Eur J Pediatr (2000) 159: 692–696

ORIGINAL PAPER

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When do children with optic pathway tumours need treatment? An oncological perspective in 106 patients treated in a single centre

Received: 1 December 1999 / Accepted: 29 March 2000

Abstract Progression patterns of optic pathway tumours (OPT) need to be precisely defined for treatment planning. In patients with neurofibromatosis type 1 (NF1), this disease is usually indolent and the available literature rarely reports progression after the age of 6 years. In patients without NF1, the disease course seems to be less favourable. We reviewed the clinical and radiological files of 106 children referred to our institution for the treatment of a symptomatic OPT since 1980. NF1 was present in 51 of them. Progression patterns in children with NF1 differed markedly from those in the other patients. A total of 83 children had tumour extension beyond the chiasm (Dodge type III). Children with NF1 had progressive tumours later during follow-up (47% after the age of 6 years), had more often proptosis and infiltrating tumours but less frequently nystagmus or increased intracranial pressure. 32 children were not treated at diagnosis because they had only mild symptoms related to the OPT. In these patients, progression occurred more often in children without than with NF1 (12/12 versus 12/20 respectively, $P = 0.04$). A high number of patients needed treatment for progression or severe symptoms after 6 years of age. Of the patients, 33% needed treatment for progression or severe symptoms after 6 years of age.

Conclusion Progression patterns of optic pathway tumours in children with neurofibromatosis type 1 differ markedly from those in other patients. This study emphasises the need for prolonged follow-up of children with optic pathway tumours, especially in neurofibromatosis type 1.

Key words Optic pathway glioma · Brain neoplasm · Neurofibromatosis

Abbreviations *NF1* neurofibromatosis type 1 · *OPT* optic pathway tumour

Introduction

Despite numerous publications on optic pathway tumours (OPT), there is still considerable controversy over their natural history and management [1, 8]. It is difficult to compare data obtained in older series, many of which fail to separate patients on the basis of tumour site, age, histopathology, or presence of neurofibromatosis. Moreover, OPT in children with neurofibromatosis type (NF1) followed by paediatric neurologists probably differ from those seen by paediatric oncologists only when treatment is needed. The disease course is more

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favourable in children with NF1 [5, 14]. Indeed, a large proportion of the OPT in patients with NF1 do not progress after diagnosis [3, 13]. This overall better outcome of children with OPT and NF1 is also evidenced when only children with symptomatic tumours are taken into account [2, 10].

The aim of this study was to analyse the presentation and the patterns of progression in all the children with progressive OPT referred for treatment to our institution between 1980 and 1998, i.e. since the availability of CT scans. We attempted to answer the following two questions as a basis for guidelines on the follow-up of children with OPT (1) how long after diagnosis can OPT progress? and (2) do the progression patterns differ according to age or the presence of neurofibromatosis?

Although criteria to start treatment remained consistent during the study period, treatment modalities varied over the last 20 years, with a progressive increase in children receiving chemotherapy. Simultaneously, irradiation was reserved for older children and at relapse. Thus, we do not report here the outcome of these patients which is better analysed for a given protocol. Outcome of these patients after irradiation or chemotherapy has been previously published [2, 11].

Patient and methods

Patient selection and treatment policies

The Department of Paediatrics of the Gustave Roussy Institute is a referral centre for the treatment of the tumours in patients with NF1 and for the treatment of brain tumours in children. Only children with symptomatic OPT are referred to our centre to undergo treatment. Treatment was performed only in patients with severe symptoms (important visual loss, complications such as increased intracranial pressure or motor deficits) either at diagnosis or during follow-up. Surgery, when performed, was always conservative. For children younger than 5 years, first line treatment was radiotherapy before 1992 and chemotherapy after this date. The chemotherapy BBSFOP protocol consisted of 16 months polychemotherapy alternating with six different drugs (procarbazine, carboplatin, cisplatin, etoposide, vincristine and cyclophosphamide) [11]. For children older than 5 years, radiotherapy was the first line treatment during the study period [2].

Definition of study parameters

The clinical and radiological files were reviewed in each case. NF1 was defined according to the criteria of the National Institute of Health Consensus conference [16]. Tumour size and extension was classified according to the criteria of Dodge et al. [6]. Type I: optic nerve alone, type II: optic chiasm with or without optic nerve involvement and type III: involvement of the hypothalamus or adjacent structures. The appearance of the tumour on CT scans or MRI was defined into two groups: infiltrating lesions (i.e. thickening of the optic pathway structures) and tumoural lesions (tumour mass developing beyond the optic pathway structures).

Progression was defined by the presence of symptoms necessitating the treatment, i.e. severe visual loss in a previously asymptomatic child or significant visual loss and complications in a previously symptomatic child. Visual loss was considered as severe when visual acuity was under 5/10 (mean of both eyes). We decided not to define progression by means of imaging since some of the NF1 patients have neuroradiological examinations before becoming symptomatic while this is rarely the case for non-NF1 patients. Moreover, some of these tumours may progress only radiologically without clinical progression and some patients may have worsening of their vision without significant increase in tumour size. Since the ultimate goal of the treatment of this disease is to preserve the vision and prevent the complications, we chose to define the need of treatment for a progressive tumour by clinical parameters rather than and/or by imaging. We compared the presentation of the disease and the interval between diagnosis and progression (i.e. need for treatment) according to the presence or absence of NF1 and the age of the patients.

Data collection and statistics

Data were entered using a database program (Medibase IV, Quanta Medical SA, Rueil-Malmaison, France) and analysed with the use of a statistical program (Statview, Abacus Concepts Inc., Berkeley, California). Means were compared with the t test and percentages were compared with the Chi-square test.

Results

A total of 106 patients referred to the Gustave Roussy Institute for the treatment of a progressive OPT between 1980 and 1998 entered the study. Median age at start of treatment was 4.5 years (range 6 months to 17 years). NF1 was diagnosed either at diagnosis or later during follow-up in 51 patients.

Patients not treated at diagnosis

A total of 32 symptomatic patients were not treated initially despite being referred to our institution for "progressive tumours". Signs of progression were considered to be too mild or equivocal to start treatment. Among these 32 patients, 20 had NF1 while 12 did not. Median follow-up for this subgroup of patients was 7 years for all the 32 patients and also for the 8 of them that did not progress. Among the 32 children not treated initially, 12 of 20 children with NF1 showed further progression within a median of 16.5 months (range 3 to 69 months) compared with 12/12 children without NF1 (median 12 months, range 3 to 94 months, $P = 0.04$). Seventy five percent of the progressions occurred during the first two years after diagnosis (Fig. 1). In 20 of 24 patients that progressed, radiological confirmation of increased tumour size was obtained. We could not show any difference neither in the clinical presentation nor in the radiological signs between patients who progressed and those who did not. The presence of NF1 did not influence the time to progression. Only 2 of the 32 patients not treated initially died of disease progression; these two patients did not have clinical signs of NF1.

Why was treatment started?

Treatment was started in the presence of an important visual loss without any other complication in 31 patients

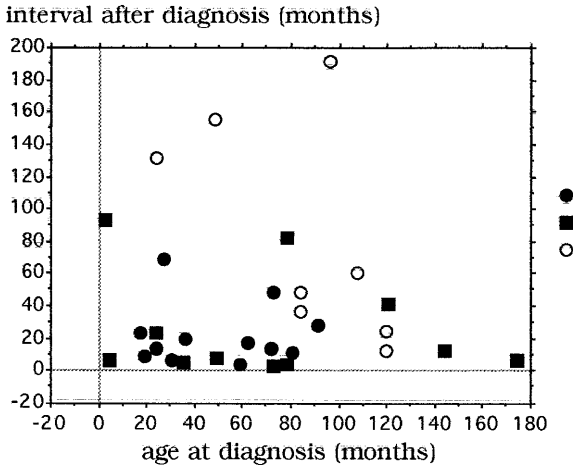

Fig. 1 Interval between diagnosis and treatment (months). Each *dot* corresponds to 1 of the 32 patients that were not treated at diagnosis although they were symptomatic. *Black circle*: children with NF1 and progressive tumours. *Black square*: children without NF1 and progressive tumours. *Empty circle*: children with NF1 that did not progress

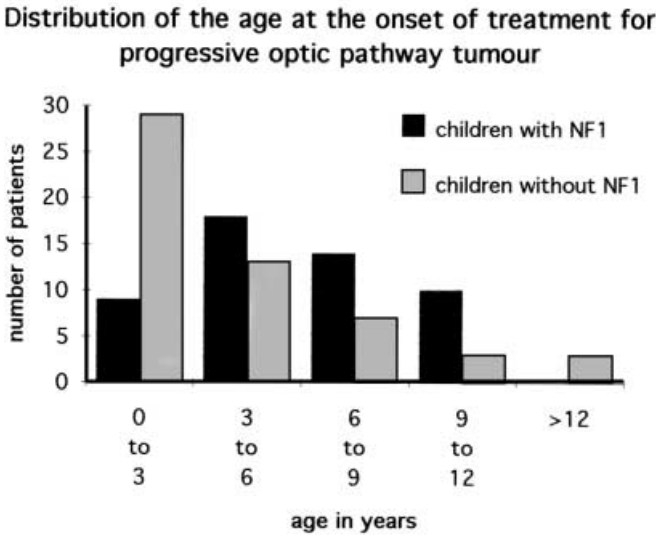

Fig. 2 Distribution of the age at the onset of treatment for progressive OPT

(29%, 18 NF1 patients and 13 non-NF1 patients), because of a complication associated with visual loss in 62 (59%, 28 NF1 patients and 34 non-NF1 patients) and because a complication without visual loss in 13 (12%, 5 NF1 patients and 8 non-NF1 patients).

Age at progression

Age at start of treatment due to progression or severe symptoms differed between children with and without NF1. Figure 2 shows the age distribution at progression in the 106 children (51 with NF1 and 55 without NF1). Of 51 children with NF1, 24 (47%) had tumour progression or severe symptoms justifying treatment after the age of 6 years. Progression never occurred in children with NF1 after age 11 years. Severe symptoms in previously asymptomatic children or true progression occurred earlier in children without NF1 (before the age of 6 years in 76% of cases). However, six children without NF1 experienced late progression or became symptomatic after age 11. Mean age at progression was 5.7 ± 2.9 years in NF1 patients versus 4.1 ± 4.0 years in non-NF1 patients ($P = 0.011$).

Presenting signs

Presenting signs also differed between children with and without NF1 (Table 1). Proptosis was significantly more frequent in patients with NF1 (21.5% versus 5.5%, $P = 0.03$) whereas increased intracranial pressure and nystagmus were more frequent in patients without NF1 ($P = 0.005$ and 0.03 respectively). The distribution of the other manifestations were similar in the two groups.

Table 1 Presentation at progression and NF1. (*NS* not significant)

	With NF1 (n = 51)	Without NF1 (n = 55)	P
Clinical signs			
Severe visual loss	30	19	
Moderate visual loss	10	11	NS
Visual loss not measurable	11	25	
Nystagmus	4	13	0.03
Proptosis	11	3	0.03
Oculomotor palsy	6	12	NS
Seizures	2	6	NS
Ataxia	2	4	NS
Motor deficit	4	7	NS
Increased intracranial pressure	6	18	0.005
Diencephalic cachexia	2	7	NS
Diabetes insipidus	1	1	NS
Precocious puberty	5	2	NS
Radiological signs			
Dodge type I	5	1	
Dodge type II	11	6	NS
Dodge type III	35	48	
Infiltrating lesion	15	5	0.007
Tumoural lesion	36	50	NS

Radiologically, infiltrating lesions were more frequent in children with NF1 (15/51 versus 5/55, $P = 0.007$). The distribution of Dodge tumour stages was similar in patients with or without NF1 with a large majority of type 3 tumours (69% and 87% respectively). When we compared the children who progressed early (before 4 years of age) with those who progressed later, nystagmus and increased intracranial pressure were significantly more frequent in the former (Table 2). Diencephalic cachexia did not occur after age 4 whereas precocious puberty was only observed after the age of 4 years. Radiological signs at progression were similar in younger and older children.

Table 2 Presentation at progression according to age. (*NS* not significant)

	Before 4 years ($n = 54$)	4 Years and above ($n = 52$)	*P*
Clinical signs			
Severe visual loss	22	27	
Moderate visual loss	5	16	NS
Visual loss not measurable	24	12	
Nystagmus	17	0	< 0.001
Proptosis	6	8	NS
Oculomotor palsy	11	7	NS
Seizures	5	1	NS
Ataxia	2	4	NS
Motor deficit	3	8	NS
Increased intracranial pressure	16	8	0.07
Diencephalic cachexia	9	0	< 0.001
Diabetes insipidus	0	2	NS
Precocious puberty	0	7	0.02
NF1	20	31	0.02
Radiological signs			
Dodge type I	1	5	
Dodge type II	8	9	NS
Dodge type III	45	38	
Infiltrating lesion	9	11	NS
Tumoural lesion	45	41	NS

Discussion

OPT have various pattern of evolution, especially in patients with NF1 [1, 15]. Spontaneous radiological regression of the OPT has even been documented in some patients [17]. As an attempt to define treatment indications and surveillance policies for OPT, we reviewed our personal cases to define the progression pattern of OPT seen by the paediatric oncologist, i.e. OPT that need treatment during their evolution.

This study confirms that OPT mainly progress or become symptomatic during the entire first decade of life, but significantly later in children with than without NF1 (5.7 years versus 4.1 years, $P = 0.01$). This is in keeping with previous reports where patients with OPT and NF1 tended to be older [2, 5, 14, 18]. None of the patients with NF1 had tumour progression after the age of 12 years. Recently, the Adult Neurofibromatosis Group of Creteil (same geographic area as our paediatric oncology clinic) reported accordingly that none of their 20 adult NF1 patients with OPT had progression of their tumour during the surveillance [4]. OPT (usually low grade glioma) diagnosed during childhood only progresses during childhood. OPT observed in adults, usually in patients without NF1, may have a totally different behaviour and more frequent malignant histology [1, 15]. Our findings also emphasise the need for lengthy follow-up of these patients. Of the children with NF1 who were treated, 50% progressed after the age of 6 years. This is in contradiction with previous findings in smaller series that were used as a basis for the consensus statement from the NF1 Optic Pathway Glioma Task Force [15]. In their report on the natural history of a selected sample of children with NF1 and OPT, Listernick et al. [14] found that 25/33 children were symptom-free at the time of diagnosis with normal ophthalmological findings in 21 children. All eight symptomatic OPT were diagnosed before age 6 and they concluded that OPT rarely progress after age 6. When we analysed more patients who required treatment for progressive tumours or tumours with severe symptoms, nearly 50% of the progressions occurred in patients with NF1 after age the age of 6 years.

Ophthalmological (and/or radiological) surveillance should be proposed for all the children with NF1 even if the initial MRI is normal as OPT may emerge in children with NF1 after normal neuroimaging results [12]. This close surveillance should continue at least until age 12. In children below the age of 4 years, documenting progressive visual loss is difficult and MRI surveillance should be added to the clinical surveillance.

The interval between OPT diagnosis and progression (i.e. the need for treatment) may be over 1 year, with intervals of more than 5 years in some of our patients. Few studies mention the duration of symptoms prior to presentation or progression indicating treatment. Symptoms generally occur 2 to 12 months before diagnosis, but longer periods have been reported [7]. Among our 32 patients who were not treated initially because their symptoms were mild, 8 did not progress during follow-up (8/20 with NF1, 0/12 without NF1). Thus, once the OPT is symptomatic, while all non-NF1 children will progress further, this is not the case in children with NF1. Smaller series of NF1 patients with OPT have suggested that this tumour may remain stable [3, 14], but follow-up was shorter and most of the children had no symptoms related to the tumour. These findings support a "wait and see" attitude in children with NF1 and OPT, in the absence of visual or life-threatening symptoms. Some NF1 children may then avoid treatment and its side-effects [9]. This attitude is also safe, as survival of patients not treated at the onset of symptoms was similar to those reported for the whole cohort [2, 10]. When patients are not treated at diagnosis, follow-up needs to be very regular (e.g. every 3 months) during the first 2 years when almost all the progressions are observed. However, for non-NF1 patients, once symptoms are present, it is not justified to postpone treatment and risk further deterioration of the patient's condition.

In addition to age at progression, we found other differences between NF1-OPT and non-NF1-OPT when presentation was analysed at start of treatment (progression or severe symptoms). Proptosis due to optic nerve involvement was more frequent in children with NF1 as mentioned in previous reports [5, 14]. Indeed, intra-orbital OPT without extension to the chiasm (Dodge type I) are almost exclusively seen in patients with NF1 (Table 1). In our study, and also in the literature, clinical presentation was more severe in non-NF1 children, with nystagmus, seizures, motor deficits, cranial nerve palsies and increased intracranial pressure [5, 14, 18]. The frequencies of the symptoms recorded in our

patients is comparable to those reported in the large compilation of studies reviewed by Dutton [7]. Listernick et al. [13] similarly reported that children with OPT and without NF1 had frequently nystagmus and increased intracranial pressure at diagnosis (5/19 and 12/19 respectively) whereas these symptoms were not observed in any patients with NF1, although only a few of them were symptomatic.

As regards the radiological aspect of the tumours, the infiltrating subtype was significantly more frequent in children with NF1 in our study (29% versus 9%, $P = 0.007$). Regarding the association of NF1 and this architectural form of OPT, the available literature is controversial, but most of the studies were done before the availability of CT scans [1, 7]. It is likely, as our study focused on children with progressive and symptomatic tumours, that we may even have overestimated the frequency of the invasive tumoural form in children with NF1. This infiltrative and indolent form of disease is certainly more frequent in children with NF1, but rare in children without NF1.

Our study justifies to extend the follow-up of children with NF1 and OPT up to the age of 12 years. Late progressions have been observed but most of the patients not treated at diagnosis of symptomatic OPT went on treatment within the first 2 years. Symptomatic OPT in NF1 patients may not progress further while they always do so in non-NF1 patients. Thus treatment may be postponed only in NF1 patients if symptoms are mild or absent. The evolution of childhood OPT is clearly limited to the first decade of life and physicians should keep this in mind when designing treatment protocols.

Acknowledgements This work was supported by a grant from the Fondation de France and the Fédération Nationale des Centres de Lutte Contre le Cancer to V.L. The authors also thank Dr. David Young for editing the manuscript.

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