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Optic glioma warranting treatment in children

LM Kaufman and O Doroftei

Abstract

Purpose **To describe cases of optic pathway glioma (OPG) warranting treatment in children.**

Methods **This is a retrospective review of pediatric patients treated for OPG. The clinical data and imaging studies were obtained from the medical records and radiology files of patients seen at the Pediatric Neuro-Ophthalmology Clinic at the University of Illinois, Chicago and the private office of the author (LMK).**

Results **A total of seven cases with an age range of 3–48 months at presentation were reviewed. Three of the patients were also ultimately diagnosed with neurofibromatosis type 1. Presenting symptoms included proptosis, decreased vision, gaze deficit, and nystagmus. Four patients underwent biopsies that confirmed OPG. Six of the patients were treated with intravenous chemotherapy, with three patients requiring a second chemotherapy cycle. One patient was successfully treated with an en-bloc optic nerve excision. Two patients underwent unilateral enucleation owing to globe complications.**

Conclusion **Although benign tumours, OPG can behave very aggressively in young children. Both chemotherapy and en-bloc excision can be employed for treatment.**

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Keywords: optic pathway glioma; juvenile pilocytic astrocytoma; childhood; treatment; chemotherapy

Introduction

Optic pathway glioma (OPG) is a low-grade astrocytic tumour that can involve the visual pathways from the optic nerves to the visual cortex. These tumours account for 4–8% of all brain tumours in children.[1] In approximately 50% of these patients, OPG occurs in isolation; the other 50% of these patients have neurofibromatosis type 1 (NF1).[2] There is a 15–20% incidence of OPG in patients with NF1.[3,4]

The clinical presentation of OPG is quite variable depending on the tumour location and extent.[4–7] Many patients are asymptomatic.[4,5] Patients with tumours within the orbit present with proptosis, strabismus, and/or visual loss. Intracranial OPG can present with visual and endocrine impairment. Papilledema or optic atrophy may be evident.

Once OPG is diagnosed, most cases show a very indolent growth or are non-progressive, with little or no change in the clinical status.[4,5] As an example; Figure 1 shows a representative MRI cut from a patient the author (LMK) has followed for 8 years. This patient's clinical findings and imaging results have remained unchanged during this whole period of observation. Spontaneous regression of OPG has also been reported.[8,9]

In a minority of the cases of OPG, the tumour shows aggressive local expansion, leading to progressive deterioration in vision.[6] It is not known why some tumours grow aggressively whereas others remain static. OPG in NF1 has been reported to behave less aggressively than OPG in isolation.[2] Younger age at presentation is also a risk factor for growth.[10]

Treatment for progressive OPG is available with chemotherapy, radiotherapy, or surgery. Multiple studies have been reported on the advantage of chemotherapy for OPG in young children, but no widely accepted protocol yet exists.[11–13] Each patient with OPG requires a team approach, with individualized treatment.

In this article, we present a case series of seven young children with aggressive OPG threatening vision and warranting treatment to arrest tumour progression and salvage remaining vision.

Department of Ophthalmology and Visual Sciences, Section of Pediatric Ophthalmology and Adult Strabismus, University of Illinois at Chicago, Chicago, IL, USA

Correspondence:
LM Kaufman,
Department of Ophthalmology and Visual Sciences, Section of Pediatric Ophthalmology and Adult Strabismus, University of Illinois at Chicago,
1855 West Taylor Street, Chicago, IL 60612, USA
Tel: +1 312 996 9122;
Fax: +1 312 413 4916.
E-mail: idoc00@sbcglobal.net

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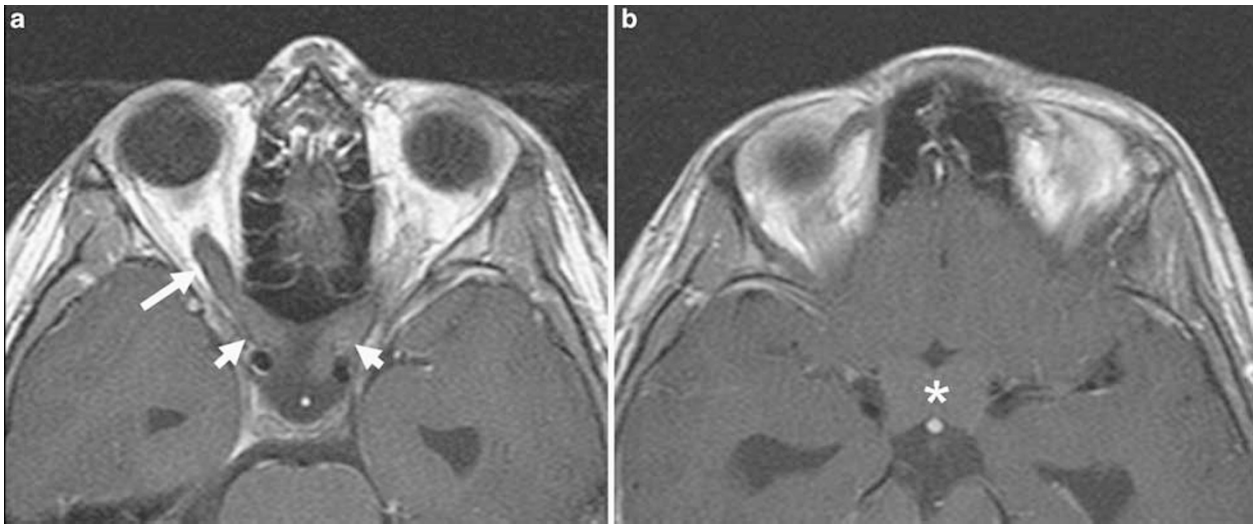


Figure 1 Brain MR images from a patient with neurofibromatosis type 1. At the age of 9 years his first brain MRI was obtained (ordered to work-up attention deficit disorder), and revealed glioma involving posterior intraorbital optic nerve on the right, bilateral intracanalicular and intracranial optic nerves, and chiasm. Serial MRI's performed on a yearly basis over the ensuing 8 years revealed no change in the extent of the glioma. Serial eye exams during this time period also revealed stable findings; visual acuity 20/70+ OD and 20/60− OS, Lisch nodules, and symmetric temporal optic pallor OU. The patient received no treatment for the glioma. (**a**, **b**) T1–weighted post-contrast axial brain MR images obtained when the patient was 9 years old. (**a**) Image shows glioma involving the right intraorbital optic nerve (long arrow), and bilateral intracanalicular and intracranial optic nerves (short arrows). (**b**) Chiasm is diffusely enlarged due to glioma (asterisk).

Materials and methods

At the Pediatric Neuro-Ophthalmology clinic at the University of Illinois at Chicago and the private pediatric ophthalmology practice of the author (LMK), a search of charts was performed to identify pediatric patients treated for OPG. Seven patients were identified, and all are included in this report. Patients with OPG that did not require treatment are excluded from this study. Clinical information was obtained from the patients' medical files and medical imaging files. The information collected included general demographic data, symptoms and signs at the time of presentation, eye findings noted during serial ophthalmologic examinations, the results from serial medical imaging studies, biopsy results, NF1 work-up results (determined by referral to a pediatric Geneticist), and the treatment regimens. A more detailed clinical report, with items such as visual field, colour vision, and exophthalmometry could not be obtained in most cases because of the very young ages of the patients. Medical imaging was performed with computed tomography (CT) and/or MRI, in most cases every 6 months after diagnosis.

Criteria for the recommendation to treat (and re-treat) the OPGs included documented progression of the tumour or extensive involvement at the time of presentation. The decision to suggest treatment represented a consensus of opinion of the medical team that included a pediatric ophthalmologist, pediatric neurologist, and pediatric oncologist.

An Institutional Review Board/Ethics Committee approved this study, and the work is HIPAA-compliant.

Results

Patients' ages ranged from 3 to 48 months (average 22 months) at the time of presentation for medical evaluation. Four girls and three boys are included. Follow-up was available for all patients, and ranged from 40 months to 13 years (average 67 months).

Table 1 presents the demographic information, chief complaint, eye findings, and medical imaging results of all the patients at the time of their presentation for medical care. In four of the patients, the diagnosis of OPG was confirmed by biopsy (Table 1). In the remaining three, the index of suspicion was high enough based on the clinical setting to warrant treatment for OPG despite a lack of tissue confirmation. Three of the patients were ultimately diagnosed with NF1 (Table 1). Clinical photographs and serial medical imaging studies of the patients are presented in Figures 2–8.

Five of the seven patients presented with progressive proptosis evident over a time ranging from 6 weeks to 6 months. Patient No. 3 was thought by her local pediatrician to have signs of precocious puberty, prompting a brain MRI that revealed an extensive OPG.

Table 1 Findings at presentation

Pt	*Age/race/sex*	*Chief complaint*	*Vision*	*Optic discs*	*Other eye findings*	*Glioma extent by imaging*	*Biopsy*	*Systemic findings*
1	3 mo WM	Increasing proptosis OD since birth	Afix OD, CSM OS	Swollen disc OD	Proptosis OD>OS	Entire course ON OD>OS, chiasm	JPA	NF1
2	48 mo WF	Increasing proptosis and decreasing VA OS × 6 mo	20/25 OD, LP OS	Swollen disc OS	Proptosis OS, RAPD OS, 8° LXT, Lisch nodules	Entire course ON OS, intracanalicular and intracranial ON OD, chiasm		NF1
3	7 mo AF	Rule-out precocious puberty	CSM OU	Trace temporal pallor OU	Slight RAPD OD	Intracranial ON OU, chiasm, both optic tracts and radiations		No precocious puberty
4	39 mo WM	Increasing proptosis and decreased upgaze OS × 6 wk	15/30 OD, 10/30 OS	Swollen disc OS	Proptosis OS, RAPD OS, 6° LhT, limited upgaze OS	Intraorbital ON OS	JPA	
5	12 mo WF	Increasing proptosis OD × 3 mo	Afix OD, CSM OS	Trace diffuse pallor OD	Proptosis OD, RAPD OD, 8° RXT, limited rotations OD	Entire course ON OD, right side chiasm	JPA	
6	15 mo HM	Increasing proptosis OS × 2 mo	CSM OD, Afix OS	Swollen disc OS	Proptosis OS, RAPD OS, 20° LXT	Entire course ON OU, chiasm		NF1
7	32 mo BF	Nystagmus, poor vision	Afix OD, Poor fix OS	Diffusely pale OU	Searching nystagmus, 16° RXT	Chiasm, both optic tracts and radiations	JPA	

Abbreviations: A = Arab; Afix = affixation; B = black; C = central fixation; F = female; H = Hispanic; JPA = juvenile pilocytic astrocytoma; LhT = left hypotropia; LP = light perception; LXT = left exotropia; M = maintained fixation; M = male; mo = months; NF1 = neurofibromatosis type 1; OD = right eye; ON = optic nerve; OS = left eye; OU = both eyes; Pt = patient; RAPD = relative afferent pupil defect; RXT = right exotropia; S = steady fixation; VA = Visual acuity; W = white; wk = weeks.

Subsequent evaluation of patient #3 by a university-based pediatric endocrinologist ruled-out precocious puberty; thus, the discovery of her OPG was serendipitous.

Loss of vision at presentation was profound (poor fixation, afixational, or light perception) in six eyes of five patients. Only patient #3 seemed to have bilateral, relatively preserved vision at the time of presentation.

Treatment for patients #1, 2, and 4–5, and 6 was recommended because of a history of progressive proptosis, and medical imaging showing extensive disease (Figures 2, 3, and 5–7). Patients #3 and 7 were offered treatment based on the extent of involvement documented by their initial brain MRI (Figures 4 and 8), and also for patient # 7 because of the profound loss of vision and sensory nystagmus apparent at her presentation.

For the initial treatment of the OPG, five of the patients (#2, 3, and 5–7) were enrolled in the Children's Oncology Group Chemotherapy Protocol A9952 (Chemotherapy for progressive low grade astrocytoma in children less than 10 years old). As per the protocol, the children without NF1 (patients #3, 5, 7) were randomized into one of two different chemotherapy regimens, Regimen A and Regimen B. Regimen A consisted of carboplatin i.v. and vincristine i.v. for 60 weeks. Regimen B consisted of thioguanine p.o., procarbazine p.o., lomustine p.o., and vincristine i.v. for 52 weeks. Also, as per the protocol, the children with NF1 (patients #2, 6) were non-randomly assigned to Regimen A, so as to avoid the alkylating agents procarbazine and lomustine (known to cause leukaemia in susceptible patients, ie, patients with NF1).

Patient #1 presented at 3 months of age with progressive proptosis of the right eye noted since birth. See Table 1 for the initial clinical findings. The MRI showed an OPG involving both optic nerves and the chiasm, with marked volume expansion of the optic nerve on the right (Figure 2a–c). Treatment for the OPG with chemotherapy as per the protocol was immediately recommended, but deferred 1 month as the patient's family sought a second opinion. At 4 months of age, the patient started chemotherapy off the protocol with carboplatin i.v. and vincristine i.v. for 72 weeks. Between 3 and 5 months of age, there was a marked increase in his right eye proptosis resulting in exposure keratopathy, and ultimately, a corneal perforation. The right eye was deemed unsalvageable, and enucleated. At the same time, an incisional biopsy of the optic nerve mass was obtained, and revealed juvenile pilocytic astrocytoma.

Patient #4 presented at 39 months of age with a 6-week history of progressive proptosis and limited upgaze of the left eye (Table 1). The CT scan revealed a large optic nerve mass confined to the left orbit (Figure 5a). He was

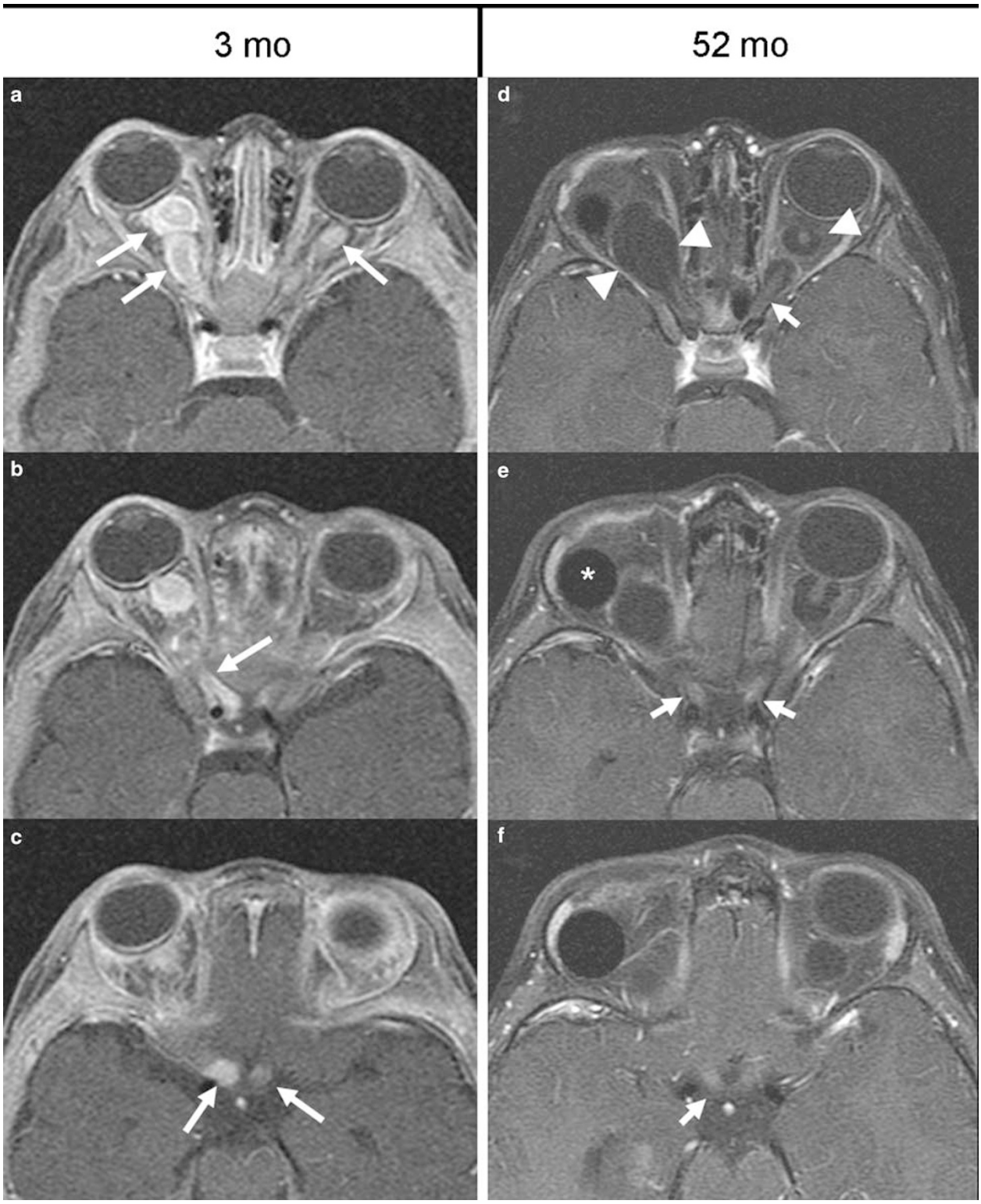


Figure 2 T1-weighted post-contrast fat suppression axial orbit MR images of patient #1 at 3 months of age (**a**–**c**) and at 52 months of age (**d**–**f**). Pre-treatment images show enhancing optic glioma involving intraorbital optic nerves (**a**, arrows), intracanalicular optic nerves (only right side visualized in this cut) (**b**, arrow), and both intracranial optic nerves just proximal to the chiasm (**c**, arrows). After treatment with chemotherapy and enucleation of the right eye, shrinkage, and decreased enhancement of the glioma is evident within the intraorbital, intracanalicular, and intracranial optic nerves bilaterally (**d**–**f**, short arrows). Arrowheads (**d**) show cyst-like expansion of the optic nerve sheath bilaterally. Asterisk (**e**) indicates acrylic orbital implant after enucleation.

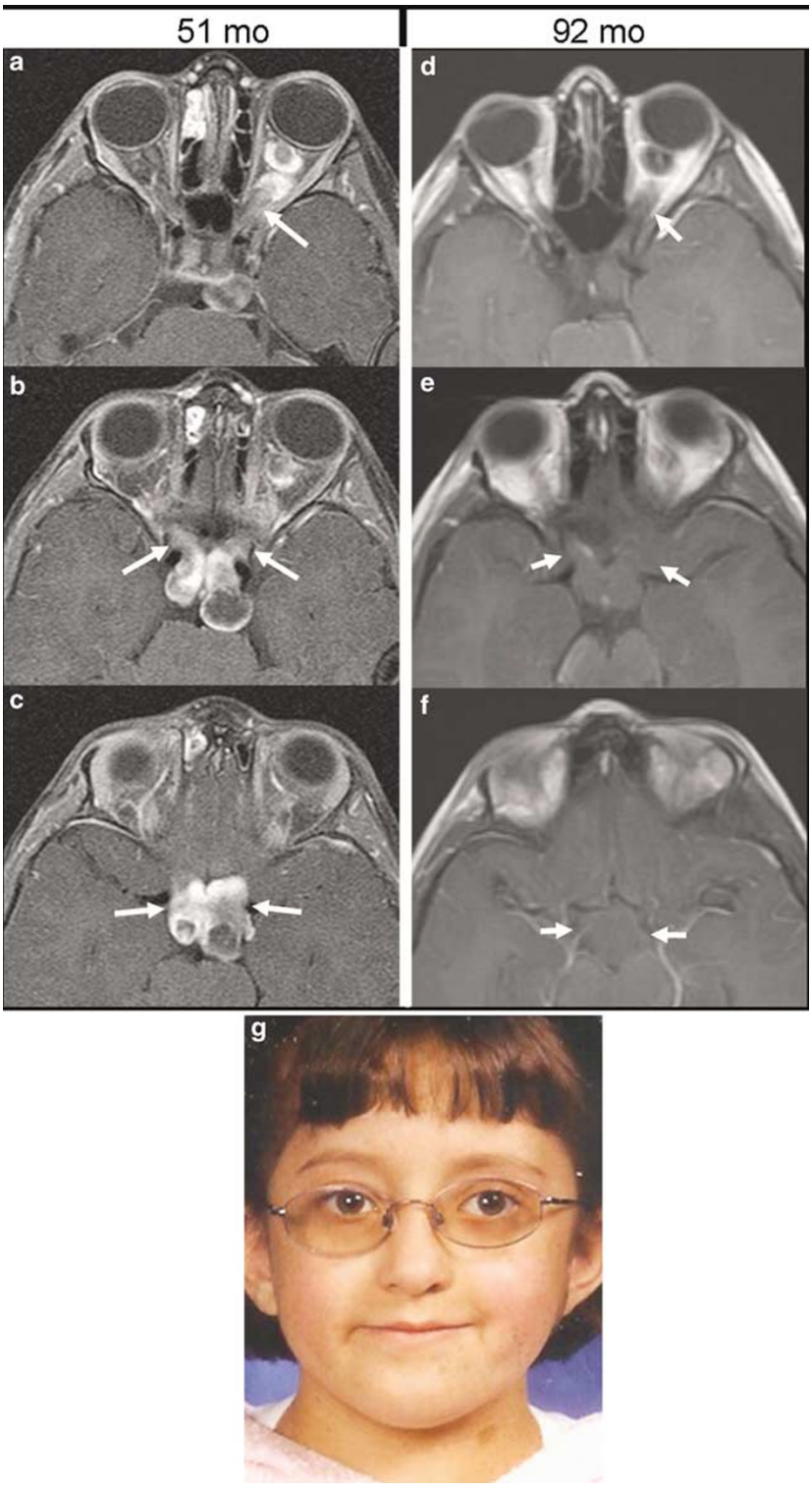


Figure 3 (**a**–**f**) Axial orbit MR images obtained from patient #2. (**a**–**c**) T1-weighted post-contrast fat suppression images obtained at the age of 51 months show glioma involving left intraorbital optic nerve (**a**, arrow), both intracranial optic nerves (**b**, arrows) and chiasm (**c**, arrows). Gliomatous cysts extend from the posterior aspect of the chiasm filling the suprasellar cistern. (**d**–**f**) T1-weighted post-contrast images obtained at the age of 92 months. The patient had been treated with chemotherapy. There is marked reduction in the enhancement and cystic components of the glioma. The entire left optic nerve, right intracranial optic nerve and chiasm (short arrows) remain enlarged. (**g**) External photograph of patient #2 at 7 years of age. Mild proptosis and exotropia of the left eye is evident. A café-au-lait spot is seen on the left side of her neck.

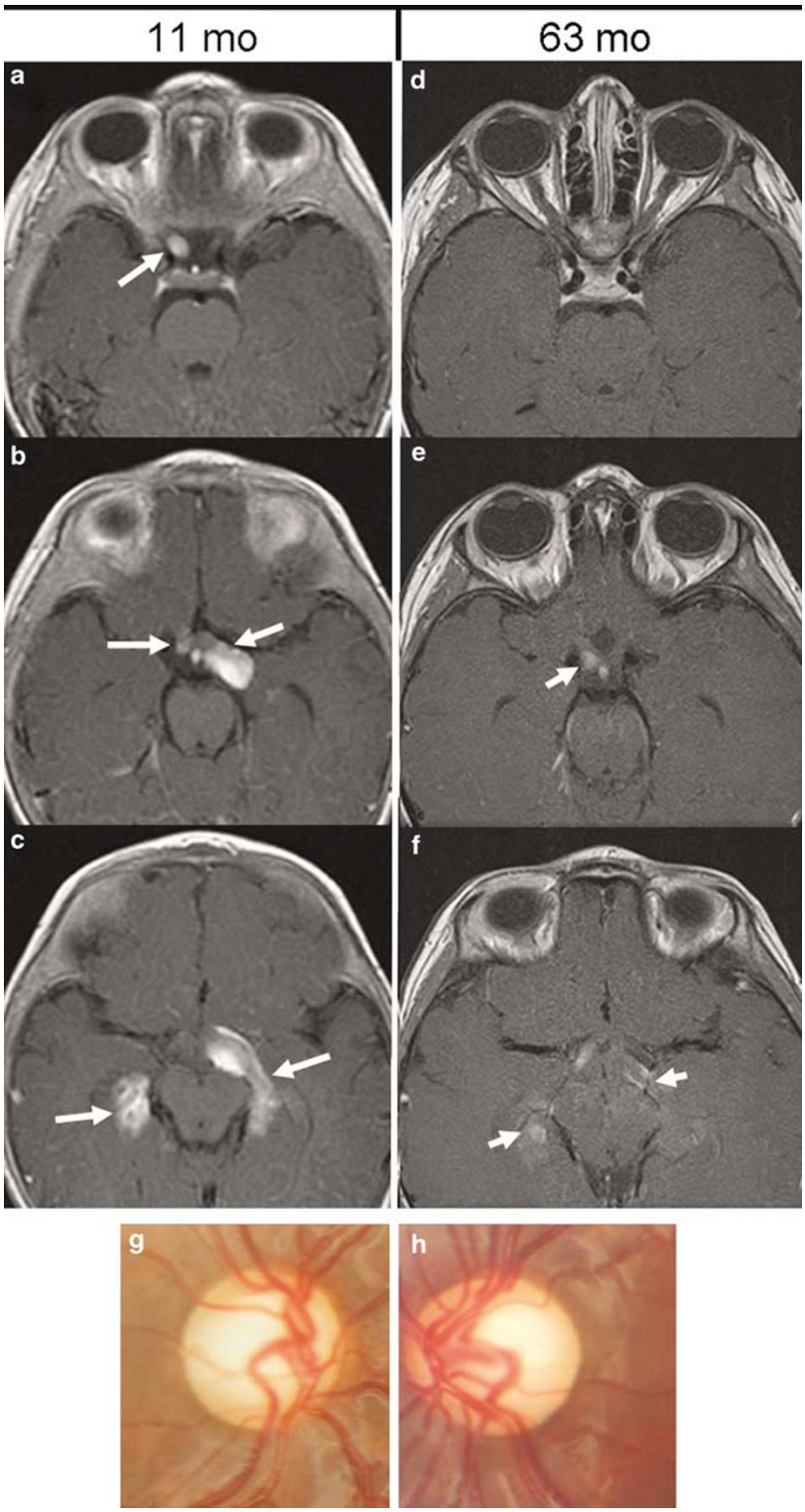


Figure 4 (**a**–**f**) T1-weighted post-contrast axial orbit MR images of patient #3 at 11 months of age (**a**–**c**) and at 63 months of age (**d**–**f**). Images show glioma involving the intracranial optic nerve on the right (**a**, arrow), chiasm (**b**, arrows), and optic radiations bilaterally (**c**, arrows). (**d**–**f**) Images obtained after treatment with chemotherapy reveal marked reduction in enhancement of the tumour. Glioma involvement of the chiasm and optic radiations is still evident (short arrows). (**g**, **h**) Right (**g**) and left (**h**) optic disc photographs of patient #3 obtained at 5 years of age show deep central cups with central pallor, and intact rims.

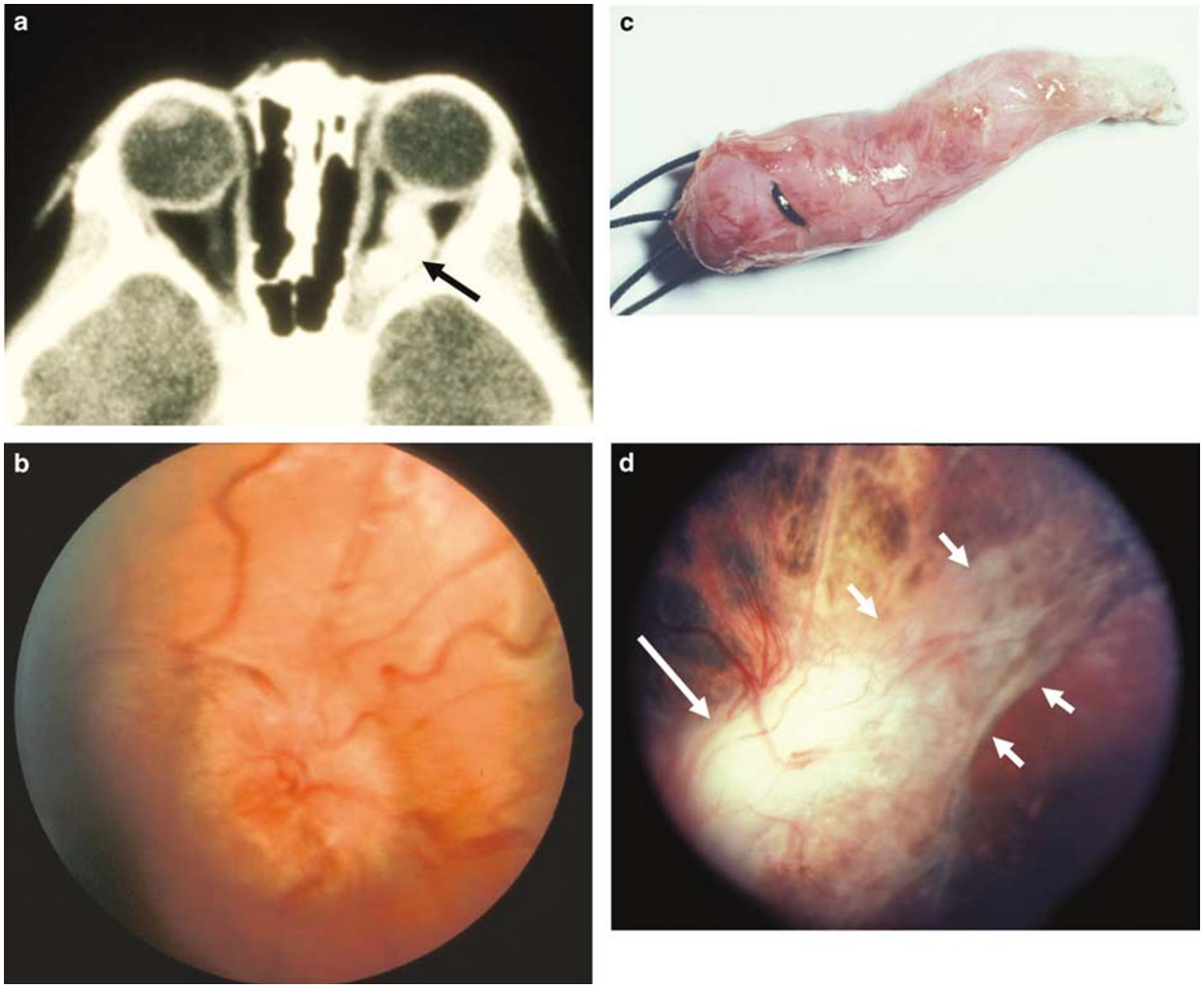


Figure 5 (**a**) Axial orbit CT scan with contrast of patient #4 obtained at the age of 39 months shows enhancing glioma involving the left intraorbital optic nerve (arrow). (**b**) Fundus photograph of patient #4 at the age of 39 months. Image shows marked swelling of the left optic disc. (**c**) Patient #4 was treated with an en-bloc excision of the orbital optic glioma of the left eye. Photograph shows the excised specimen. (**d**) Fundus photograph of the left eye of patient #4, 3 months after the optic nerve excision. Image shows optic disc pallor (long arrow) and tractional retinal detachment (short arrows).

then observed for one month; vision, proptosis, and papilledema (Figure 5b) were seen to markedly worsen. As the mass seemed contained within the orbit, it was elected to treat with an en-bloc excisional biopsy of the intraorbital optic nerve (Figure 5c). The globe was left *in situ*. The pathological specimen was interpreted as juvenile pilocytic astrocytoma. Four months after the surgery, the patient's left eye developed a tractional retinal detachment (Figure 5d), ultimately leading to phthisis. The left eye was enucleated when the patient was 15 years old.

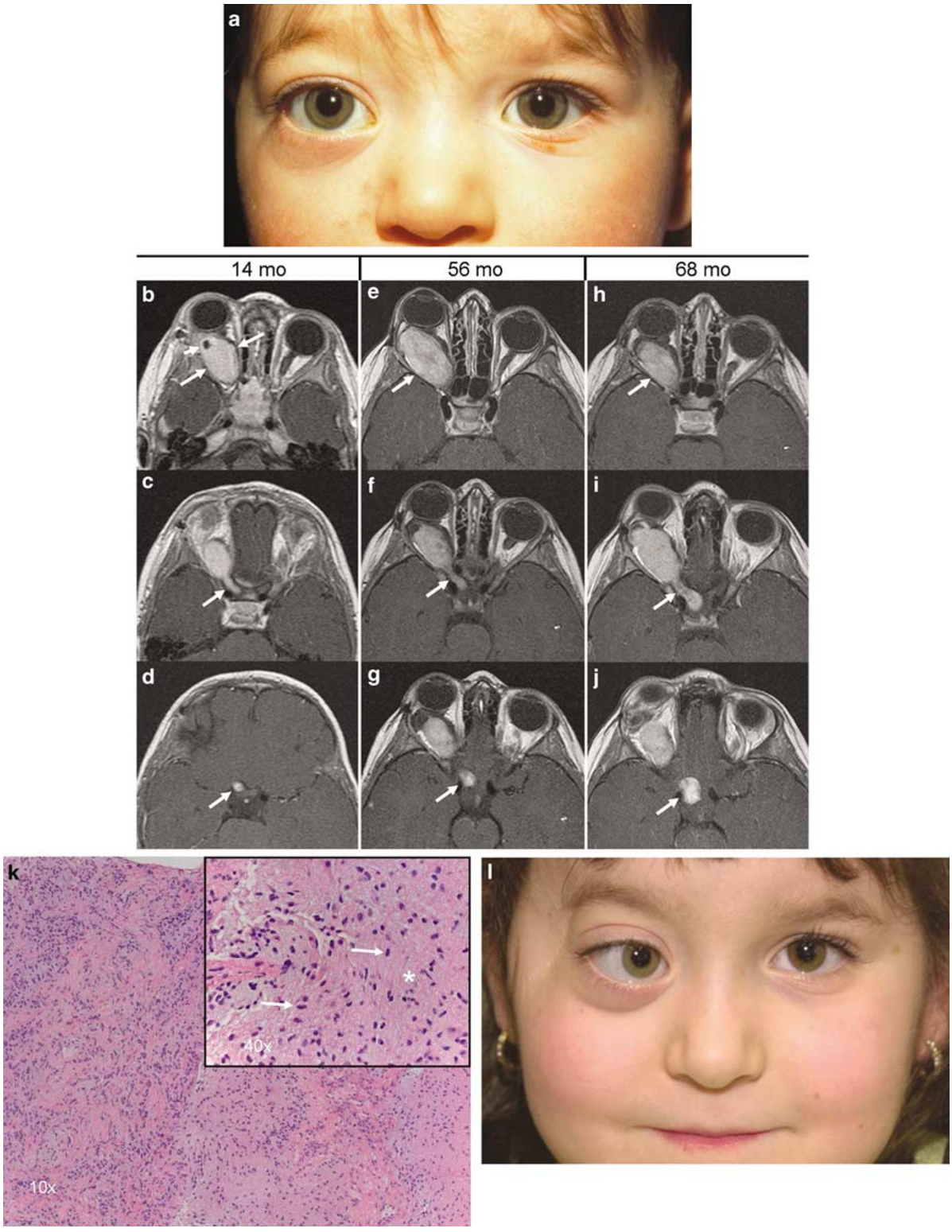
Outcome

Patients #1–3 have shown a long-term arrest of their OPG in response to the treatment of their tumours with one course of chemotherapy. These tumours' favourable responses, as noted in post-treatment serial MRIs, appear as a modest shrinkage in the tumour volumes and less enhancement with contrast. In no cases did the MRI appearance of the OPG substantially 'melt away' in response to the chemotherapy. For patient #4, the tumour excision has appeared curative.

The treatment and long-term outcome for the four patients responsive to single treatment are presented in Table 2. For this group, follow-up ranged from 40 months to 13 years. Comparisons of initial to final vision and proptosis are difficult to make in this group because of the young age at presentation and the enucleation of two of the eyes. In general, the vision loss sustained by these patients seems not to have progressed after initiation of treatment (compare visions in Tables 1 and 2).

Side-by-side comparisons of patients' #1–3 initial and final MRIs are shown in Figures 2–4.

After the completion of their initial course of chemotherapy, patients #5–7 showed further progression of their OPG as determined by serial MRIs. Considering the patients' ages, the results from their serial eye examinations did not seem sensitive or accurate enough to document clinical deterioration. The initial treatment



of these patients and their clinical and MRI findings at the time of tumour progression are detailed in Table 3. Tumour progression was noted 29, 5, and 44 months after completion of their initial course of chemotherapy for patients #5–7, respectively. All three of these patients ultimately received a second course of chemotherapy (Table 3).

For patients #6 and 7, the second course of chemotherapy was started within the same month that tumour progression was documented by MRI. Patient #5 started her second chemotherapy course 16 months after progression was noted, a delay in consideration of a surgical resection of the tumour. The second chemotherapy regimens for these patients are shown in Table 3.

Final MRIs were available for patients #6 and 7, 23 and 30 months, respectively, after completion of their second course of chemotherapy (Figures 7 and 8). For both these patients, the tumour showed no further growth since the start of their second course of chemotherapy (Table 4). Patient #5 had just started her second course of chemotherapy at the time of this writing. Serial MRIs of patient #5, from the time progression of the OPG was first noticed at 56 months of age to the most recent scan at 68 months, show slow but continuous growth of the OPG.

The eye findings of patients #5–7 at their final examination are shown in Table 4. Considerable loss of vision was evident in four out of six eyes, similar to the findings at the initial presentations.

Discussion

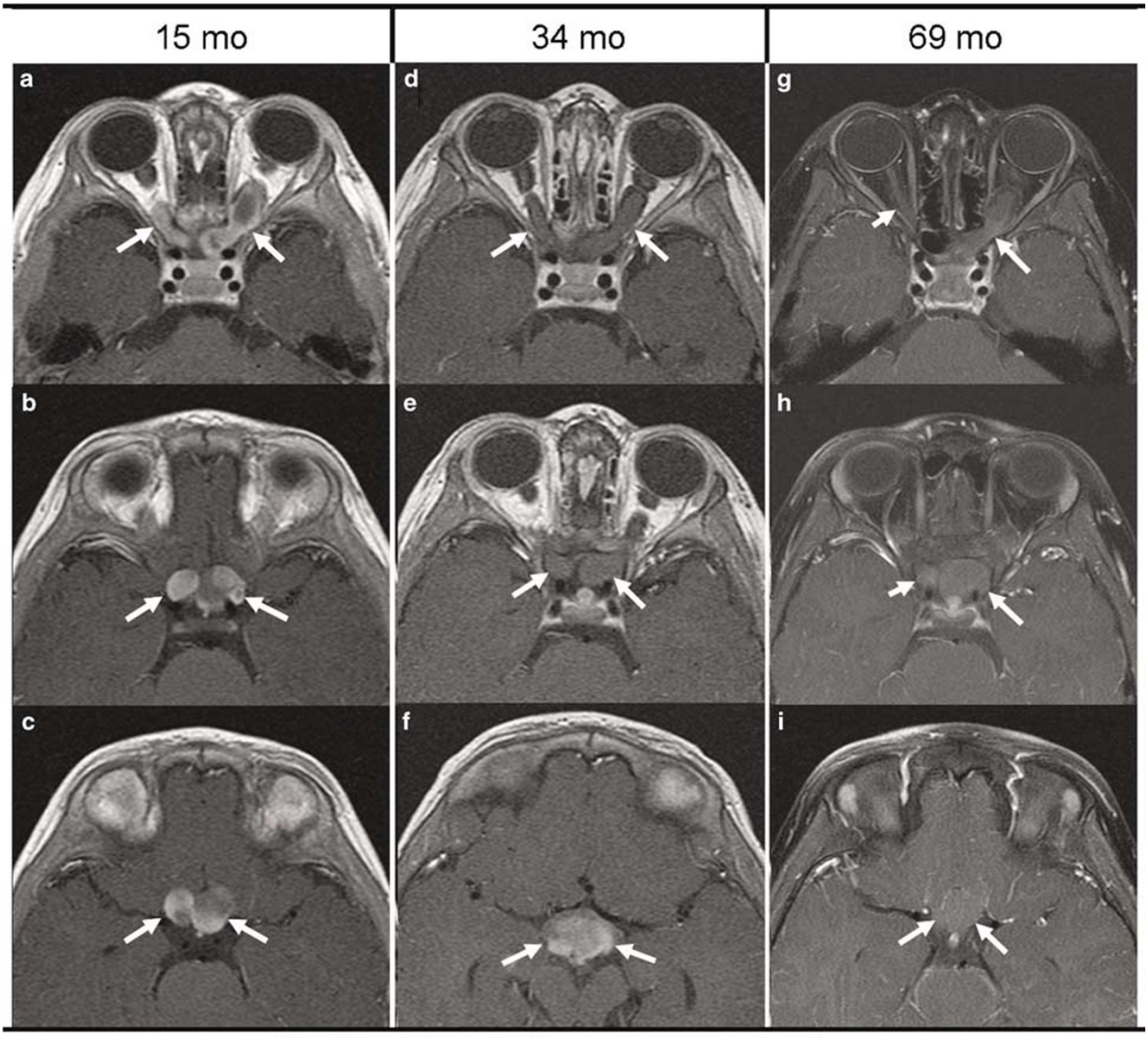
Herein are described seven young patients with OPG causing a variety of visual system symptoms and signs: proptosis, decreased visual acuity, strabismus, nystagmus, optic atrophy, and papilledema. Treatment was recommended for all the patients, and in three cases the tumour progressed even after an initial course of chemotherapy.

Our report demonstrates that OPG can behave aggressively with local expansion resulting in progressive clinical findings. Treatment of our patients was deemed advisable to arrest further damage to the visual system. Although the majority of patients with OPG have an indolent or asymptomatic course, numerous studies have documented symptomatic progression of OPGs such that treatment was necessary to preserve vision or life.[14–21] Thiagalingam *et al*[14] reported a retrospective case series on 54 patients with NF1 and OPG drawn from a regional neurofibromatosis clinic. Without selecting their patients for aggressive growth of OPG (as performed in the present study), the authors noted that 31.5% of their patients had undergone treatment for progressive disease. Astrup[15] reported on consecutive unselected patients with OPG drawn from a neurosurgical practice. Thirteen out of 25 patients (52%) received treatment for enlarging tumours. Singhal *et al*[16] identified patients with OPG from a regional neurofibromatosis database and a regional tumour registry in England. Out of a total of 34 patients, 25 (73%) had received treatment for progressive vision loss.

The factors or conditions that direct the growth of OPGs are poorly understood. Possible cellular mechanisms controlling OPG formation have recently been elucidated in NF1-associated OPG. The clinical entity NF1 results from a defective NF1 gene on chromosome 17q11.2.[22] The product of the NF1 gene is a protein termed neurofibromin.[23] NF1 patients are born with one intact NF1 allele and one dysfunctional allele from a germline mutation. Later dysfunction of the previously intact NF1 allele in a somatic cell results in a complete loss of neurofibromin in that cell. If this 'second hit' occurs in a vulnerable cell during an age of vulnerability, the cell loses mitotic control and develops into a tumour line.[24] This complete loss of NF1 gene expression has been demonstrated in all NF1-associated tumours, including OPG.[25] In these vulnerable cells, neurofibromin acts as a tumour suppressor.[26]

Neurofibromin is a guanosine triphosphatase-activating protein for Ras (an important component of the signal transduction pathway used by growth factors to initiate cell growth and differentiation), and has been proposed to regulate cell growth by inhibiting Ras activity.[23] In the absence of neurofibromin, Ras activity is unabated. Neurofibromin may also play a role in

Figure 6 (**a**) Photograph of patient #5 at 12 months of age showing proptosis of the right eye that had been increasingly evident over the prior 3 months. (**b**–**j**) T1-weighted post-contrast axial orbit MR images of patient #5 at 14 months of age (**b**–**d**), at 56 months (**e**–**g**), and at 68 months (**h**–**j**). Pre-treatment images show enhancing optic glioma involving the right optic nerve (**b**, long arrows), intracanalicular portion of the right optic nerve (**c**, arrow), and right side of chiasm (**c**, arrow). A cystic component in the tumour is evident anteriorly (**a**, short arrow). Images obtained after treatment with chemotherapy show stability of the right intraorbital glioma (**e** and **h**, arrows), but progression of the glioma involving the right intracranial optic nerve (**f** and **i**, arrows) and right side of the chiasm (**g** and **j**, arrows). (**k**) Microphotographs of biopsy specimen obtained from the right orbit of patient #5. Low power image of cross-section through the tumour mass shows a moderately cellular tumour with spindle-shaped cells embedded in a collagenous matrix. High-magnification image (inset) shows cells with spindle-shaped nuclei (arrows) and pilocytic processes (asterisk). No mitotic figures were evident. Biopsy specimen is consistent with a juvenile pilocytic astrocytoma. (**l**) Photograph of patient #5 at 68 months of age. Note proptosis, esotropia, and hypotropia of the right eye.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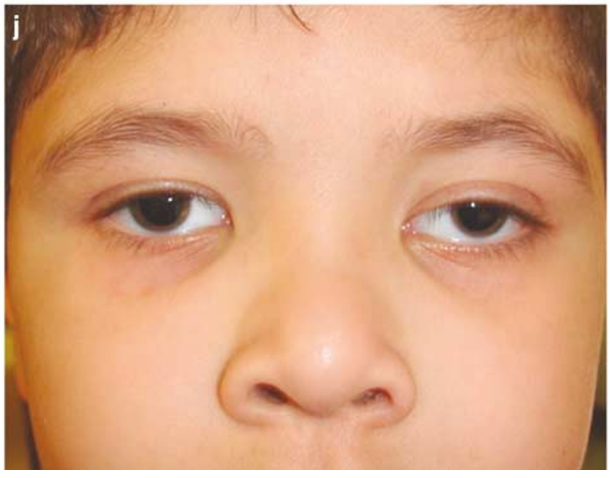
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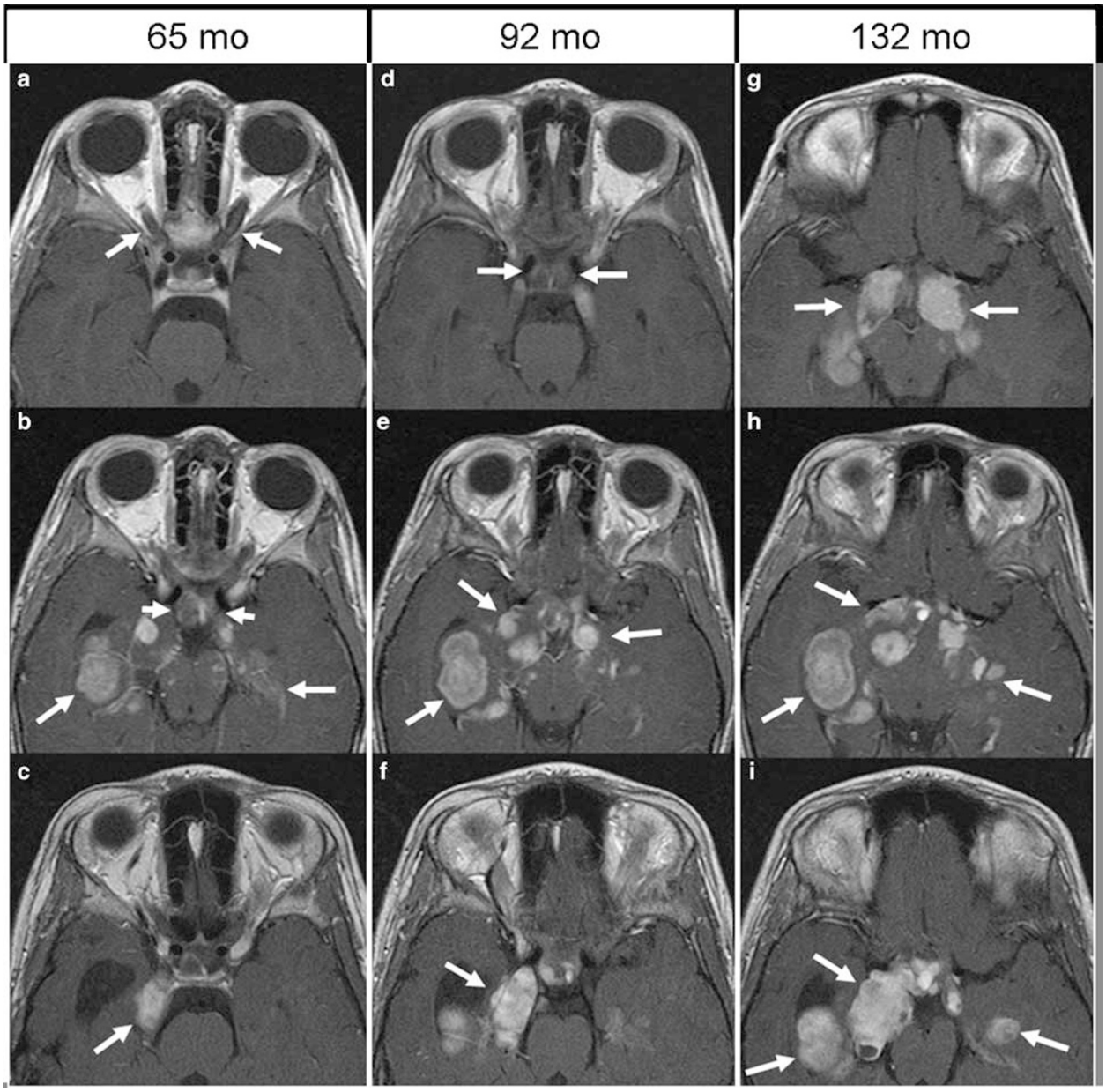

Figure 8 T1-weighted post-contrast axial orbit MR images of patient #7 at 65 months of age (**a**–**c**), at 92 months (**d**–**f**), and at 132 months (**g**–**i**). Early images show enhancing optic pathway glioma involving the chiasm (**b**, short arrows) and optic radiations (**b**–**c**, long arrows). The optic nerves appear free of tumour (**a**, arrows). The chiasm appears unchanged (**d**, arrows), but increased growth of the tumour within the optic radiations (**e**–**f**, arrows) is noted in the 92 month study. The patient was treated with a second course of chemotherapy. The final images at 132 months of age show no further increase in the extent of the glioma (**g**–**i**, arrows).

Figure 7 (**a**–**i**) Axial orbit MR images obtained from patient #6. Pre-treatment T1-weighted post-contrast images obtained at 15 months of age show enhancing glioma involving the entire course of both optic nerves (**a**, arrows), and optic chiasm (**b**–**c**, arrows). The patient was treated with chemotherapy. (**d**–**f**) T1-weighted post-contrast images obtained at 34 months of age show less enhancement within the optic nerves, no change in the size of the intraorbital and intracanalicular optic nerves (**d**, arrows), and enlargement of the glioma within the intracranial optic nerves (**e**, arrows) and chiasm (**f**, arrows). The patient was treated with a second course of chemotherapy. (**g**–**i**) T1-weighted post-contrast fat suppression images obtained at 69 months of age show decreased glioma involvement in the right intraorbital (**g**, short arrow) and intracranial optic nerve (**h**, short arrow), no change in the left optic nerve (**g**–**h**, long arrows), and less enhancement and decreased size of the chiasm (**i**, arrows) as compared to the study at 34 months of age. (**j**) Photograph of patient #6 at 62 months of age. Note mild ptosis, proptosis, and exotropia of the left eye.

regulating other tumour suppressor genes such as TSC2, and other growth pathways such as mTOR.[27]

The role of neurofibromin in the genesis of OPG is limited to patients with NF1. In the cells of sporadic OPG (ie, not associated with NF1), the expression of the NF1 gene and neurofibromin levels are normal, thus implicating an alternate pathway to OPG formation.[28,29]

Another cellular factor that may play a role in OPG growth is DNA topoisomerase IIalpha, an essential nuclear enzyme required for chromatin condensation and chromosome segregation during mitosis. Expression of DNA topoisomerase IIalpha has been shown to correlate with tumour cell proliferation in pediatric OPGs.[30]

At the macroscopic level, growth of OPG has been reported to be associated with sporadic, non-NF1 cases and younger age at presentation.[2,10] All of our patients were 4 years of age or younger at presentation, and four out of seven had sporadic OPG. In a series reported by Singhal *et al*[16], 11 out of 17 NF1-associated OPG patients and 14 out of 17 sporadic OPG patients received treatment for progressive OPG disease. These authors also noted that the average age at diagnosis of all their OPG patients (treated and untreated) was 5.0 and 5.8 years of age for the NF1 and sporadic OPG patients, respectively. In Astrup's[15] series, four out of 12 NF1-associated OPG patients and nine out of 13 sporadic OPG patients were treated for progressive disease. The mean age at diagnosis for the NF1 OPG patients was 3 years, and 6 years for patients with sporadic OPG. Khafaga *et al*[17] identified OPG-treated patients at a national cancer referral centre, and noted that 32 out of 50 patients had sporadic OPG *vs* 18 out of 50 with NF1-associated OPG. The mean age of all the patients in Khafaga's series was 4 years at the time of diagnosis. Listernick *et al*[2] reported on 36 patients with OPG. They found no significant difference between the children with NF1-associated OPG and those with sporadic OPG as to age at diagnosis or sex distribution. Progressive disease was seen in 12% of patients with NF1 OPG as compared to 63% of those with sporadic OPG.

In actuality, the association of OPG growth with sporadic, non-NF1 cases may be factitious, as selection bias can be identified in these aformentioned studies. Because of the known association of NF1 with OPG, many asymptomatic patients with NF1 undergo medical imaging of the brain for screening purposes.[4] (At the authors' institution, only symptomatic patients undergo imaging.) This type of screening of NF1 patients will result in the identification of patients with mild, asymptomatic, and/or indolent OPGs that do not require treatment. In contrast, with sporadic OPG, only patients with symptomatic disease undergo brain imaging. Asymptomatic patients with sporadic OPG are identified only by serendipity; the prevalence of asymptomatic sporadic OPG in the general population can only be known with massive screening initiatives. Thus, most reports comparing the aggressiveness of NF1-associcated OPG *vs* sporadic OPG will be biased towards mild disease in NF1 patients, and towards advanced disease in non-NF1 patients.

In a natural history study reported by Listernick *et al*,[4] patients with NF1-associated OPG were collected prospectively from a neurofibromatosis clinic. Of 227 children with NF1 seen in the clinic, 176 (77%) underwent neuroimaging, including many asymptomatic patients. Thirty-three children (19%) were found to have OPG; 'Although eight tumours were discovered because of ophthalmologic complaints or evidence of precocious puberty, 25 children (76%) were free of symptoms at the time of diagnosis. Twenty-one children (64%) had normal ophthalmologic findings at diagnosis; six children, all with chiasmal tumours, had previously unrecognized decreased visual acuity. Only three children (9%) had evidence of either tumour growth or deteriorating vision after diagnosis'. Thus, this type of series of patients with NF1-associated OPG is strongly biased towards mild OPG disease.

Czyzyk *et al*[31] reported on 83 children with OPG: 34 out of 51 (66.7%) children with NF1-associated OPG and 29 out of 32 (90.6%) children with sporadic OPG had received treatment for progressive disease. However, this apparent significant difference in treatment rates is tainted by selection bias: the NF1 patients were collected from the 'Department of Pediatrics of the Central Hospital and Pediatric Neurology Unit in Rzeszow and the Department of Neurology of the Children's Memorial Health Institute in Warsaw, the sporadic OPG cases were all collected from the Neurological and/or Neurosurgical Department of the Children's Memorial Health Institute in Warsaw'. It is to be expected that the most severe cases of OPG in Poland were referred to their Capital's children's hospital for neurosurgery, thus biasing the sporadic disease numbers towards more advanced disease.

Listernick *et al*[2] tried to avoid this bias in their comparative study mentioned above. Patients with NF1-associated OPG were recruited from a neurofibromatosis clinic, but only children with symptomatic NF1-associated OPG were included in the study for comparison to patients with sporadic OPG. Progressive disease was seen in 12% of patients with symptomatic NF1-associated OPG as compared to 63% of those with sporadic OPG. Even though this difference in progression rates seems compelling, the NF1 OPG patients were still drawn from a screened, high-risk population where equivocal or mild symptoms would

Table 2 Findings at final exam of patients responsive to initial treatment

Pt	*Treatment*	*Age at final eye exam*	*Length of follow-up*	*Vision*	*Optic discs*	*Other eye findings*	*Age at final imaging (length of FU)*	*Change in glioma by imaging*
1	CV from 4 to 22 mo age, enucleation OD at 5 mo age	53 mo	50 mo	20/25+ OS	Trace temporal pallor OS	Prosthesis in place OD, Lisch nodules OS	52 mo (49 mo)	Moderate decrease in enhancement and size ON OU and chiasm
2	CV from 48 to 62 mo age	88 mo	40 mo	20/25 OD, LP OS	Mild temporal pallor OD, diffuse pallor OS	1 mm proptosis OS, RAPD OS, 16° LXT, Lisch nodules	92 mo (44 mo)	Resolution of chiasm cysts, decrease in enhancement
3	TPLV from 7 to 19 mo age	60 mo	53 mo	20/30 OD, 20/40 OS	Large optic cups with central pallor OU	8° X(T)	63 mo (56 mo)	Moderate decrease in enhancement of entire mass
4	Excision of intraorbital ON OS at 40 mo age, enucleation OS at 15 yr age	16 yr	13 yr	20/20 OD	Disc OD healthy	Prosthesis in place OS	16 yr (13 yr)	No recurrence

Abbreviations: CV = carboplatin–vincristine chemotherapy; FU = follow-up; LP = light perception; LXT = left exotropia; mo = months; OD = right eye; ON = optic nerve; OS = left eye; OU = both eyes; Pt = patient; RAPD = relative afferent pupil defect, TPLV = thioguanine–procarbazine–lomustine–vincristine chemotherapy; X(T) = intermittent exotropia; yr = years.

Table 3 Findings of patients with progression after initial treatment

Pt	*Initial treatment*	*Age at progression*	*Vision at progression*	*Optic discs at progression*	*Other eye findings at progression*	*Imaging of glioma at progression*	*Additional treatment*
5	CV from 13 to 27 mo age	56 mo	LP OD, 20/20 OS	Marked pallor OD, healthy OS	Proptosis OD, RAPD OD, 16° RET, limited rotations OD	Increase in intracranial ON OD and chiasm	Temozolamide p.o. from 72 to 75 mo age
6	CV from 15 to 29 mo age	34 mo	CSM OD, poor fix OS	Trace pallor OD, marked pallor OS	Proptosis OS, RAPD OS, 20° LXT, Lisch nodules	Increase in intracranial ON OU and chiasm	Vinblastine i.v. from 34 to 46 mo age
7	CV from 32 to 46 mo age	90 mo	LP OD, CF 1 ft OS	Marked pallor OD > OS	Searching nystagmus, 20° RXT	Increase in chiasm, both optic tracts and radiations	TPLV from 90 to 102 mo age

Abbreviations: C = central fixation; CF = counting fingers; CV = carboplatin–vincristine chemotherapy; ft = feet; LP = light perception; LXT = left exotropia; M = maintained fixation; mo = months, OD = right eye; ON = optic nerve; OS = left eye; OU = both eyes; Pt = patient; RAPD = relative afferent pupil defect; RET = right esotropia; RXT = right exotropia; S = steady fixation; TPLV = thioguanine–procarbazine–lomustine–vincristine chemotherapy.

Table 4 Findings at final exam of patients with progression after initial treatment

Pt	*Age at final eye exam*	*Length of follow-up*	*Vision*	*Optic discs*	*Other eye findings*	*Age at final imaging (length of FU)*	*Change in glioma by imaging*
5	72 mo	60 mo	HM 1ft OD, 20/20 OS	Marked pallor OD, healthy OS	13 mm proptosis OD, RAPD OD, 16° RET, 12° RhT, limited rotations OD, full Goldmann visual field OS	68 mo (56 mo)	Increase in intracranial ON OD and chiasm since 56 mo age
6	62 mo	47 mo	20/25 OD, NLP OS	Slight pallor OD, marked pallor OS	2 mm proptosis OS, ptosis OS, RAPD OS, 24° LXT, Lisch nodules	69 mo (54 mo)	Decrease in enhancement in chiasm, no change in the size of glioma since scan at 34 months of age
7	97 mo	65 mo	LP OU	Marked pallor OU	Searching nystagmus, 30° XT	132 mo (100 mo)	No change since 92 mo age

Abbreviations: ft = feet; FU = follow-up; HM = hand motion; LP = light perception; LXT = left exotropia; mo = months; NLP = no light perception; OD = right eye; ON = optic nerve; OS = left eye; OU = both eyes; Pt = patient; RAPD = relative afferent pupil defect; RET = right esotropia; RhT = right hypotropia; XT = exotropia.

be investigated, thus biasing the NF1 OPG patients towards mild disease.

Despite the inherent bias in reports comparing NF1-associated OPG and sporadic OPG, the age at presentation in these two groups appears very similar in the aforementioned studies. In the report by Czyzyk *et al*,[31] all of the OPGs were found in children below 10 years of age, only slightly earlier in the sporadic group (median age 4.6 *vs* 4.8 years). None of these aforementioned studies broke down their data to show age at diagnosis of patients who required treatment *vs* patients who did not receive treatment. Thus, the data do not convincingly support the notion that progressive OPG disease is associated with younger age at presentation.

Treatment

For those patients with progressive OPG, treatment is available with chemotherapy, radiation therapy, and/or surgery. Five out of the seven patients reported here received their initial chemotherapy based on our institution's pediatric oncologist's participation in the Children's Oncology Group Chemotherapy Protocol A9952. This Protocol is now nearing its completion (enrolment closed on 31 January 2005), and the initial results should soon be available. Data showing the effectiveness of chemotherapy in the treatment of progressive low-grade glioma have been accumulating over the past 25 years. Carboplatin, cisplatin, vincristine, vinblastine, actinomycin D, lomustine, thioguanine, procarbazine, dibromodulcitol, etoposide, tamoxifen, and temozolomide, alone or in combination, as primary treatment or as adjuvant, have all been utilized.[10–13,19,32–40] Although chemotherapy has emerged as promising therapy, no regimen has yet to be universally accepted, hence the current Children's Oncology Group trial.

Treatment of low-grade glioma by surgical resection is also available.[15,17] Glioma tumour cells diffusely infiltrate brain tissue, and so, in most cases the resections are subtotal. During surgical excision of OPG, visual pathway fibres must be sacrificed, resulting in a corresponding loss of vision. Thus, surgery for OPG is usually limited to cases with (1) disease confined to the intraorbital portion of the optic nerve, and (2) ipsilateral, unilateral blindness. Our patient #4 fit these criteria, and was treated accordingly, and has shown a long-term eradication of his OPG.

Treating children younger than 5 years of age with radiotherapy to the brain carries serious side effects involving intellect and the endocrine system, thus limiting its usefulness in the treatment of OPG in early childhood.[41] Newer modalities of delivering radiotherapy, such as stereotactic radiotherapy and the

Gamma Knife, may lessen side effects and preserve effectiveness.[42,43]

Three of our patients continued to show tumour progression after their first course of chemotherapy, and received a second, non-protocol course of chemotherapy that was individualized to each patient. Similarly, failure of initial treatment of progressive OPG has been observed by others. Khafaga *et al*[17] noted that 14 (31%) of 45 patients who received treatment for OPG had tumour progression after treatment with surgery and/or radiation. Treatment failure seemed related to tumour site: 78% of their failures were in posterior tumours, and no failures were seen in patients with disease limited to the optic nerve. Posteriorly located OPGs also tend to cause more vision loss than anteriorly located tumours.[5] Overall, a more favourable outcome with OPGs is seen in patients older than 2 years of age, with NF1, and with optic nerve and/or chiasmatic lesions.[2,6,10,13]

Determining the best treatment for your next patient with progressive OPG is not currently defined in the medical literature. Comparing the success rates of the various treatment modalities, across the multiple publications on the subject, is fraught with pitfalls: many of the studies are retrospective, inclusion, and exclusion criteria are lacking, treatments are not standardized or randomized, and outcomes are not clearly stated. Large, prospective, well-controlled studies such as the Children's Oncology Group Chemotherapy Protocol A9952 are required to make outcome-based comparisons as to the effectiveness of different treatments.

Effective management of patients with OPG must involve a team approach, and depending on the circumstances, with input from ophthalmology, neuroradiology, oncology, neurosurgery, and/or radiation oncology. As patients with OPGs are most likely young children at the time of diagnosis, physicians with pediatric subspecialty training are advisable. Documented progression, as occurs in the minority of OPG patients, warrants treatment to preserve vision and life. In the authors' experience, the decision to treat relies both on the ophthalmology findings and medical imaging results, although the ophthalmologist's role may be limited in some of these patients considering the unreliability of the ocular measurements in children. The aggressive nature of the tumours as seen in this study, even after initial treatment, stresses the importance of frequent follow-up with ocular and medical imaging examinations.

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