary RNFL thickness; 9/12 eyes (75.0%) had a normal visual function and a normal nasal circumpapillary RNFL thickness.

[d]5/10 eyes (50.0%) with an abnormal visual function had an abnormal inferior circumpapillary RNFL thickness; 10/12 eyes (83.3%) had a normal visual function and a normal inferior circumpapillary RNFL thickness.

[e]Diagnostic accuracy of the temporal retinal nerve fibre layer thickness is missing for one eye.

[f]9/10 eyes (90.0%) with an abnormal visual function had an abnormal temporal circumpapillary RNFL thickness; 7/11 eyes (63.6%) had a normal visual function and a normal temporal circumpapillary RNFL thickness.

S3 Table. Diagnostic accuracy of ganglion cell layer–inner plexiform layer thickness in children with optic pathway glioma

Location	Abnormal visual function (n/N)	Abnormal GCL-IPL thickness (n/N)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Tabletop OCT (N = 15)						
Average[a]	6/15	10/15	100.0	55.6	60.0	100.0
Minimum[b,c]	5/14	11/14	100.0	33.3	45.5	100.0
Supero-Temporal[d]	6/15	7/15	83.3	77.8	71.4	87.5
Superior[e]	6/15	10/15	100.0	55.6	60.0	100.0
Supero-Nasal[f]	6/15	10/15	83.3	44.4	50.0	80.0
Infero-Nasal[g]	6/15	11/15	100.0	44.4	54.5	100.0
Inferior[h]	6/15	8/15	100.0	77.8	75.0	100.0
Infero-Temporal[i]	6/15	7/15	83.3	77.8	71.4	87.5

Abbreviations: GCL-IPL, ganglion cell layer-inner plexiform layer; NPV, negative predictive value; OCT, optical coherence tomography; PPV, positive predictive value; OCT, optical coherence tomography.

[a]6/6 eyes (100.0%) with an abnormal visual function had an abnormal average macular GCL-IPL thickness; 5/9 eyes (55.6%) had a normal visual function and a normal average macular GCL-IPL thickness.

[b]Diagnostic accuracy of the minimum ganglion cell layer-inner plexiform layer thickness is missing for one eye.

[c]5/5 eyes (100.0%) with an abnormal visual function had an abnormal minimum macular GCL-IPL thickness; 3/9 eyes (33.3%) had a normal visual function and a normal minimum macular GCL-IPL thickness.

[d]5/6 eyes (83.3%) with an abnormal visual function had an abnormal supero-temporal macular GCL-IPL thickness; 7/9 eyes (77.8%) had a normal visual function and a normal supero-temporal macular GCL-IPL thickness.

[e]6/6 eyes (100.0%) with an abnormal visual function had an abnormal superior macular GCL-IPL thickness; 5/9 eyes (55.6%) had a normal visual function and a normal superior macular GCL-IPL thickness.

[f]5/6 eyes (83.3%) with an abnormal visual function had an abnormal supero-nasal macular GCL-IPL thickness; 4/9 eyes (44.4%) had a normal visual function and a normal supero-nasal macular GCL-IPL thickness.

[g]6/6 eyes (100.0%) with an abnormal visual function had an abnormal infero-nasal macular GCL-IPL thickness; 4/9 eyes (44.4%) had a normal visual function and a normal infero-nasal macular GCL-IPL thickness.

[h]6/6 eyes (100.0%) with an abnormal visual function had an abnormal inferior macular GCL-IPL thickness; 7/9 eyes (77.8%) had a normal visual function and a normal inferior macular GCL-IPL thickness.

[i]5/6 eyes (83.3%) with an abnormal visual function had an abnormal infero-temporal macular GCL-IPL thickness; 7/9 eyes (77.8%) had a normal visual function and a normal infero-temporal macular GCL-IPL thickness.

S4 Table. Diagnostic accuracy of ganglion cell layer–inner plexiform layer thickness in children with craniopharyngioma

Location	Abnormal visual function (n/N)	Abnormal GCL-IPL thickness (n/N)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Tabletop OCT (N = 25)						
Average[a]	10/25	10/25	70.0	80.0	70.0	80.0
Minimum[b]	10/25	16/25	90.0	53.5	56.3	88.9
Supero-Temporal[c]	10/25	7/25	50.0	86.7	71.4	72.2
Superior[d]	10/25	9/25	60.0	80.0	66.7	75.0
Supero-Nasal[e]	10/25	11/25	80.0	80.0	72.7	85.7
Infero-Nasal[f]	10/25	11/25	70.0	73.3	63.6	78.6
Inferior[g]	10/25	10/25	70.0	80.0	70.0	80.0
Infero-Temporal[h]	10/25	8/25	50.0	80.0	62.5	70.6

Abbreviations: GCL-IPL, ganglion cell layer-inner plexiform layer; NPV, negative predictive value; OCT, optical coherence tomography; PPV, positive predictive value; OCT, optical coherence tomography.

[a]7/10 eyes (70.0%) with an abnormal visual function had an abnormal average macular GCL-IPL thickness; 12/15 eyes (80.0%) had a normal visual function and a normal average macular GCL-IPL thickness.

[b]9/10 eyes (90.0%) with an abnormal visual function had an abnormal minimum macular GCL-IPL thickness; 8/15 eyes (53.5%) had a normal visual function and a normal minimum macular GCL-IPL thickness.

[c]5/10 eyes (50.0%) with an abnormal visual function had an abnormal supero-temporal macular GCL-IPL thickness; 13/15 eyes (86.7%) had a normal visual function and a normal supero-temporal macular GCL-IPL thickness.

[d]6/10 eyes (60.0%) with an abnormal visual function had an abnormal superior macular GCL-IPL thickness; 12/15 eyes (80.0%) had a normal visual function and a normal superior macular GCL-IPL thickness.

[e]8/10 eyes (80.0%) with an abnormal visual function had an abnormal supero-nasal macular GCL-IPL thickness; 12/15 eyes (80.0%) had a normal visual function and a normal supero-nasal macular GCL-IPL thickness.

[f]7/10 eyes (70.0%) with an abnormal visual function had an abnormal infero-nasal macular GCL-IPL thickness; 11/15 eyes (73.3%) had a normal visual function and a normal infero-nasal macular GCL-IPL thickness.

[g]7/10 eyes (70.0%) with an abnormal visual function had an abnormal inferior macular GCL-IPL thickness; 12/15 eyes (80.0%) had a normal visual function and a normal inferior macular GCL-IPL thickness.

[h]5/10 eyes (50.0%) with an abnormal visual function had an abnormal infero-temporal macular GCL-IPL thickness; 12/15 eyes (80.0%) had a normal visual function and a normal infero-temporal macular GCL-IPL thickness.



CHAPTER 8

General discussion and future perspectives

Thanks to improved diagnostics, treatment modalities and surveillance, an increasing number of children and young adults is a survivor of a brain tumor.[1,2] Hence, awareness of and taking responsibility for the short- and long-term adverse effects caused by the brain tumor or its treatment has become increasingly important. An impaired visual function is one of these adverse effects that poses a substantial burden on the health, quality of life, and participation in daily life of children and adolescents with a brain tumor.[3–7]

More insight into the ophthalmological consequences of a brain tumor is of major importance in order to provide timely and adequate ophthalmological care in children with a brain tumor. In **chapter 3** and **chapter 4**, this thesis identified the need for additional high-quality evidence regarding the prevalence and type of ophthalmological findings and the potential role of retinal optical coherence tomography (OCT) as an objective testing method for the visual function within an unselected cohort of children with a newly diagnosed brain tumor. Evidence on these knowledge gaps is provided by the CCISS study, a nationwide prospective longitudinal cohort study (**chapter 6** and **chapter 7**). This chapter discusses the main findings of this thesis, puts them in a broader perspective and addresses perspectives for future ophthalmological research in children with a brain tumor.

REFERRAL FOR OPHTHALMOLOGICAL EVALUATION AND OPHTHALMOLOGICAL FINDINGS IN CHILDREN WITH A NEWLY DIAGNOSED BRAIN TUMOR

Ophthalmology referral patterns

Ophthalmological evaluation is currently not implemented in standard care for all children with a newly diagnosed brain tumor.[3,8] Moreover, in children who have been evaluated at brain tumor diagnosis, the ophthalmological examination is often suboptimal due to the lack of relevant tests such as the visual field (VF) examination.[9] A potential consequence of this lacking or suboptimal ophthalmological evaluation is that abnormal ophthalmological findings are not detected – or not detected in time, which can lead to a delay in initiating appropriate treatment or, if necessary, referral to a visual rehabilitation center. To this end, in **chapter 3**, we retrospectively investigated the ophthalmology referral patterns in 90 children who were diagnosed with a brain tumor between June 2018 and May 2019 and treated at the Princess Máxima Center, the tertiary national referral center for pediatric oncology care. We found that approximately two-thirds of the children in our cohort were referred for ophthalmological evaluation within six weeks from brain tumor diagnosis. Children who presented with

visual symptoms or hydrocephalus at brain tumor diagnosis were referred more often for ophthalmological evaluation. Although the referral rate in our cohort was higher compared with a recent study that reported a referral rate of 48%[3], there were still some children who were potentially at risk for ophthalmological abnormalities, but who were not referred for ophthalmological evaluation in daily practice. This particularly applied to children with a brain tumor in the cerebral hemispheres, who have been reported in previous literature to be at risk for unrecognized VF defects.[9] Conceivable reasons for this suboptimal referral for ophthalmological evaluation include the absence of (inter) national guidelines for ophthalmological evaluation that account for both tumor type and location, the lack of awareness of healthcare providers of the potential risk of visual impairment in these children, the inability of children to properly recognize and mention their visual complaints and the prioritization of tumor treatment over ophthalmological evaluation.

Prevalence and type of abnormal ophthalmological findings

To date, most studies focused on the ophthalmological findings in children with certain subgroups of brain tumors (i.e. optic pathway gliomas [OPG], craniopharyngiomas and pineal region tumors) that are already known to cause an impaired visual function.[10–14] With this in mind, we retrospectively assessed the prevalence and type of abnormal ophthalmological findings in children presenting with any type and location of a brain tumor in **chapter 3**. We found abnormal ophthalmological findings in about three-quarter (78%) of the children in our cohort, of which eye movement disorders, papilledema and VF defects were the most common findings. It is difficult to compare these findings directly to previous studies, because of the inclusion of children with different types and locations of brain tumors. In addition, the retrospective nature of this study and the absence of a standardized ophthalmological screening protocol may have introduced referral and selection bias. This possibly resulted in an under- or overestimation regarding the prevalence of abnormal ophthalmological findings in the total group of children with a newly diagnosed brain tumor. Therefore, a large prospective study with standardized ophthalmological evaluation in an unselected cohort of children with a newly diagnosed brain tumor is required to further clarify the true prevalence and type of abnormal ophthalmological findings.

To this end and as solid-base for future recommendations regarding ophthalmological evaluation in children with a brain tumor, we designed and conducted the CCISS study **(chapter 5)**. In this nationwide prospective cohort study, we assessed the prevalence and type of abnormal ophthalmological findings with a standardized ophthalmological screening protocol in 170 children with a newly diagnosed brain tumor between May 2019 and August 2021 (**chapter 6**). Our results showed an overall prevalence of abnor-

mal ophthalmological findings of 79%, which is comparable with the prevalence found in our retrospective cohort study (**chapter 3**). Nevertheless, the prevalence of the different types of ophthalmological findings differ between the two cohorts. In particular, VF defects appeared to be less common in the prospective cohort (28% versus 58%). This difference may be explained by both the use of stringent definitions regarding the presence of VF defects in the prospective study and a certain degree of selection bias in the retrospective study. Interestingly, the prevalence of visual impairment and blindness was relatively low in both cohorts considering the International Statistical Classification of Diseases and Related Health Problems. Of all children in the prospective cohort, nine percent were binocularly visually impaired of whom two percent were legally blind. These prevalence rates are lower compared to previous studies reporting visual impairment in 50%-54% of the children with a brain tumor.[3,15] Probably, the somewhat random timing of the ophthalmological evaluation (e.g. unspecified time point during follow-up) and the predefined referral criteria in previous literature contribute to these differences in prevalence rates.

Remarkably, abnormal ophthalmological findings were seen during ophthalmological examination in a substantial proportion of the children who initially presented without visual complaints (**chapter 3** and **chapter 6**). Of all children in our prospective cohort who presented without visual complaints, a quarter had VF defects and almost ten percent had a decreased visual acuity (VA) in both eyes. This can partly be explained by children's great ability to (unconsciously) adjust and compensate for their visual complaints and the inability to properly recognize and mention visual complaints.[9,16] Thus, these findings stress that a physician cannot rely solely on the child or parent's reporting of visual symptoms. This is particularly important since we found that the presence of visual complaints was predictive for referral for ophthalmological evaluation (**chapter 3**).

The impact of neurosurgery on ophthalmological outcomes in children with a newly diagnosed brain tumor remains another interesting and open point of discussion. Unfortunately, there was variability in the timing of ophthalmological evaluation (i.e. before and after neurosurgery) in our prospective cohort study. Although this variability was unavoidable due to a poor clinical condition of some children before neurosurgery, this hinders drawing solid conclusions regarding the potential beneficial or harmful effect of neurosurgery on the visual system. Previous studies have focused on the impact of surgical approaches on the visual system in brain tumor subgroups. For example, in patients with craniopharyngioma, the degree of postoperative improvement, normalization and deterioration of the visual function differed between surgical approaches (i.e. transcranial versus endoscopic endonasal) in favor of the endoscopic endonasal approach.[17–22]

Lastly, it is important to investigate to what extent the abnormal ophthalmological findings in children at brain tumor diagnosis are (ir)reversible after initiating appropriate oncological and/or ophthalmic treatment. This is particularly important because an impaired visual function can significantly affect the sensorial development as well as the physical, psychological and social well-being of children.[23] Factors that may contribute to irreversible ophthalmological abnormalities include a relatively long time from symptom onset to diagnosis and treatment, prolonged hydrocephalus with subsequent (severe) papilledema and optic atrophy and an unfavorable tumor location along the visual pathway.[24–26] However, future longitudinal studies are required to explore these potential prognostic factors for the visual outcome in more detail. This information can be helpful to define better strategies in treatment and follow-up.

The feasibility and reliability of ophthalmological examination

The high prevalence of abnormal ophthalmological findings regardless of the presence of visual symptoms emphasize the importance of standardized ophthalmological evaluation at brain tumor diagnosis. However, although an ophthalmological screening protocol and age-adapted testing methods were used in the CCISS study, the results of **chapter 6** demonstrated that it still remains challenging to perform a complete and reliable traditional ophthalmological examination in children recently diagnosed with a brain tumor. In particular, VA measurement and VF examination could not be performed or were not reliable, respectively, in 11% and 33% of the children in the CCISS study at brain tumor diagnosis. These missing ophthalmological data were mostly due to a poor clinical condition of the patient or logistical reasons. For instance, in children with cerebellar mutism syndrome, a condition characterized by the onset of mutism or severely reduced speech and emotional lability after cerebellar or fourth ventricle surgery[27], it was often not possible to perform the ophthalmological examination within the predetermined time frame of four weeks from brain tumor diagnosis.

These difficulties in performing the ophthalmological examination at brain tumor diagnosis demonstrate the need for patient-centered planning and care by specialized ophthalmic staff and age-appropriate equipment.[4] In addition, the question arises whether the potential benefits of ophthalmological examination shortly after diagnosis weigh against the possible patient burden of intensive ophthalmological testing. Depending on several risk factors such as tumor location, tumor volume, the presence of hydrocephalus and whether or not the (type of) neuro-oncological treatment depends on the results of the ophthalmological examination, it may be better to postpone intensive ophthalmological tests several weeks after diagnosis when the child is feeling more comfortable. This will most likely also improve test reliability.

OPTICAL COHERENCE TOMOGRAPHY

The aforementioned challenges regarding the traditional ophthalmological examination in children with a newly diagnosed brain tumor reflect the need for objective, less time-consuming testing methods. One testing method that is proposed in the literature and as such is outlined in detail in **chapter 1** is optical coherence tomography (OCT), a non-invasive imaging method that provides cross-sectional images of human retinal morphology in vivo.[28,29] Until recently, young and/or non-cooperative children were not amenable to OCT imaging, because this technique uses a chin-rest tabletop system that requires good fixation and cooperation. However, the development of a handheld OCT device has overcome these limitations and has proven to be reliable in young and/or non-cooperative children.[30–32] Nowadays, there are multiple applications for the use of OCT in children including the diagnosis and monitoring of retinal disorders, optic nerve disease, nystagmus, intraocular tumors and neurodegenerative conditions.[33–38]

The applicability of retinal OCT in children with a brain tumor

The current body of evidence on the applicability of retinal OCT in children with a brain tumor at diagnosis and during follow-up is limited to studies in children with OPG or craniopharyngioma.[39–50] The systematic literature review in **chapter 4** demonstrated that retinal nerve fiber layer (RNFL) thickness and ganglion cell layer – inner plexiform layer (GCL-IPL) thickness measurements have a relative moderate to high sensitivity and specificity in detecting an abnormal visual function in children with OPG. However, drawing solid conclusions on the diagnostic accuracy and prognostic value of OCT based on this literature review is difficult due to heterogeneity and a considerable risk of bias of the included studies.

In **chapter 7**, evidence on the diagnostic accuracy of retinal OCT to discriminate an abnormal visual function (i.e. decreased VA and/or VF defects) in children with different types of brain tumors was provided by data of the CCISS study. We found relatively high negative predictive values of the average circumpapillary RNFL thickness (83%) and average macular GCL-IPL thickness (82%), but the positive predictive values (respectively 33% and 57%) were low, demonstrating a moderate diagnostic capacity to discriminate an abnormal visual function. Therefore, currently we do not recommend using RNFL thickness and GCL-IPL thickness measurements to influence clinical care decision making or as replacement for a thorough ophthalmological examination in children with a newly diagnosed brain tumor. However, given the relatively high negative predictive values, normal RNFL thickness and GCL-IPL thickness measurements could provide a certain amount of reassurance that the visual function is normal in children who are not able to cooperate with traditional VA and/or VF examination at brain tumour diagnosis.

The majority of studies on the applicability of retinal OCT in children with a brain tumor have focused on measuring the circumpapillary RNFL thickness instead of the GCL-IPL thickness. Circumpapillary RNFL thickness measurements are known to be affected by axonal swelling, axonal atrophy and blood vessel artifacts which potentially reduce their reliability and accuracy.[51,52] In line with this, in **chapter 7** we demonstrated a large variability of continuous average and quadrant-specific RNFL thickness measurements in both children with a normal visual function and abnormal visual function at brain tumor diagnosis. This variability could be explained by the relatively large number of children with papilledema or optic atrophy in the CCISS cohort. Ganglion cell layer – inner plexiform layer thickness measurements are generally less affected by the presence of papilledema or artifacts caused by large retinal vessels and are therefore theoretically a more reliable outcome measure of the visual function in children with a brain tumor compared to the RNFL thickness. Another potential advantage of measuring the GCL-IPL thickness compared to the RNFL thickness is a more accurate representation of the VF since it identifies the exact location of the ganglion cell rather than the accumulation of axons.[42,53,54] This may be particularly helpful in the detection of VF defects in children who are not cooperative with traditional VF examination. Nevertheless, although the variability of average and sector-specific continuous GCL-IPL thickness measurements in **chapter 7** were smaller compared to the RNFL thickness measurements, the diagnostic accuracy of both measurements for the detection of an abnormal visual function in children at brain tumor diagnosis turned out to be moderate. The heterogeneity of tumour subtypes, tumour locations, various ophthalmological findings and the variability in the timing of OCT imaging in our CCISS cohort may have contributed to this moderate diagnostic accuracy.

Facilitators and barriers to implement OCT imaging in the pediatric population

Evaluating potential facilitators and barriers that influence the clinical use of OCT imaging is critical for its implementation in daily practice. As outlined before, in children unable to complete traditional ophthalmological examination, OCT may be helpful as a rapid, non-invasive and objective testing method to provide indirect information about the child's visual status and assist in treatment decisions. In addition, in young children who are not cooperative with tabletop OCT imaging when awake, handheld OCT imaging can be performed under general anesthesia.[37] Nevertheless, several barriers of OCT imaging need to be considered. First, the biometric properties of a child's eye are different compared with those of an adult eye. In particular, the child's eye has a shorter axial length, steeper corneal curvature and greater astigmatism and refractive error. Age-specific adjustments in the handheld OCT protocol (e.g. adjusting the OCT reference arm position and correction of refractive errors) are needed to optimize the image ac-

quisition in young children.[30] Next, interpretation of quantitative retinal layer thickness measurements may be complicated by the lack of incorporation of pediatric normative reference data in present-day OCT devices. This means that retinal layer thickness measurements are not automatically compared with measurements of healthy age-matched individuals, as is the case in the adult population. This is particularly important because previous studies showed that circumpapillary RNFL measurements are significantly thicker in children compared with adults.[55,56] Fortunately, age-based normal values for retinal thickness measurements in the pediatric population are available for different OCT devices.[56] Furthermore, the implementation of handheld OCT imaging in daily practice is limited by its lack of automatic retinal layer segmentation and the inability to acquire serial measurements at the same location. The latter may complicate the use of retinal thickness measurements in the follow-up of children with a brain tumor. Lastly, the handheld OCT device is currently not widely available in (neuro)ophthalmic departments. Using the handheld OCT device in daily practice requires adjustments regarding logistics (i.e. organization of general anesthesia) and specific training and expertise of the ophthalmic staff. In addition, purchasing the handheld OCT device is quite expensive, which restricts its access to mostly large and/or specialized centers. Therefore, future research should focus on the development of a low-cost, portable and reliable OCT system that can increase its access to ophthalmic care, particularly in low resource countries.

Longitudinal ophthalmological follow-up in children with a brain tumor is needed

The research described in this thesis attributes to a better knowledge of the ophthalmological findings and diagnostic accuracy of retinal OCT in children recently diagnosed with a brain tumor. However, besides this knowledge on the ophthalmological findings at brain tumor diagnosis, a better understanding of long-term visual impairment and its impact on the daily life of childhood brain tumor survivors is of utmost importance to provide patient-centered ophthalmological care for children with different types and locations of brain tumors.

Until now, studies investigating long-term visual outcomes in children with a brain tumor mainly focused on subgroups of brain tumors including OPGs and craniopharyngiomas. The total burden of long-term visual impairment in these patient populations is high, as one to two third of the children with OPG and about half of the children with craniopharyngioma have evidence of long-term vision loss.[10,57–59] To our knowledge, studies investigating long-term visual outcomes in children with all types of brain tumors are currently not available. To this end, the two-year follow-up data of our ongoing CCISS study will provide new insights into the prevalence and risk factors (e.g. tumor volume,

tumor location, hydrocephalus and different treatment modalities) of long-term visual impairment in the entire group of children with a brain tumor. The outcomes of this study could also be used to develop evidence-based clinical practice guidelines regarding age-appropriate testing, timing, and frequency of ophthalmological examinations in children with a brain tumor. This will ultimately result in earlier detection of vision loss in those children who are at risk for long-term visual impairment and in a lower burden of ophthalmological examinations in children with a stable visual situation after diagnosis and brain tumor treatment. In addition, it will elucidate the potential role of ophthalmological examination in detecting tumor recurrence or tumor progression. Finally, the outcomes of this longitudinal study can be used for counselling children with a brain tumor and their caregivers regarding the risk of acquired visual impairment, which may result in better acceptance, improved quality of life and more adequate rehabilitation.

Besides a better understanding of the prevalence and risk factors of long-term visual impairment in children with a brain tumor, the long-term outcomes of the CCISS study will provide insight into the prognostic value of retinal OCT. As outlined above in this discussion, the diagnostic capacity of RNFL thickness and GCL-IPL thickness measurements is moderate. This may be due to multiple factors, of which some will affect the OCT measurements less strongly when analyzing the follow-up data (e.g. because of the resolution of severe papilledema). Previous retrospective studies in patients with a tumor along the visual pathway have suggested that thinning of the RNFL and/or GCL-ILP is predictive of vision loss.[43,60,61] If we can confirm these findings in a prospective manner, this may be useful to clinicians when determining if a child needs to start with oncological treatment. Furthermore, the longitudinal OCT thickness measurements could be used to assess the relationship between the severity of papilledema (as measured with the Frísen scale), the degree of RNFL and GCL-IPL thinning and functional vision loss.[53,62,63]

FUTURE PERSPECTIVES FOR OPHTHALMOLOGICAL RESEARCH IN CHILDREN WITH A BRAIN TUMOR

In order to further improve ophthalmological care for children with a brain tumor, several steps need to be taken. For the development of future ophthalmological guidelines, structured reporting on visual outcomes in both clinical care and scientific reports is of major importance. The use of various testing methods and definitions in current practice makes it challenging to draw uniform conclusions. Furthermore, the collaboration between different specialisms, such as pediatric (neuro)ophthalmologists, oncologists, neurologists and neurosurgeons needs to be optimized to create more awareness

of visual impairment and provide children with a brain tumor with the best possible ophthalmological care. Together with the outcomes of longitudinal ophthalmological follow-up studies, this will ultimately lead to the realization of evidence and risk-based ophthalmological guidelines at brain tumor diagnosis and during follow-up. In this way, children identified as being at risk for vision loss could benefit from more intensive ophthalmological monitoring, while in children not at risk, further ophthalmological follow-up can be downsized.

Besides the implementation of personalized risk-based ophthalmological guidelines in children with a brain tumor, future research should focus on the reliability and feasibility of ophthalmological testing methods. In particular, the inability to perform a reliable VF examination in a substantial proportion of the children in the CCISS study reflects the need for a more objective and less time-consuming VF testing method. Pupil perimetry, which maps the visual sensitivity across the VF by objectively measuring pupil responses to onsets of bright stimuli, may fulfill these requirements.[64–66] The use of a head mounted device with a built-in eye tracker and virtual reality environment will improve the applicability of pupil perimetry in children. Although studies investigating (virtual reality) pupil perimetry in children with a brain tumor are lacking, recent studies in neurologically impaired adults have shown promising results regarding the use of pupil perimetry for the detection and monitoring of VF defects.[67,68]

Another field of improvement of future ophthalmological care in children with a brain tumor concerns innovative (neuro)imaging techniques such as diffusion tensor imaging (DTI) tractography and electrophysiological monitoring with visual evoked potentials (VEP). These techniques may be particularly useful for intraoperative guidance and to predict postoperative visual outcomes in children with a brain tumor along the visual pathway.[69–72] For example, previous studies have shown promising results for the prediction of postoperative visual outcomes by DTI tractography in adults with suprasellar tumors[73] and by intraoperative VEP in adults with pituitary tumors and craniopharyngiomas.[74,75] Future studies that combine these techniques along with OCT imaging in children with a brain tumor will be incredibly valuable for a better understanding of the visual pathway and the postoperative visual function.

Finally, future studies in children with a brain tumor should focus on the development of reliable at-home monitoring of the visual function with telemedicine techniques. Telemedicine has the potential to improve patient experience by reducing the total number of physical outpatient visits and subsequent lowering patient burden. In ophthalmology, various applications of telemedicine techniques have been described including remote VA and VF assessment.[76–78] In children with a brain tumor along the visual pathway who

require regular outpatient ophthalmological examinations, at-home monitoring of the visual function may provide reassurance in case of a stable visual situation or timely warning in case of visual disturbances. Another potential advantage of telemedicine is that part of the ophthalmological care will remain guaranteed during global crises such as the recent COVID-19 pandemic.[79]

CONCLUSION

In conclusion, this thesis highlights that prospective nationwide research reveals a high prevalence of abnormal ophthalmological findings in children with a newly diagnosed brain tumor regardless of the presence of visual symptoms. These findings emphasize the importance of standardized ophthalmological evaluation at brain tumor diagnosis and the awareness of clinicians for ophthalmological abnormalities in this patient group. In addition, the diagnostic capacity of retinal OCT thickness measurements to discriminate an abnormal visual function in the entire group of children with a newly diagnosed brain tumor is moderate. Therefore, retinal OCT thickness measurements should not affect clinical care decision making nor should they replace a thorough ophthalmological examination at brain tumor diagnosis. Future longitudinal follow-up studies will provide insight into the risk of long-term visual impairment and the prognostic value of retinal OCT for later visual outcomes and will guide us to the realization of personalized risk-based recommendations for ophthalmological screening and monitoring in children with a brain tumor.

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CHAPTER 9

English summary

Nederlandse samenvatting

ENGLISH SUMMARY

Brain tumors are the most common solid tumors in children with an estimated age-adjusted incidence of 6.21 per 100,000. Recent advances in the diagnosis, treatment and surveillance of childhood brain tumors have considerably improved survival, with a current five-year survival rate reaching 75% in developed countries. This improved survival rate stresses the importance of awareness of the adverse effects coinciding with the brain tumor or its treatment. One of these adverse effects is an impaired visual function, which poses a substantial burden on the health, quality of life, and participation in daily life of children with a brain tumor.

This thesis provides insight into the ophthalmological consequences in children with a newly diagnosed brain tumor and in the potential role of retinal optical coherence tomography (OCT) as an objective, non-invasive testing method of the visual function.

Chapter 1 presents a general introduction with the aims and outline of this thesis. This chapter provides background information on childhood brain tumors, the anatomy of the visual pathways, the mechanisms of visual impairment in childhood brain tumors and on multiple testing methods to examine the visual function in children with a brain tumor.

In **chapter 2** we performed a systematic review including 84 studies to provide an extensive overview of the visual function in children with a newly diagnosed craniopharygioma. Craniopharyngiomas are rare, slow-growing brain tumors located near the optic chiasm that often cause visual impairment. The results of our systematic review demonstrated that about half of the children with craniopharyngioma are visually impaired at diagnosis, with decreased visual acuity (41%) and visual field defects (38%) being the most commonly reported. Other frequently reported ophthalmological findings include fundoscopic (33%) and orthoptic (13%) abnormalities. Most of the included studies were of moderate quality due to missing or incomplete information on visual outcomes and selection bias. In addition, variations among the included studies regarding ophthalmological testing methods and outcome definitions precluded a meta-analysis.

In **chapter 3** we retrospectively investigated the ophthalmology referral pattern and the prevalence and types of abnormal ophthalmological findings in 90 children with a newly diagnosed brain tumor who were treated at a single tertiary referral center in the Netherlands, the Princess Máxima Center for Pediatric Oncology Utrecht. Approximately two-thirds of the children (67%) in our study were referred for an ophthalmological

evaluation within six weeks from brain tumor diagnosis. In the children who were evaluated, abnormal ophthalmological findings were present in 78%, with eye movement disorders (66%), papilledema (44%) and visual field defects (58%) being the most common findings.

In **chapter 4** we reported a systematic review to assess the diagnostic accuracy and prognostic value of retinal OCT for the evaluation of the visual function in children with a brain tumor. Only five diagnostic studies in children with an optic pathway glioma (OPG) were eligible for inclusion. These studies reported a moderate to good diagnostic accuracy of retinal nerve fiber layer (RNFL) and ganglion cell layer – inner plexiform layer (GCL-IPL) thickness measurements for the detection of an abnormal visual function in children with OPG. However, the wide variety of OCT devices, OCT protocols, visual function parameters and definitions and the considerable risk of bias of included studies limited the drawing of solid conclusions.

The results of chapter 3 and chapter 4 identify the need for additional high-quality data and evidence regarding the ophthalmological consequences and the potential role of retinal OCT in children with a newly diagnosed brain tumor. To this end, we designed and conducted the CCISS study (‘*Child Central nervous tumors InSight in Sight’)*, a prospective nationwide longitudinal cohort study investigating visual impairment in children newly diagnosed with a brain tumor between May 2019 and August 2021 in the Netherlands. Children with all types of brain tumors were eligible for inclusion in the study. The rationale and design of the CCISS study are described in **chapter 5**.

In **chapter 6** we prospectively assessed the prevalence and types of abnormal ophthalmological findings in 170 children with a newly diagnosed brain tumor who participated in the CCISS study. Abnormal ophthalmological findings were present in 79% of the children at brain tumor diagnosis, of which papilledema (52%), gaze deficits (34%), visual field defects (28%), nystagmus (25%) and strabismus (20%) were the most common findings. Remarkably, we found ophthalmological abnormalities during examination in the majority of children (65%) who initially presented without visual symptoms. These findings stress the importance of standardized ophthalmological examination and the awareness of clinicians for latent ophthalmological abnormalities in children with a newly diagnosed brain tumor.

The diagnostic accuracy of retinal OCT to discriminate an abnormal visual function in 115 children participating in the CCISS study is reported in **chapter 7**. We showed relatively high negative predictive values of average circumpapillary RNFL thickness (83%) and average macular GCL-IPL thickness (82%), but the positive predictive values (re-

spectively 33% and 57%) are low, demonstrating a moderate diagnostic accuracy. This is also is in line with the low to moderate sensitivity and specificity. In addition, there were limitations including incomplete retinal layer analyses, the lack of a normality database for children in current OCT software and the relatively small subgroup analyses in our study. Therefore, at this moment, RNFL thickness and GCL-IPL thickness measurements cannot be used for clinical care decision making in children with a newly diagnosed brain tumour, nor should these measurements replace the thorough standard ophthalmological examination.

Finally, in **chapter 8** we discussed the main findings of this thesis within the context of recent literature and addressed perspectives for future ophthalmological research in children with a brain tumor.

NEDERLANDSE SAMENVATTING

Een hersentumor is de meest voorkomende vorm van solide kanker bij kinderen. Elk jaar wordt bij ongeveer 120 kinderen in Nederland een hersentumor ontdekt. Gelukkig zijn de overlevingskansen van kinderen met een hersentumor, als gevolg van medische vooruitgang, aanzienlijk verbeterd. De gemiddelde vijfjaarsoverleving bedraagt op dit moment ongeveer 75% in ontwikkelde landen. Als gevolg van de hogere overlevingskansen is er meer aandacht gekomen voor de korte- en lange termijngevolgen van een hersentumor en de behandeling hiervan. Een van deze mogelijke gevolgen is het ontwikkelen van een verminderd gezichtsvermogen zoals een verminderde gezichtsscherpte, gezichtsvelduitval en oogbewegingsstoornissen. Dit kan een aanzienlijke invloed hebben op de gezondheid, de kwaliteit van leven en de deelname aan het dagelijkse leven. Een tijdige en betrouwbare vaststelling van een verminderde oogfunctie is daarom erg belangrijk. Hierdoor kan op tijd gestart worden met behandeling, kan de behandeling van de tumor waar nodig worden aangepast en kan het kind, indien nodig, verwezen worden voor passende revalidatie.

Het doel van dit proefschrift is om inzicht te geven in de oogheelkundige gevolgen bij kinderen met een nieuw ontdekte hersentumor en om de mogelijke rol van retinale optische coherentie tomografie (OCT) als objectieve en niet-invasieve testmethode van de visuele functie te onderzoeken.

Hoofdstuk 1 geeft een algemene inleiding en beschrijft de doelstellingen en de opzet van dit proefschrift. Dit hoofdstuk bevat achtergrondinformatie over hersentumoren bij kinderen, de anatomie en ontwikkeling van de visuele banen, de mechanismen van een verstoorde visuele functie en de verschillende oogheelkundige testen die beschikbaar zijn om de visuele functie te meten bij kinderen met een hersentumor.

In **hoofdstuk 2** hebben we een systematisch review uitgevoerd bestaande uit 84 studies om de visuele functie bij kinderen met een nieuw ontdekt craniopharyngeoom in kaart te brengen. Een craniopharyngeoom is een zeldzame, langzaam groeiende hersentumor in de buurt van het chiasma opticum (de kruising van de oogzenuwen in de hersenen). Door deze ligging kan een craniopharyngeoom voor een verstoorde visuele functie zorgen. In ons review vonden we dat bij ongeveer de helft van de kinderen met een nieuw ontdekt craniopharyngeoom sprake is van een verstoorde visuele functie, waarbij een afgenomen gezichtsscherpte (in 41% van de kinderen) en gezichtsvelddefecten (in 38% van de kinderen) het vaakst werden gerapporteerd. Daarnaast werden er soms afwijkingen gevonden tijdens fundoscopie (in 33% van de kinderen) en het orthoptisch onderzoek (in 13% van de kinderen). De kwaliteit van de geïncludeerde studies werd

over het algemeen als matig beoordeeld door missende of onvolledige informatie over de visuele uitkomsten en vooraf geselecteerde patiëntpopulaties. Daarnaast kon er door variëteit in oogheelkundige meetmethoden en uitkomst definities tussen studies geen meta-analyse worden uitgevoerd.

In **hoofdstuk 3** is het doel om retrospectief inzicht te krijgen in het oogheelkundig verwijspatroon en in de prevalentie en het type oogheelkundige afwijkingen bij 90 kinderen met een nieuw ontdekte hersentumor die behandeld zijn in het tertiaire nationale verwijzingscentrum voor kinderoncologische zorg, het Prinses Máxima Centrum voor Kinderoncologie in Utrecht. Ongeveer tweederde van de kinderen in ons cohort (67%) werd binnen zes weken rondom diagnose van de hersentumor verwezen voor oogheelkundige evaluatie. Bij 78% van deze verwijzingen werden abnormale oogheelkundige bevindingen gevonden tijdens oogheelkundig onderzoek, waarvan oogmotiliteit- en oogstandstoornissen (66%), papiloedeem (44%) en gezichtsvelddefecten (58%) het meeste voorkwamen.

In **hoofdstuk 4** hebben we een systematisch review uitgevoerd om de diagnostische accuratesse en de prognostische waarde van retinale OCT voor de evaluatie van de visuele functie in kinderen met een hersentumor te onderzoeken. Door middel van retinale OCT kunnen er hoogwaardige beelden (dwarsdoorsnedes) worden gemaakt van het netvlies. Slechts vijf diagnostische studies in kinderen met een optic pathway glioma (OPG) waren geschikt voor inclusie in het review. Deze studies rapporteerden een matige tot goede diagnostische accuratesse voor diktemetingen van de retinal nerve fiber layer (RNFL) en ganglion cell layer – inner plexiform layer (GCL-IPL). De grote verscheidenheid aan OCT apparaten, OCT protocollen, visuele functie parameters en uitkomst definities en het aanzienlijke risico op bias in de geïncludeerde studies maakt het echter moeilijk om betrouwbare conclusies te trekken.

De resultaten van hoofdstuk 3 en hoofdstuk 4 onderstrepen het belang van aanvullend prospectief onderzoek naar de oogheelkundige gevolgen van een nieuw ontdekte hersentumor bij kinderen en naar de mogelijke rol van retinale OCT bij deze groep kinderen. Daarom hebben we de KIZZ studie (*'Kinderhersentumoren InZicht in Zicht'*) ontworpen en uitgevoerd, een prospectieve landelijke longitudinale cohortstudie. Alle kinderen, die tussen mei 2019 en augustus 2021 in Nederland gediagnosticeerd werden met een hersentumor, kwamen in aanmerking voor deelname aan de studie. In de studie zijn alle typen hersentumoren meegenomen. De rationale en opzet van de KIZZ studie zijn beschreven in **hoofdstuk 5**.

In **hoofdstuk 6** hebben we de prevalentie en het type abnormale oogheelkundige bevindingen onderzocht bij 170 kinderen met een nieuw ontdekte hersentumor die deelnamen aan de KIZZ studie. Bij 79% van de kinderen waren abnormale oogheelkundige bevindingen aanwezig; papiloedeem (52%), oogmotiliteitsstoornissen (34%), gezichtsvelddefecten (28%), nystagmus (25%) en oogstandsafwijkingen (20%) kwamen het vaakst voor. Opvallend is de mate van latente afwijkingen: bij een meerderheid van de kinderen (65%) die geen oogheelkundige klachten had, werd toch oogheelkundige afwijkingen gevonden. Deze bevindingen benadrukken het belang van gestandaardiseerd oogheelkundig onderzoek bij diagnose van een hersentumor en het belang van kennis en bewustzijn van clinici van de mogelijke latente oogheelkundige afwijkingen bij kinderen met een recent gediagnosticeerde hersentumor.

In **hoofdstuk 7** onderzochten we de diagnostische accuratesse van retinale OCT om een abnormale visuele functie te herkennen in 115 kinderen die deelnamen aan de KIZZ studie. We vonden relatief hoge negatief voorspellende waarden voor de gemiddelde circumpapillaire RNFL diktemeting (83%) en de gemiddelde maculaire GCL-IPL diktemeting (82%): kinderen met een normale gemiddelde RNFL- en GCL-IPL diktemeting die ook een normale visuele functie (een goede gezichtsscherpte en/of gezichtsveld) hadden. Maar de positief voorspellende waarden bleken laag (respectievelijk 33% en 57% voor de gemiddelde RNFL- en GCL-IPL diktemeting): kinderen met een abnormale gemiddelde RNFL- en GCL-IPL diktemeting die ook een abnormale visuele functie hadden. Dit toont een matige diagnostische accuratesse aan, wat ook in overeenstemming is met de lage tot matige sensitiviteit en specificiteit. Bovendien waren er beperkingen in de retinale laagsegmentatie, zijn er geen normaalwaarden voor kinderen beschikbaar in de hedendaagse OCT software en waren er alleen relatief kleine subgroep analyses mogelijk. Daarom kunnen deze dikte metingen van de netvlieslagen het grondig oogheelkundig onderzoek niet vervangen. Het is bovendien nog niet haalbaar om RNFL- en GCL-IPL diktemetingen te gebruiken voor besluitvorming over de therapie bij kinderen met een nieuwe ontdekte hersentumor.

Tenslotte zetten we in **hoofdstuk 8** de hoofdbevindingen en discussiepunten van dit proefschrift uiteen binnen de context van recente literatuur. Daarnaast beschrijven we onze suggesties voor toekomstig oogheelkundig onderzoek bij kinderen met een hersentumor.



APPENDICES

List of publications

Dankwoord (acknowledgements)

About the author

LIST OF PUBLICATIONS

Related to this thesis

Nuijts MA, Stegeman I, Porro GL, Bennebroek CAM, van Seeters T, Proudlock FA, Schouten-van Meeteren AYN, Imhof SM. Diagnostic accuracy of retinal optical coherence tomography in children with a newly diagnosed brain tumour. Accepted for publication in Acta Ophthalmologica.

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DANKWOORD (ACKNOWLEDGEMENTS)

Dit proefschrift is tot stand gekomen door de inbreng, steun en hulp van veel personen. Graag wil ik iedereen die hier direct of indirect aan heeft bijgedragen hartelijk bedanken. Een aantal personen wil ik graag in het bijzonder bedanken.

Te beginnen met alle kinderen en hun ouders/verzorgers die hebben deelgenomen aan de studies in dit proefschrift. Jullie enorme veerkracht, wijsheid en belangeloze bereidheid om mee te doen aan studies motiveerde mij om door te gaan op de momenten dat het onderzoek minder goed ging dan gehoopt. Jullie vormen de kern van dit proefschrift en zijn mijn inspiratie om me de rest van mijn carrière in te zetten voor innovatie en verbetering van de zorg.

Het KIZZ team: prof. dr. S.M. Imhof, dr. A.Y.N. Schouten – van Meeteren en dr. I. Stegeman. *''The strength of the team is each individual member. The strength of each member is the team'' – Phil Jackson*

Prof. dr. S.M. Imhof, beste Saskia, enorm bedankt voor de mogelijkheid om dit proefschrift onder jouw hoede te mogen schrijven. Vanaf het begin van mijn promotietraject heb je mij alle vertrouwen en ruimte gegeven. Jouw optimisme, aanstekelijke enthousiasme en relativeringsvermogen waren vaak precies wat ik nodig had. Ik waardeer het zeer dat je deur altijd open stond voor een praatje over het alledaagse leven, een goed gesprek over persoonlijke ontwikkeling en voor alle bemoedigende woorden en steun op de momenten dat ik het moeilijk had de afgelopen jaren.

Dr. A.Y.N. Schouten – van Meeteren, beste Netteke, heel erg bedankt voor de fijne begeleiding tijdens mijn promotietraject. Ik bewonder jouw verhelderende kijk op dingen en de manier waarop je lastige onderwerpen bespreekbaar weet te maken. Je bent een duizendpoot en soms vroeg ik me af hoe je binnen no-time kon reageren op mijn mails en binnen no-time mijn manuscripten kon voorzien van waardevolle feedback. Jouw onvermoeibare inzet voor de beste patiëntenzorg vormt daarnaast een grote inspiratie voor mijn toekomst in de kliniek.

Dr. I. Stegeman, beste Inge, heel veel dank voor je fijne en toegankelijke begeleiding. Ik denk dat je de afgelopen jaren regelmatig op je tanden hebt moeten bijten, wanneer wij weer eens met (onrealistische) nieuwe ideeën voor ons onderzoek kwamen of te snel conclusies wilden trekken uit onze onderzoeksresultaten. Bedankt voor je geduld, het zelfvertrouwen dat je me hebt gegeven en de spiegel die je me hebt voorgehouden op de momenten dat ik het nodig had.

Geachte leden van de beoordelingscommissie en/of promotiecommissie: dr. K.M. van Baarsen, prof. dr. J.H. de Boer, prof. dr. K.P.J. Braun, prof. dr. M.M. van Genderen, prof. dr. J. Heutink, dr. L. Meijer, prof. dr. N.E. Schalij-Delfos en prof. dr. T. Seute. Bedankt voor uw energie en tijd om mijn proefschrift te beoordelen en zitting te nemen in de commissie.

Prof. J.H. de Boer en dr. D.G. van Vuurden, beste Joke en Dannis, hartelijk dank voor de fijne begeleiding en de waardevolle adviezen als mijn onafhankelijke supervisoren.

Een groot woord van dank aan alle personen die ondersteunend zijn geweest in de uitvoering van het onderzoek in dit proefschrift. Suzan van Zadelhoff, Petra Fernhout, Annette Timmermans en Truus de Groot, dank voor de logistieke ondersteuning en dat ik altijd bij jullie terecht kon met vragen. Tamara Marees en Marianne van Es-Gulinck, bedankt voor jullie ondersteuning bij de regelgeving rondom wetenschappelijk onderzoek. Ariën Broere, dank voor de technische ondersteuning bij het gebruik van de handheld OCT. Ferry van de Goede en Ruud Verweij, dank voor jullie hulp bij de ICT-vraagstukken.

Co-auteurs, veel dank voor de fijne samenwerking, jullie kritische blik op en waardevolle toevoegingen aan de manuscripten.

Prof. M.A. Grootenhuis en dr. R.R.L. van Litsenburg, beste Martha en Raphaële, veel dank voor jullie hulp en ideeën voor het project over visus-gerelateerde kwaliteit van leven. Ik ben heel benieuwd naar het eindresultaat van onze gezamenlijke studie.

Dr. Frank Proudlock and dr. Viral Sheth from the University of Leicester, many thanks for your help with analyzing the handheld OCT data.

Tom Seeters, bedankt voor je hulp bij het beoordelen van MRI scans voor de KIZZ studie. Ik waardeer het zeer dat je, zelfs toen je niet meer in het UMC Utrecht werkzaam was, in je avonduren tijd vrij maakte om samen met Marloes en mij de scans gedetailleerd te beoordelen.

De staf en oogartsen in opleiding van het UMC Utrecht, veel dank voor het prettige werkklimaat, jullie hulp bij inclusies en interesse in mijn onderzoek. Mede dankzij jullie heb ik me altijd thuis gevoeld op de afdeling.

Het anesthesie- en MRI team uit het Prinses Máxima Centrum voor Kinderoncologie; zonder jullie bereidheid en hulp was het nooit gelukt om zoveel handheld OCT scans uit te voeren bij de patiënten die deelnamen aan de KIZZ studie. Veel dank om hier tijd voor vrij te maken in een vaak, overvolle, MRI planning.

Alle deelnemende centra aan de KIZZ studie (Amsterdam UMC, Erasmus MC, Prinses Máxima Centrum voor Kinderoncologie, UMC Groningen en het UMC Utrecht) en in het bijzonder de lokale hoofdonderzoekers: drs. C.A.M. Bennebroek, dr. N.C. Naus en dr. J.R. Pott; ontzettend bedankt voor jullie hulp bij de inclusie van nieuwe patiënten en de dataverzameling. Ik kan me voorstellen dat jullie af en toe gek werden van mijn mails over de KIZZ studie, maar uiteindelijk hebben we deze multicenter studie samen toch mooi voor elkaar weten te krijgen. Carlien, je enthousiasme en mails met vragen over hoe ik dingen had aangepakt prikkelde mij om bepaalde zaken te heroverwegen.

Het kinderneuro-oncologieteam team uit het Prinses Máxima Centrum voor Kinderoncologie; dank voor jullie hulp bij de inclusie van patiënten voor de KIZZ studie en de interessante tumorboard- en researchbesprekingen. Een speciaal woord van dank voor Evelien en Niels. Zonder jullie hulp was het nooit gelukt om zoveel patiënten te includeren; vaak was de informatiebrief door jullie al uitgereikt voordat ik erover kon beginnen. Eva, het was fijn om te kunnen sparren met een klinische collega onderzoeker binnen de neuro-oncologie. Ik ben ervan overtuigd dat jij je promotietraject tot een mooi einde weet te brengen en ik ben benieuwd naar de resultaten van de SuSPeCT-studie.

Het kinderoogheelkunde team uit het UMC Utrecht, lieve kinderoogartsen (Elsbeth, Giorgio, Michelle, Özlem, Willemien), orthoptisten (Aicha, Denise, Irem, Meike, Pascale en Sacha), toa's (Cordula, Dagmar, Jos, Marjolein, Melanie en Yvonne) en secretaresses (in het bijzonder Heidi, Hetty en Ingrid); ik vond het bijzonder om deel uit te mogen maken van jullie warme team. Jullie zijn van onschatbare waarde geweest voor de KIZZ studie, of het nu ging om het zien van een extra patiënt op jullie spreekuur, het maken van een extra gezichtsveldonderzoek of OCT-scan of het inplannen van afspraken. Daarnaast was er altijd ruimte voor een gezellig praatje en wederzijdse interesse. Giorgio, veel dank voor je hulp bij het beoordelen van de gezichtsveldonderzoeken, hier leek maar geen einde aan te komen. Ik bewonder je creatieve ideeën voor toekomstig onderzoek en ik ben benieuwd naar de ontwikkelingen in de komende jaren.

Vele studenten hebben de afgelopen jaren een bijdrage geleverd aan dit proefschrift, wat niet zelden heeft geresulteerd in een publicatie. Beste Coco, Josje, Luka, Marinde, Marloes, Martijn, Nienke en Sanneke; dank voor al jullie inzet, enthousiasme en frisse blik. Ik vond het een hele eer om jullie te mogen begeleiden tijdens een van jullie eerste ervaringen met de onderzoekswereld. Nienke, een speciaal woord van dank aan jou. Jouw betrokkenheid en zorgvuldigheid in de afgelopen jaren hebben een mooie bijdrage geleverd aan meerdere hoofdstukken van dit proefschrift.

De kinderartsen, neonatologen, physician assistants, verpleegkundig specialisten en arts-assistenten van het Máxima Medisch Centrum in Veldhoven. Bedankt voor alles wat ik van jullie in de kliniek mag leren, de interesse in mijn onderzoek en de ruimte die ik heb gekregen om mij voor te bereiden in de aanloop naar mijn verdediging. Het is ontzettend fijn om mij verder klinisch te mogen ontwikkelen op een plek met zo'n prettige en open werksfeer.

Lieve (oud) collega onderzoekers bij de oogheelkunde; jullie hebben als geen ander bijgedragen aan de fijne werksfeer tijdens mijn promotietijd. Fleurieke, Kamil en Nienke, dank dat jullie mij geïntroduceerd hebben in de onderzoekswereld. Anna, ik waardeer je eerlijkheid en ik heb genoten van je heerlijke baksels. Sara, je behulpzaamheid en oprechte interesse in de medemens zijn tekenend. Roos, wat hebben we samen met Bas veel gelachen in het B-hok en later in het A-hok. Ik heb genoten van je bruisende persoonlijkheid, je typische uitspraken en onze gedeelde liefde voor slechte entertainment programma's. Bas, het laatste half jaar van mijn promotietraject bleek een stuk efficiënter, maar ook een stuk minder gezellig zonder jouw eindeloze verhalen. Dank voor je hulp bij analyses, de nekmassages en de lekkere cocktails. Evianne, ik had me geen betere collega kunnen wensen tijdens de laatste fase van mijn promotietraject. Dank voor je gezelligheid, je luisterende oor, het kritisch meedenken en je goede (werkgerelateerde en niet-werkgerelateerde) adviezen. Brendan, ik heb genoten van ons ARVO avontuur in Denver en onze wandeltocht door de sneeuw in de Rocky Mountains. Wouter, wij zijn samen begonnen aan onze promotietijd en ik wens je veel succes met een mooie afronding ervan. Carlyn, Lude, Janneau, Casper, Q-hokkers, dank jullie wel voor de koffietjes, congressen en gezellige borrels. Cansu en Jytte, jullie zijn de nieuwste aanwinsten voor de groep, dank voor jullie gezelligheid in de laatste maanden. Els, ik weet zeker dat je een fantastische oogarts gaat worden.

Lieve vrienden uit Noorbeek; mede dankzij jullie steun, stimulatie en de nodige afleiding is dit proefschrift tot stand gekomen. Samen opgroeien in een klein dorp heeft de basis gevormd voor hechte vriendschappen. Ondanks dat we niet meer allemaal in Noorbeek wonen, is het fijn om elkaar ieder jaar terug te zien tijdens de dorpse tradities, zoals carnaval, Denhalen of de Bronk.

Lieve vrienden uit Margraten; dank voor jullie oprechte interesse, bourgondische etentjes en onvergetelijke (sportieve) uitstapjes. Deze afleiding was van onschatbare waarde tijdens dit promotietraject.

Lieve vriendinnen uit Maastricht, Femke, Inge, Jessie, Laurèl, Lieke, Manouk, Milou; dank voor de fantastische herinneringen aan mijn studententijd en ver daarbuiten. Ik ben

trots om te zien hoe we ieder onze eigen weg bewandelen, maar we elkaar onderweg niet uit het oog verliezen. Manouk, jij weet als geen ander hoe het is om hier vandaag te staan en ik ben dan ook blij dat je mijn paranimf bent.

Lieve Vera, jij staat altijd voor mij klaar, in goede én slechte tijden. Daar ben ik je enorm dankbaar voor. Ik koester onze vriendschap en kijk uit naar alle leuke momenten, die we samen met Luc en Job, gaan beleven.

Lieve familie en schoonfamilie, dank voor jullie interesse en gezelligheid de afgelopen jaren. Juan en Ziva, jullie zorgen met jullie heerlijke karakter voor de nodige luchtigheid tijdens serieuze gesprekken. Jullie worden vast en zeker geweldige bruidskindjes. Lieve opa Twanny en oma Wilma & opa Ernest en oma Tiny; ook al snapten jullie soms niet goed wat mijn onderzoek nu precies inhield, jullie boden altijd een luisterend oor en waren altijd oprecht geïnteresseerd. Lieve opa's, ik hoop dat jullie het goed hebben daarboven.

Lieve Colin, je bent met je spontaniteit, vrolijkheid en gezelligheid een aanwinst voor ons gezin. Dank je wel voor het thuis dat je voor Steffie hebt gecreëerd.

Lieve Steffie, ik had me geen beter zusje kunnen wensen. De afgelopen jaren is onze band alleen maar sterker geworden en daar ben ik heel blij mee. Ik ben ontzettend trots op je en kan nog veel leren van jouw beslisvaardigheid, doelmatigheid en relativeringsvermogen. Jij kent me als geen ander en ik ben dankbaar dat ik altijd bij je terecht kan. Dank je wel dat je vandaag als paranimf aan mijn zijde staat.

Lieve papa en mama, dankzij jullie heb ik een fijne, liefdevolle jeugd gehad en heb ik alle kansen gekregen om mezelf te ontwikkelen. Ik prijs me gelukkig met jullie als ouders. Papa, jouw verhalen thuis aan de keukentafel vormden voor mij een grote inspiratiebron om zowel dokter als onderzoeker te worden. Dank voor je liefdevolle support de afgelopen jaren. Mama, wat heb ik de afgelopen jaren vaak aan je gedacht en wat mis ik je liefde, goede adviezen en stralende lach. Ik hoop dat je vanuit de hemel hebt kunnen meegenieten van dit avontuur en dat we elkaar ooit weer tegenkomen.

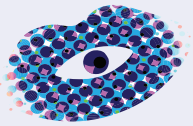
Liefste Job, dank voor je onvoorwaardelijke liefde, je inlevingsvermogen en je niet aflatende geloof in mij wanneer ik dit zelf wel eens kwijt ben. Kortom, dank voor wie je bent. Ik hou onbeschrijfelijk veel van je en ik kijk ernaar uit om de rest van ons leven samen te delen.

ABOUT THE AUTHOR

Myrthe Nuijts was born on February 28, 1994, in Leiderdorp, the Netherlands. She is the daughter of Rudy and Astrid and has a younger sister, Steffie. She grew up in Noorbeek, a small village in the South of the Netherlands. After graduating from secondary school (Gymnasium) at the Sophianum in Gulpen in 2012, she started Medical School at the University of Maastricht. During this time she was an active member of the society for medical students (MSV Pulse) and she was part of the organizing committee of the annual symposium for biomedical and medical students (MOSA Conference). In 2016 she followed an elective in Neurology at the Steve Biko Hospital in Pretoria, South Africa. She explored her interest in research during her scientific internship at the department of pediatric surgery at the Maastricht University Medical Center which resulted in her first publication.

After obtaining her Master's degree in Medicine in 2018, she started with her PhD under the supervision of prof. dr. S.M. Imhof, dr. A.Y.N. Schouten – van Meeteren and dr. I. Stegeman at the department of ophthalmology at the University Medical Center Utrecht and at the department of pediatric neuro-oncology at the Princess Máxima Center for Pediatric Oncology Utrecht. The results of her research on visual impairment in children with a brain tumor are described in this thesis. She presented her research at several national and international scientific conferences, including the annual meeting of the Dutch Ophthalmological Society (NOG), the annual Dutch Ophthalmology PhD Students Congress (DOPS), the Congress of the International Society of Paediatric Oncology (SIOP, virtual 2021), the Association for Research in Vision and Ophthalmology (ARVO, Denver, May 2022) and the International Symposium on Pediatric Neuro-Oncology (ISPNO, Hamburg, June 2022). She also followed the Clinical and Translational Oncology (CTO) PhD program.

In December 2022 she started working as a pediatric resident (not in training) under the supervision of dr. F. Halbertsma and dr. L. Niers at the Máxima Medisch Centrum Veldhoven. Myrthe lives together with Job with whom she will tie the knot in the summer of 2023. She enjoyes playing handball, skiing and spending time with her family and friends.



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