Visual pathway glioma: an erratic tumour with therapeutic dilemmas

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Abstract

***Objective*—Our experience in children with visual pathway glioma (VPG) was reviewed to delineate its clinical characteristics.**

***Design*—The charts and imaging studies of 21 children with VPG who were followed up in our centre during the last 12 years were reviewed and summarised.**

***Results*—VPG accounted for 13.1% of all brain tumours treated during this period. Sixty two per cent of the children with VPG had neurofibromatosis type 1 (NF-1). Among these, more than 60% were detected as part of routine work up. In some cases decreasing visual function preceded the appearance of the VPG on imaging studies. Tumour growth rate was markedly unpredictable. All treatment modalities employed led to tumour shrinkage and stabilisation for a variable period, but none was successful in totally eradicating the tumour. Complications were less severe after chemotherapy compared with radiotherapy. Three children died, none with NF-1, with a globular hypothalamic/chiasmatic tumour and accompanying electrolyte abnormalities.**

***Conclusions*—NF-1 is a favourable prognostic marker for VPG. Whenever possible a period of observation is necessary before treatment is initiated, during which time tumour size and visual function should be closely followed up; an untoward change in either of these is an indication for the start of treatment, preferably chemotherapy first. The combination of a globular hypothalamic/chiasmatic glioma and electrolyte abnormalities in a child without NF-1 are related to a poor prognosis.**

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Keywords: optic glioma; neurofibromatosis; chemotherapy; radiation therapy.

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Visual pathway glioma (VPG) is a tumour with multiple faces. Although in some cases it may progress, invading neighbouring structures and causing visual loss, in others it remains stable for many years or even shrinks, with spontaneous improvement of related symptoms.[1–5] The tumour may appear in children with and without neurofibromatosis type 1 (NF-1), and despite the fact that it may behave differently in the two groups, there are no clear markers to differentiate these VPGs. With the improvement of neuroimaging techniques, and with more patients with NF-1 having a thorough evaluation, more VPGs are being detected in these patients during routine work up before any symptomatology.[6–12] Although the appropriate treatment of children with VPG remains controversial,[13 14] more data are available nowadays to help in decision making. Our knowledge of the relatively benign course of these lesions in NF-1 and the potentially adverse effects of radiotherapy in the young age group is steadily increasing, while the chemotherapeutic treatment of VPG has become more standardised.[15–18] Nevertheless, many diagnostic and therapeutic questions remain unanswered.

In the present study we summarised the clinical data of 21 children with VPG who have been followed up in our oncology service over the last 12 years. The aim of the study was to highlight the diagnostic and therapeutic dilemmas in the management of these patients.

Table 1 Presenting features and tumour morphology of patients with VPG

	No of patients
Presenting symptoms	
Diencephalic syndrome	3
Nystagmus	1
Spasmus nutans	1
Headaches	3
Visual loss	5
Routine evaluation of NF-1	8
Tumour morphology	
Optic nerve glioma	5
Chiasmatic/hypothalamic glioma	7
Diffuse visual pathway glioma	9

Patients and methods

The study group included all children referred for treatment and follow up of VPG at our Department of Pediatric Hematology-Oncology from 1983 to 1994. The diagnosis was based on computed tomography and magnetic resonance imaging (MRI) studies of the brain performed for various reasons (table 1). Each child was routinely evaluated and followed up by a member of the paediatric brain tumour team: oncologist, neurologist, radiologist, ophthalmologist, and endocrinologist. The frequency of follow up varied according to the clinical situation of the patient. Imaging studies were also performed in accordance with the clinical situation and not less than once a year in stable cases.

All the charts were retrospectively reviewed. Based on the imaging appearance, the tumour was categorised as: (a) optic nerve glioma, which consists of a fusiform widening of the optic nerve; (b) chiasmatic/hypothalamic glioma, which presents as a globular mass in

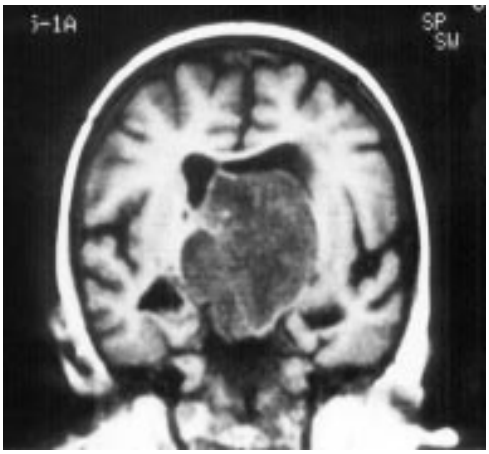

Figure 1 MRI, coronal cut, T1 weighted (600/27). Large suprasellar and hypothalamic solid mass, compatible with hypothalamic/chiasmatic glioma.

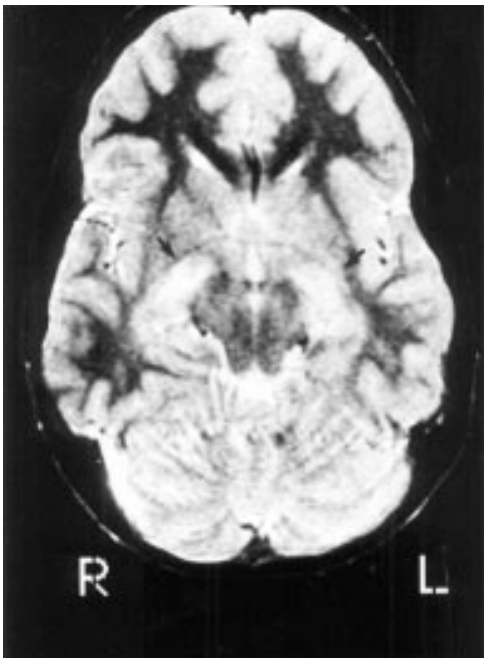

Figure 2 MRI, axial cut, T2 weighted (2800/90). Hyperintense signal is noted in the visual pathways on both sides (arrows), indicative of infiltration by the optic glioma.

the region of the optic chiasm (fig 1); or (c) diffuse visual pathway glioma, in which the signal abnormality may extend anywhere along the entire visual pathway, from the optic nerves backward to the visual cortex (fig 2).[16]

Results

Of the 160 children with brain tumours treated and followed up at our department during the study period, 21 (13.1%) had a VPG. The latter included 13 of 29 patients with NF-1 (45%) who were followed up during the same period because of neoplastic disease.

The age range of the children at presentation was 6 months to 7 years (mean 3.4 years); the male/female (M/F) ratio was 13/8 (1.6/1). In the NF-1 group, the mean age at diagnosis was 5.5 years and the M/F ratio was 9/4 (2.25/1). The pertinent data of the children are summarised in tables 1 and 2. In three children with NF-1 we were able to observe the slow evolution of optic nerve glioma over a course of about three to five years (fig 3). In one of them, visual deterioration preceded by almost two years the appearance of glioma in the MRI study.

Although in general we were able to divide the children according to tumour appearance, into those with optic nerve glioma, hypothalamic/chiasmatic globular tumour (fig 1), and diffuse posterior visual pathway tumour[10] (fig 2), there was some overlap among the groups. In 16 children there was also posterior involvement of the optic tracts. The tumour involved the chiasm in 17 children. In the group of children with globular chiasmatic/hypothalamic tumours, there was also some involvement of the optic pathways anteriorly or posteriorly. Six of the seven patients in this group did not have NF-1. In 17 children, unilateral or bilateral optic atrophy with some degree of visual loss and visual field defect was found.

Initiation of treatment was recommended when there was either imaging evidence of continuous tumour progression or objective visual deterioration. Twelve children (four with NF-1) underwent some intervention. Nine

Table 2 Course of patients with VPG

Patient No	*NF-1 present (yes/no)*	*Intervention*	*Course*	*Years with stable tumour*
1	Yes	Follow up alone	Stable	3
2	Yes	Follow up alone	Stable	3
3	Yes	Follow up alone	Stable	3
4	Yes	Follow up alone	Stable	3
5	Yes	Follow up alone	Stable	4
6	Yes	Follow up alone	Stable	3
7	Yes	Follow up alone then CTX	Slow evolution	5
8	Yes	Follow up alone then CTX	Slow evolution	3
9	Yes	CTX	Spontaneous shrinkage then regrowth	6
10	Yes	CTX	Stabilisation	4
11	Yes	CTX	Stabilisation	4.5
12	Yes	XRT	Stabilisation	5
13	Yes	Biopsy+CTX	Stabilisation	9
14	No	Follw up alone then CTX	Progression, spontaneous stabilisation progression	4
15	No	CTX	Temporary stabilisation	2
16	No	CTX	Stabilisation, late visual improvement	8
17	No	Surgery+CTX	? Progression	1
18	No	Surgery+CTX	Stabilisation	4
19	No	Surgery+CTX+XRT	Progression, death	
20	No	Surgery+CTX+XRT	Progression, death	
21	No	Surgery+CTX+XRT	Progression, death	

CTX = chemotherapy; XRT = radiotherapy.

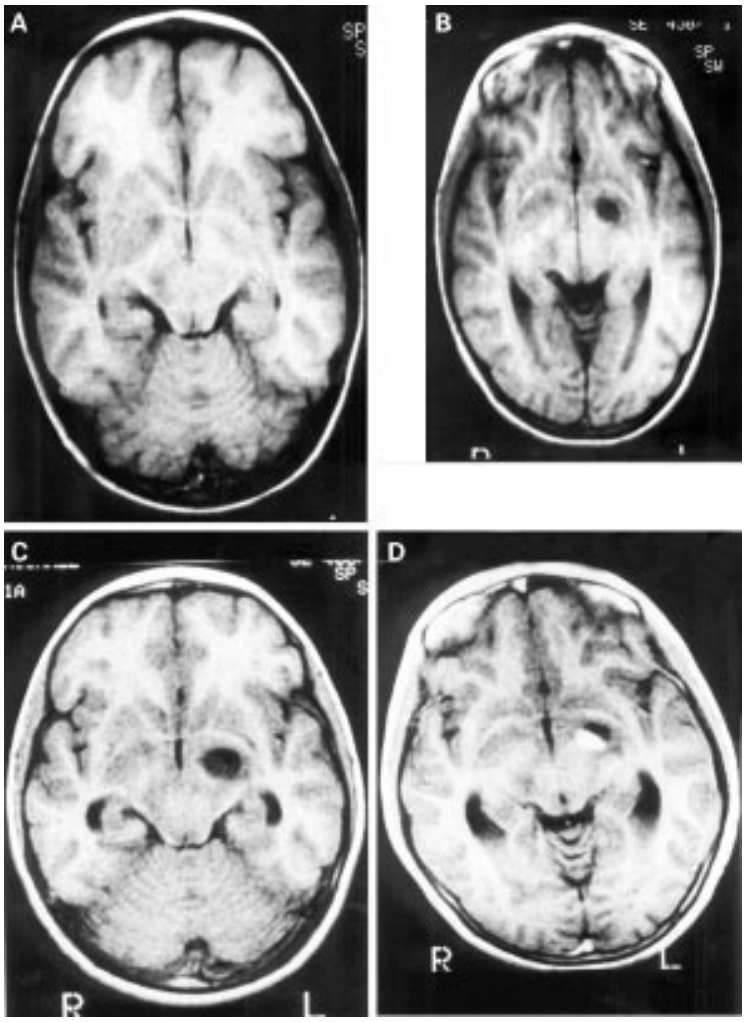

Figure 3 MRI, axial cuts, T1 weighted (400/10), at the level of the optic tracts. (A) Normal; (B) follow up two years later: a cystic lesion is seen on the left; (C) one year after (B) the lesion has enlarged; (D) same examination as (C) after gadolinium injection: partial enhancement of the lesion is noted.

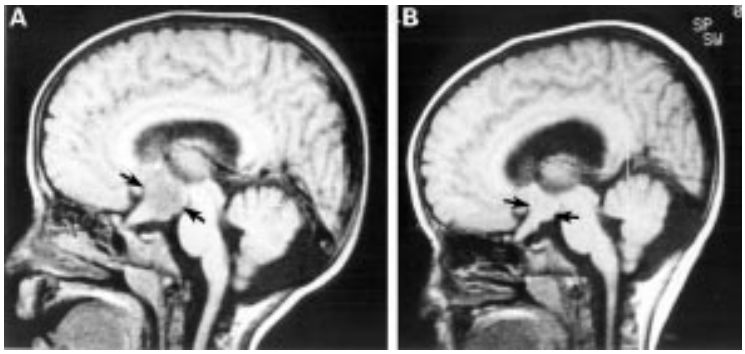

Figure 4 Short TR/TE-T1 weighted sagittal images. Partial involution of hypothalamic/chiasmatic glioma between 7/88 (A) and 1/90 (B).

received chemotherapy, for diencephalic syndrome in three patients and for tumour progression in the rest. The chemotherapeutic regimen was an 18 month course of vincristine 1.5 mg/m^2, with actinomycin D 15 μg/kg up to 1989[9] and with VP-16 100 mg/m^2 since 1990; recently, this has been replaced by carboplatin and vincristine.[18] Three children underwent tumour irradiation for tumour progression; two others also received radiotherapy at other centres. Tissue examination was performed in six children, and the results were compatible with pilocytic astrocytoma in all.

Table 3 Treatment complications

Complication	*No of patients*	*Treatment*
Mental retardation	2	XRT
Precocious puberty	1	XRT
	1	CTX
	1	Surgery+XRT+CTX
Hypothyroidism	1	XRT
Cataracts	1	XRT
Severe peripheral neuropathy	1	CTX

CTX = chemotherapy; XRT = radiotherapy.

Neither mode of treatment (chemotherapy or radiation) resulted in more than about 30% tumour shrinkage; in one child more than 50% of the tumour mass was surgically excised. However, except for three children who died of the tumour, both chemotherapy and radiation led to long term stabilisation of tumour growth. Neither mode helped in regaining lost visual ability, as measured by visual field and visual acuity testing.

In some children the VPG had a very irregular course. In one NF-1 patient the tumour showed spontaneous shrinkage of about 50%, but after six years regrowth was noted, necessitating the initiation of chemotherapy (table 2, number 9) (fig 4). In one girl who did not have NF-1 the tumour first increased about 15% in size, then stabilised for five years, and then grew again (table 2, number 14). In another child without NF-1 significant visual field recovery was noted after 13 years of follow up, eight years after finishing chemotherapy, without a significant change in tumour size. Therefore no direct effect of the chemotherapy can be claimed (number 16).

Treatment complications are summarised in table 3. Three patients, all from the non-NF group, died. All had chiasmatic/ hypothalamic globular tumour causing significant hypothalamic dysfunction and electrolyte abnormalities: one had diabetes insipidus and two had hypodipsic hypernatraemia. One girl also showed precocious puberty as well as a non-obstructive hydrocephalus and ascites related to hyperproteinaceous cerebrospinal fluid.

Discussion

Classically, the VPGs are considered to comprise 3 to 6% of all primary childhood central nervous system tumours.[7] NF-1 is present in about 50% of the cases. According to our experience, however, the incidence of this tumour is more than twofold the accepted rate. This higher figure can be explained to some degree by the higher rate of diagnosis of asymptomatic NF-1 patients. If only the non-NF children are considered, the incidence of VPG in our population was 5%. In all our patients the tumour was diagnosed during the first 10 years of life; the patients with NF-1 tended to be diagnosed at an older age than those without.

Visual loss was the most frequent manifestation leading to diagnosis and a prominent symptom in our patients. The objective evalua-

tion and follow up of the visual loss may be very difficult. In small uncooperative children or in those who are attention deficient, an accurate measurement of visual fields or visual acuity is almost impossible. Moreover, it seems that visual deterioration may precede the appearance of the glioma on imaging studies by a year or more. We recently observed a 29 year old woman with NF-1, the mother of one of our patients, in whom optic nerve glioma was found three years after visual deterioration was noted.

Although the study of visual evoked potentials may indicate the presence of glioma, it is not sensitive enough to replace either MRI or clinical examination of visual acuity and fields.[8] In such a situation, having a NF-1 child with subjective visual deterioration but without objective proof, or with very minimal thickening, if at all, of the optic nerve on imaging study of the brain, poses a significant dilemma regarding the decision to initiate chemotherapy. Notably, in our treated patients, although visual deterioration was arrested, lost visual ability was not regained. Thus, the exact point at which chemotherapy should be started is not always clear.

The vast majority of childhood VPGs are pilocytic astrocytomas. In the six patients who underwent tissue study, the results were the same. However, unlike the tumours that have a similar histology but in other locations (for example, the cerebellum), the course of childhood VPG is very variable and unpredictable. The tumour may characteristically remain stable for years. In our patients, long lasting tumour stabilisation, apart from the up to 30% reduction in tumour size, was the main achievement of treatment. However, similar stabilisation also occurred spontaneously in the untreated children.

Regarding affected NF-1 patients, Packer *et al* have suggested that gliomas found during their routine work up should not be treated so long as there is no evidence of progressive disease.[15] Considering the unpredictability of tumour growth, any decision regarding treatment is complicated. In the NF-1 group we observed patients who enjoyed long periods of tumour stabilisation with and without treatment. Even in children in whom the tumour involved a very large portion of the visual pathways, anteriorly from the chiasm or posteriorly up to the lateral geniculate bodies, tumour size remained stable for many years.

NF-1 patients may be affected by any of the three imaging based types of tumour, but optic nerve glioma and diffuse visual pathway tumours are much more common. In our study, NF-1 was a favourable prognostic marker. The relatively benign behaviour of the tumour in patients with NF-1 justifies the question raised by Packer *et al*[10]: are all abnormal lesions of the visual pathway in NF-1 children gliomas? The lesions that clearly need to be differentiated from true gliomas are the hamartomas or dural ectasias.[19] Thus, even more care is needed in evaluating the neuroimaging studies in NF-1 patients and even more caution in the treatment considerations.

Key messages

- The growth rate of VPG is unpredictable and erratic, especially in children with NF-1
- Follow up needs both MRI of brain and visual function studies (funduscopic examination, visual fields and acuity, if possible)
- Only symptomatic or growing tumours need treatment
- Although both chemotherapy and radiotherapy should decrease or stabilise tumour growth, chemotherapy, with less side effects, should be used initially
- Tumour progression is treated with chemotherapy, surgery, or radiotherapy
- Patients without NF-1 who have globular tumours and electrolyte abnormalities may have a poor prognosis

Clearly, it is very important to conduct a good follow up of visual ability by testing acuity and visual fields. It is also important to determine that vision is not deteriorating even though the tumour still seems unchanged in size.

The appropriate use of any one of the three modes of treatment (surgery, radiotherapy, or chemotherapy) is not yet fully agreed upon. It is well accepted that radiotherapy may cause significant side effects that may manifest years after treatment. The young age group is especially prone to intellectual deficits from radiotherapy, but other disturbances, such as moyamoya disease, endocrine disorders, and a wide range of vasculopathies, may occur as well.[20–22] During the last 20 years, the role of chemotherapy in the treatment of newly diagnosed VPGs has been established. We originally used actinomycin D and vincristine, but later VP-16 was substituted for the actinomycin. More recently carboplatin, which is better tolerated, achieves a higher rate of objective response, and has potentially fewer long term side effects than VP-16, has been introduced.[18] Other protocols have also been suggested, with reported tumour regression and improved visual function.[23–25] A major advantage of chemotherapy is that it enables the postponement or possible elimination of radiotherapy.

Treatment side effects in the present study were significant: persistent neuropathy due to chemotherapy, cataract formation, developmental deficit, and endocrinopathies due to radiotherapy.

All three children who died in the present series were in the non-NF-1 group, and all had chiasmatic/hypothalamic globular tumour with significant electrolyte disorder due to hypothalamic dysfunction. We presume that the hypothalamic-electrolyte abnormality is the harbinger of a worse prognosis.

Thus, children with newly diagnosed VPG should undergo repeated MRI studies and visual function evaluations for documentation of disease progression. If the disease does progress, chemotherapy should be started,

probably carboplatin and vincristine alone.[18] After completion of chemotherapy, the child should be further observed for the effect of treatment. The overall response rate may be expected to be approximately 60% and the stabilisation rate around 92%.[18] If and when further progression occurs, additional chemotherapy or radiotherapy, or surgery, should be considered.[16 26 27]

Our group of patients clearly shows the dilemmas associated with VPG follow up and treatment: the very irregular growth pattern of the tumour, sometimes with spontaneous, unexplained regression, or long periods of stability; the need for very good functional evaluation of visual ability; and presumably the better long term prognosis in NF-1 patients. It is possible that in the future molecular genetic markers will be able to simplify decision making in these patients. For the present, however, clinical considerations have to be weighed cautiously.

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