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Neurofibromatosis type 1 associated optic pathway glioma in children – a follow up of 10 years or more

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Abstract

Introduction: Optic pathway gliomas (OPGs) are a common manifestation of Neurofibromatosis type 1 (NF1) and can cause significant visual morbidity. Very long-term follow-up of children with NF1-associated OPG's has not been reported previously.

Design: Retrospective observational case series.

Methods: This study included children with a documented follow-up of at least 10 years. Three final outcomes were evaluated: visual acuity (VA) per eye (i.e. in the more severely affected eye), VA per patient (i.e. VA when both eyes are open), and presence of optic nerve head pallor.

Results: 45 children were included with a mean follow-up time of 14 years (range 10-21). At the end of follow-up, abnormal VA (considered as moderate to severe impairment) in the more severely affected eye was present in 36% of the patients and in both eyes in 11%. Optic nerve head pallor of one or both nerves was present in 62%. In a multivariate analysis, only initial VA and optic nerve head appearance at presentation were found to predict the final outcomes. All patients but one who were asymptomatic at presentation and had normal VA and normal appearing nerves preserved their good vision in both eyes. Only one patient who had normal VA and normal appearing nerves at presentation had moderate to severe VA loss at long term follow-up.

Conclusion: In this study, children with NF1-associated OPG who had a normal initial exam had excellent very long-term visual and anatomical outcomes. VA and optic nerve head appearance at presentation predict long term outcome.

Neurofibromatosis type 1 associated optic pathway glioma in children – a follow up of 10 years or more

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Introduction

Neurofibromatosis type 1 (NF1) is one of the most common genetic diseases worldwide irrespective of gender or ethnic origin[1, 2] with an incidence of approximately 1:3,500[3]. It is autosomal dominant caused by mutation in the tumor suppressor gene *NF1* with approximately half of cases due to sporadic mutations [4]. Optic pathway gliomas (OPGs) are the most common orbital and intracranial manifestation of NF1 and occur in 15-20% of patients, typically presenting in young children[5]. These tumors can affect any portion of the anterior and posterior visual pathway – one or both optic nerves, chiasm, optic tract and hypothalamus [6-8].

Although OPGs are generally benign, one-third to half of these tumors will cause significant morbidity, mainly vision loss and endocrine abnormalities[9-11]. While negative prognostic factors have been established (such as young age and post-chiasmal involvement of the tumor[7, 12]), their clinical behavior can vary dramatically. In a large study of patients with NF1-associated OPGs from two large NF1 referral centers, there was no single specific epidemiological factor that could serve as a predictor of the need for future treatment[13]. There are currently no reliable indicators of vision preservation, the main clinical objective in these patients[14, 15].

Since NF1-related OPGs are generally slow growing benign tumors, natural history and/or treatment results are crucial in deciding on the correct management. Previous reports of follow-up periods have been relatively short [9, 16-20] or have included a mixed population of patients with NF1-associated OPGs and sporadic OPGs, the latter group known to be more progressive with a worse prognosis[16, 19, 20]. In this study we report a cohort of patients who have NF1-associated OPGs and a follow-up period of at least 10 years.

Methods

Institutional Review Board approval was obtained and the study complied with all guidelines of the Health Insurance Portability and Accountability Act (HIPAA). This retrospective study included all children with NF1-associated OPGs seen from 01/1985 to 07/2007 at the Ann & Robert H. Lurie Children's Hospital of Chicago, a tertiary pediatric care hospital. All children fulfilled the National Institutes of Health Consensus Development Conference diagnostic criteria of NF1[21] and had clinical follow-up of at least 10 years. Children with presumed mosaic NF1 were excluded. Ophthalmologic follow-up of those who had evidence of OPG was as follows: ophthalmologic evaluation at diagnosis and then every 3 months in the first year after diagnosis, every 4-6 months in the second year and then an annual exam for at least 10 years. Eye exams included VA (with variable reliability as these were very young children), sensorimotor exam, anterior segment exam, pupillary reaction, intraocular pressure and optic nerve evaluation. Magnetic resonance imaging (MRI) of the brain and orbits was performed on the same schedule. Patients who developed changes in their visual exam or MRI scans were followed more closely.

We collected the following demographic information: gender, race, age at diagnosis of NF1, age at diagnosis of OPG and family history of NF. Clinical

and radiographic features at presentation and follow-up as well as any evidence of clinical and/or radiological progression, treatment and treatment outcome were collected. To define tumor extent we applied the Dodge criteria[22] to the MRIs: Stage 1 corresponds to tumors limited to one optic nerve; stage 2 to tumors involving the chiasm with or without optic nerve involvement; and stage 3 to tumors involving the chiasm and posterior visual pathways. In general, treatment was initiated if there was evidence of vision deterioration by 2 lines change from baseline on two separate visits and/or radiological evidence of growth, although the approach varied over the study period.

In 2013, the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) group published an international consensus on the recommended functional outcome measures when reporting on children with NF1-associated OPGs[14]. As per their recommendations, visual acuity and optic nerve pallor (presence or not) where chosen as parameters for our primary outcomes. Visual quality of life (QOL) questionnaires were not used.

Visual acuity outcomes are reported both per-eye (i.e. the more severely affected eye) and per-subject (i.e. VA with both eyes open). Since our main inclusion criteria was a follow-up period of at least 10 years, all patients were at least 10 years old at the last follow-up; therefore, final Snellen VA was available for all patients. For the purpose of statistical analysis, visual outcomes were grouped into three categories: (1) 20/30 or better, (2) 20/40 to 20/80, and (3) 20/100 or worse. These were based on the standardized Pediatric Eye Disease Investigator Group (PEDIG) scale for visual impairment[18, 23]. We defined mild or no visual impairment as those patients who had 20/30 vision or better.

Results

Of the 132 patients with NF1-related OPGs who were seen in our hospital between 01/1985 to 07/2007, 45 patients had a follow-up period of at least 10 years. There were 32 females (71%) and 13 males (29%). Eight patients (18%) had a family history of NF1. Most patients (37, 82%) were Caucasian with 7 (16%) Hispanic and 1 (2%) African-American.

The clinical characteristics of our population are presented in Table 1. Most patients (35, 78%) had no visual complaints at the time of diagnosis. However, 47% had abnormal optic head appearance (swollen/edematous or pale) on fundoscopic exam (11, 25% unilateral and 10, 22% bilateral) while 14 (31%) had other signs attributable to OPG including proptosis (6, 13%), strabismus (6, 13%) or abnormal VA (14, 31%). Abnormal visual acuity was considered as moderate to severe impairment (20/40 or worse).

A relative afferent pupillary defect was present in 10 patients (22%). The tumor was limited to one optic nerve (stage 1) in 13 patients (29%), the optic chiasm with or without involvement of the optic nerve (stage 2) in 21 patients (47%) and in the posterior visual pathways and the chiasm (stage 3 in 11 patients (24%).

A plexiform neurofibroma of the orbit, eyelid and periocular region was present in 2 patients (4%). Hydrocephalus was present in 4 patients (9%), precocious puberty or growth hormone deficiency/excess in 19 (42%) and 10 (22%) patients had second tumors identified, presumably low grade gliomas (4 in brainstem, 3 in cerebral hemisphere, 2 in cerebellum lesion and one in spinal cord).
During follow-up 18 patients (40%) needed treatment for their OPG due to increase of OPG size on imaging and/or visual deterioration. The average time from OPG diagnosis to treatment in these patients was 10 months (range 0-61 months). In most patients (16, 89%) the first treatment modality was chemotherapy. Two patients (11%) underwent surgery. No patient underwent radiotherapy.

Main results for final parameters are presented in Table 2. At the end of follow up 40 (89%) kept their good vision (i.e mild to no impairment) when both eyes were open and 29 (64%) had good vision in both eyes separately. Four patients had a normal initial VA in one eye but ended with poor vision (moderate impairment or worse). Of those, 3 patients had an abnormal optic nerve appearance at the initial exam. Most patients who ended up with poor vision had a posterior location of the tumor. None of the children with stage 1 tumor, and only one child with stage 2 tumor, had poor vision when both eyes open at the end of follow up (Table 3). Seven patients (16%) were diagnosed with OPG in the 2nd five years of life. All of whom ended up with normal vision in both eyes.

Univariate and multivariant analysis for all outcomes are presented in Table 4. Visual acuity and optic nerve head appearance at presentation were the strongest predictors of VA at the end of follow-up. Similarly, optic nerve head appearance at presentation was the strongest predictor of its appearance at the end of follow-up. Of all patients who ended up with worse than mild impairment only one patient had a normal eye exam at presentation.

Discussion

Although NF1-associated OPGs are benign, up to one half of these tumors will cause significant morbidity, most commonly vision loss[2]. However, the clinical behavior of an individual tumor can vary so dramatically that predicting the natural history of an individual NF1-associated OPG has been impossible[5]. Fisher et al [24] demonstrated that there was poor correlation between radiographic and visual acuity outcomes in children with OPG. Understanding the natural history of these tumors is crucial in order to make evidence-based decisions regarding treatment. Previous studies of the natural history of NF1-related OPG have been confounded by small number of patients [25] and relatively short and variable follow-up periods [9, 16-20]. Clinical deterioration has been documented after long periods of apparent stability[9, 25] with almost half showing evidence of tumor progression after the age of 6 years[26] and even during adolescence[10]. Therefore, it has been recommended that these patients be followed annually with periodic ophthalmologic examinations and MRI scans until age 8 and biannually until age 18[9]. Segal et al.[17] identified 44 patients with NF1-associated OPGs; of those patients 8

(18%) were symptomatic and the mean age at diagnosis of NF1 was 3.59 years, of OPG diagnosis 5.59 years and of vision loss 5.7 years. Thiagalingam et al.[9] reported 54 patients with NF1-associated OPGs, 11% of whom had clinical progression following diagnosis. Progression occurred mostly within 1 year from diagnosis of OPG (22/28 patients with progression), and in the remaining 6 patients between 1 to 6 years from diagnosis. The average age at the time of progression was 8.3 years (range, 5–14 years). Balcer et al.[10] reported 43 patients with NF1-associated OPGs of whom 20 (47%) reported visual loss at a median age of 4 years; however, three patients developed VA loss for the first-time during adolescence. In addition, previous reports combined NF1-associated OPG and sporadic OPG, confounding interpretation of the results[16, 19, 20, 27-29]. Contrary to the natural history of the former, sporadic OPGs are known to grow inexorably and have a much worse visual prognosis.

Although posterior optic tract involvement and young age < 2 years are known predictors of poor visual outcomes, the focus of most previous reports was on radiographic changes and treatment strategies. To the best of our knowledge, this study reports the longest VA follow-up period for these patients. Almost 90% of the patients demonstrated preserved VA of 20/30 or better when both eyes are open and almost two thirds kept their good vision also in their bad eye with an average follow-up of 14.1 years (10.0-21.2 years); those numbers are similar to what Segal et al[17] found in 44 patients with the same condition but with a shorter follow-up. In addition, all patients who were diagnosed with OPG in the 2nd part of the first decade of life ended up with normal vision in both eyes implying that children who develop OPG later in life have an excellent prognosis. In our cohort, only one patient with a completely normal initial exam ended up with poor vision. In addition, no children with stage 1 tumor at diagnosis had poor vision with both eyes open at the end of follow up.

The main limitation of our report is its retrospective nature. In addition, since we focused only on children with a very long follow up of at least 10 years many of our initial cohort were lost to follow-up. It is possible that the children without visual issues secondary to their disease were more likely to discontinue regular follow-up, perhaps strengthening our conclusions.

In summary, our study represents the first very long follow-up of patients with NF1-related OPGs.

The findings of this study can serve as a valuable tool in decision making so as to minimize screening neuroimaging of asymptomatic NF1 children who have a normal ophthalmologic exam. Even if an OPG is present, the longterm prognosis with observation alone is excellent. However, when there is a clinical suspicion of a tumor based on either the physical or ophthalmologic exam neuroimaging is indicated.

In conclusion, we identified that VA and optic nerve head appearance at presentation can predict long term visual outcomes. In addition, almost all children with NF1-associated OPG who had normal visual exams at diagnosis had good vision in both eyes at long term follow-up.

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Table 1. Clinical characteristics of patients with neurofibromatosis type 1 (NF1)-related optic pathway glioma (OPG)

Median age at diagnosis of NF1 in years (range)		2.2 (0.0-10.3)
Median age at diagnosis of OPG in years (range)		3.0 (0.0-10.4)
Exam at presentation	Abnormal VA in in one eye	14 (31%)
	Abnormal VA in in both eyes	6 (13%)
	Proptosis	6 (13%)
	Strabismus	6 (13%)
	Abnormal optic nerve head	One eye: 11 (25%), Both eyes: 10 (22%)
	RAPD	10(22%)
Orbitofacial plexiform neurofibromas		2 (4%)
Other brain tumors		10 (22%)
Endocrinopathy		19 (42%)
Mean follow up period in years (range)		14.1 (10.0-21.2)

OPG, optic pathway glioma; VA, visual acuity; RAPD, relative afferent pupillary difference

Table 2. Main outcomes of patients with Neurofibromatosis type 1 related optic pathway glioma after a follow up of at least 10 years.

	Initial exam			End of follow up		
	VA per subject	VA per eye	Optic nerve head appearance***	VA per subject	VA per eye	Optic nerve head appearance
Normal*	39 (87%)	31 (69%)	24 (53%)	40 (89%)	29 (64%)	17 (38%)
Abnormal**	6 (13%)	14 (35%)	22 (49%) Unilateral, 11 (24%) Bilateral 10 (22%)	5 (11%)	16 (36%)	28 (62%) Unilateral, 6 (13%) Bilateral 22 (49%)

VA, Visual acuity

*Normal visual acuity was considered as mild to no impairment (20/20 to 20/30)** Abnormal visual acuity was considered as moderate to severe impairment (20/40 or worse)*** Optic nerve head edema or pallor was considered abnormal

Table 3. Visual outcomes of patients with Neurofibromatosis type 1 related optic pathway glioma related to tumor location.

Tumor location*	VA per subject		VA per eye	
	Normal**	Abnormal***	Normal	Abnormal
Stage 1	13/13 (100%)	0/13 (0%)	10/13 (77%)	3/13 (23%)
Stage 2	20/21 (95%)	1/21 (5%)	16/21 (76%)	5/21 (24%)
Stage 3	7/11 (64%)	4/11 (36%)	3/11 (27%)	8/11 (73%)
Total	40/45 (89%)	5/45 (11%)	29/45 (64%)	16\45 (36%)

VA, Visual acuity

*Using the Dodge criteria ** Normal visual acuity was considered as mild to no impairment (20/20 to 20/30) *** Abnormal visual acuity was considered as moderate to severe impairment (20/40 or worse)

Table 4. Uni and multivariant analysis for final visual acuity and optic nerve head appearance in children with Neurofibromatosis type 1 associated optic pathway gliomas

variant	Vision per eye		Vision per subject		ONH pallor	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
Gender	0.80		0.57		**0.04**	0.16
Race (White vs. non white)	0.50		0.99		0.13	
Family history of NF	0.10		**0.02**	0.44	0.94	
Age at NF diagnosis	0.11		0.57		0.55	
Age at OPG diagnosis	**0.02**	0.50	0.36		0.39	
Initial symptoms	**<0.01**	0.54	0.32		0.06	
Glioma location	0.15		**0.02**	0.12	0.08	
OFNF	0.67		0.13		0.72	
Hydrocephalus	0.99		0.38		0.59	
Endocrinopathy	0.43		0.40		0.61	
Other brain tumors	0.68		0.90		0.20	
RAPD	**<0.01**	0.10	0.90		**<0.01**	**<0.01**
Abnormal ONH appearance	**<0.01**	**0.03**	**0.03**	0.29	**<0.01**	**<0.01**
VA initial (per eye)	**<0.01**	**0.01**	0.09		**0.03**	0.13
VA initial (per subject)	**<0.01**	0.06	**<0.01**	**<0.01**	0.28	