

Management of diffuse glioma in children: a retrospective study of 27 cases and review of literature

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Abstract

Gliomas are the most common CNS tumours in children and present either as circumscribed tumours or diffusely infiltrative neoplasms. Diffuse gliomas develop both in the cerebral hemispheres and the brainstem and have a poor prognosis. Guidelines for the therapy of these tumours are still debated. In this study, we reviewed the clinical features of 27 consecutive patients with diffuse gliomas admitted to the Department of Paediatrics of CHR Citadelle, University of Liège, between 1985 and 2005. We review their clinical presentation, diagnosis, treatment and outcome with reference to the published literature.

Key words : Diffuse gliomas ; children ; clinical study ; supratentorial ; brainstem.

Introduction

Paediatric central nervous system (Hunter *et al.*, 2002) tumours represent 20% of all childhood cancer (age 0-14 years). Gliomas account for 42% to 66% of all paediatric CNS tumours. By decreasing frequency, they consist of pilocytic astrocytomas (21% and 16% of CNS tumours from 0-14 and 15-19 years, respectively), ependymomas (10-15% of CNS tumours) and a group of astrocytic and oligodendroglial tumours WHO grade II, III and IV that are usually referred together as diffuse gliomas, as they show a distinctively infiltrative pattern of growth (WHO classification 2007) (see Table 1). At the microscopic level the distinction between the diffuse gliomas and the more circumscribed ones, particularly pilocytic astrocytomas, is somewhat artificial as pilocytic astrocytomas can be shown to permeate the brain parenchyma over mm to centimetres (WHO classification 2007). At the clinical level, the treatment of pilocytic tumours may be challenging as they tend to localize in the optic chiasma/hypothalamus and central grey nuclei in children. However, pilocytic astrocytomas, as a whole, have a slow growth and a low rate of recurrence. Their management is primarily surgical and their overall prognosis is favourable when amenable to complete surgical resection. By contrast, diffuse gliomas show a wide range of growth rate, a tendency to progress towards anaplasia and recurrence is the rule. Their treatment comprises surgery, irradiation and chemotherapy but their prognosis remains poor, particularly for high grade and brainstem tumours.

In this review, we have only included low grade and high grade diffuse gliomas as defined above. As in adults, diffuse gliomas can show histological features of astrocytic, oligodendroglial or mixed differentiation, but in children, tumours with an oligodendroid appearance are relatively rare (Razack *et al.*, 1998). Based on their morphological features and proliferative rate, they are usually grouped as high-grade (WHO grade III and IV) or low-grade (Brada *et al.*, 2003) tumours. By contrast with adults, where glioblastomas are the most frequent primary CNS tumours, high grade supratentorial gliomas are infrequent in children (Peris-Bonet *et al.*, 2006) and represent 6%-12% of all primary paediatric brain tumours (Pollack, 1994). In the U.S., from 1995 to 1999, the overall incidence of paediatric high-grade gliomas was 0.63 per 100,000 person-year (Broniscer *et al.*, 2004). Location in the brainstem is seen in 3%-9% of paediatric primary CNS tumours, a figure much higher than in adults (Pollack, 1994). Whether low-grade or high-grade, brainstem gliomas are particularly challenging for the oncologist as surgery is usually not an option.

Because of the low incidence of diffuse childhood gliomas, few randomised studies have been reported that specifically address the paediatric population and the guidelines for treatment are still debated. Furthermore, the

patterns of genetic alterations are still poorly documented in child tumours, preventing the development of targeted therapies.

Finally, long term toxicity is always a major concern when treating a child, limiting the use of drugs and radiation.

In this paper, we review 27 consecutive cases of diffuse gliomas, diagnosed and treated in the Department of Paediatrics, Hôpital de la Citadelle (University of Liège), between 1985 and 2005. The charts were carefully reviewed for clinical, radiological and pathological features of the brain tumours and for patient's outcome under the various therapeutic regimens that were recommended at time of diagnosis.

Table 1 WHO grading of gliomas

	WHO grade	Histological sub-type			
		Astocytic tumours	Oligodendroglial tumours	Oligoastrocytic tumours	
Diffuse Gliomas	Low grade	Grade I	Pilocytic astrocytoma (ICD-O code 9421/1)	-	-
		Grade II	Diffuse Astrocytoma (ICD-O code 9400/3)	Oligodendroglioma (ICD-O code 9450/3)	Oligoastrocytoma (ICD-O code 9382/3)
	High grade	Grade III	Anaplastic astrocytoma (ICD-O code 9401/3)	Anaplastic oligodendroglioma (ICD-O code 9451/3)	Anaplastic oligo-astrocytoma (ICD-O code 9382/3)
		Grade IV	Glioblastoma (ICD-O code 9440/3)	-	-

Patients and methodology

Twenty-seven consecutive cases of paediatric diffuse glioma were diagnosed and treated in the Department of Paediatrics, University of Liège, Hôpital de la Citadelle, between 1985 and 2005. Paediatric group was defined as 0-16 years of age. Charts were carefully reviewed for patients and tumours characteristics (displayed in Tables 2 and 3). Diagnosis was made either on histology or on the combination of clinical and radiological features. The percentage of cases with diagnosis based on histology was 96% (26/27). Follow up was not systematically organized in the hospital and was made through general neurosurgical or oncologists consultations. No child was lost or excluded from the follow up. Except for one patient with grade II astrocytoma who died of tumour progression after 20 years, death always occurred within the 2 years following diagnosis. Among survivors, the mean follow up was 5.8 years (1.6-10.7). All patients were treated according to the gold standard protocols prevailing at the time of diagnosis, including the BB SFOP protocol (carboplatin, procarbazine, etoposide, cisplatin, vincristin and cyclophosphamide) (Dufour *et al.*, 2006), the HIT-GBM 89 (CCNU, vincristin and prednisolone), the 8-in-1 regimen (vincristine, CCNU, procarbazine, hydroxyurea, cisplatin, cytarabine, dacarbazine, and methylprednisolone) (Finlay *et al.*, 1995) and Temozolomide alone.

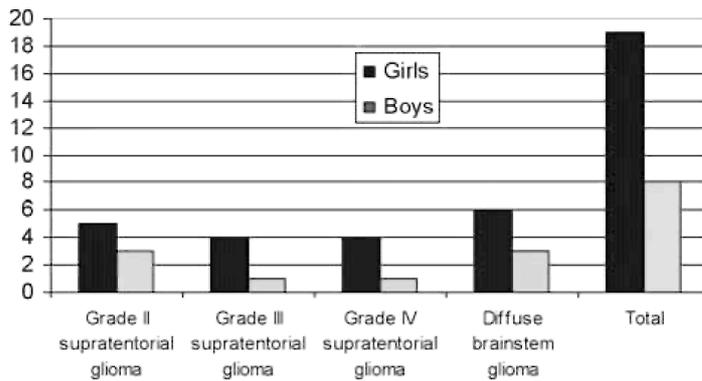
Results

Epidemiology

Among the 27 followed children, 19 were female and 8 were male. The sex ratio (girl/boy) was 5/3 for grade II supratentorial gliomas, 4/1 for grades III supratentorial gliomas, 4/1 for grades IV supratentorial gliomas and 6/3 for diffuse brainstem gliomas (Fig. 1).

The mean age at diagnosis was 8.9 y (0.2-15.3). High grade glioma predominantly occurs in young patients and 85% (12/14) of patients with grades III and IV gliomas were < 10 y. By contrast, grade II glioma tend to develop in older patients, since 58% (7/12) of patients with grade II glioma were over 10 y.

FIG. 1. — Sex distribution.



Genetic background

Two patients had a particular personal history suggestive a possible genetic background favouring the development of brain tumours. The first (case 1) had Langerhans cell histiocytosis treated by chemo- and radiotherapy until the age of one year and developed a temporal oligodendroglioma grade II at the age of 15 years. The second patient (case 9) had a family history of type 1 neurofibromatosis and developed a thalamic astrocytoma grade III at the age of 4 y.

Presenting symptoms

The mean interval between onset and diagnosis was 5 months with a maximum of 30 months. This interval was of 4.3 months for supra-tentorial infiltrative gliomas and of 5.4 months for diffuse brainstem gliomas.

In supratentorial tumours, the mean time before diagnosis was of 3,6 months for grade II, 6 months for grade III and 4 months for grade IV gliomas.

Symptoms leading to delayed diagnosis were isolated headache (24 and 30.05 months) and behavioural changes (12 months).

Conversely, diagnosis was made early for cases presenting with visual disturbance of acute onset or cranial nerve palsies (0.23 and 0.94 month), intracranial hypertension (1.48, 0.99, 0.33, 0 and 1.05 months), generalized seizures (0 and 0.13 months), limb paresia (0.46 and 1.25 months) and ear nose throat (ENT) manifestations such as dysphagia or dysarthria (0.99 and 0.33 month).

Symptoms at onset were related to tumour location (Tables 4 and 5). Visual disturbance and ataxia were mostly seen with brainstem tumours. Headache, hemiparesia and vomiting were frequent and encountered with all tumour types and location. Acute raised intracranial pressure was frequently present in high grade supra-tentorial gliomas. Ataxia, vertigo, dysarthria, dysphagia and hemihypoesthesia were only seen in brainstem glioma. Finally, asthenia was only reported in high grades tumours, either supra- or infra-tentorial.

The neurological examination at diagnosis was abnormal in a majority of patients. However, it was reported as normal for 7 patients, 5 with a temporal tumour, 1 with a left parietal tumour and the last with a tectal tumour.

Treatment and outcome

Grade II supratentorial gliomas ($n = 8$)

The five-year survival was 90% (Fig. 2) and the mean follow up of survivors was 4.7 years (1.6-10).

Complete resection was obtained in 5 cases. All patients achieved complete remission without adjuvant treatment (cases 1, 2, 3, 6, 7).

Biopsy alone was performed in 3 patients. The first patient achieved partial remission at 10 years (case 4). The second died after 0.3 years of evolution because of tumour progression despite radiotherapy (case 5). The third (case 8) had tumour recurrence 10 years after diagnosis, with progression to anaplasia (grade III astrocytoma). The patient died after 20.2 years of tumour progression despite radio- and chemotherapy.

Therefore, complete resection was associated with a better prognosis, as reported in the literature (Campbell *et al.*, 1996) (Wisoff *et al.*, 1998) (Kramm *et al.*, 2006).

FIG. 2. — Survival rate by tumour type.

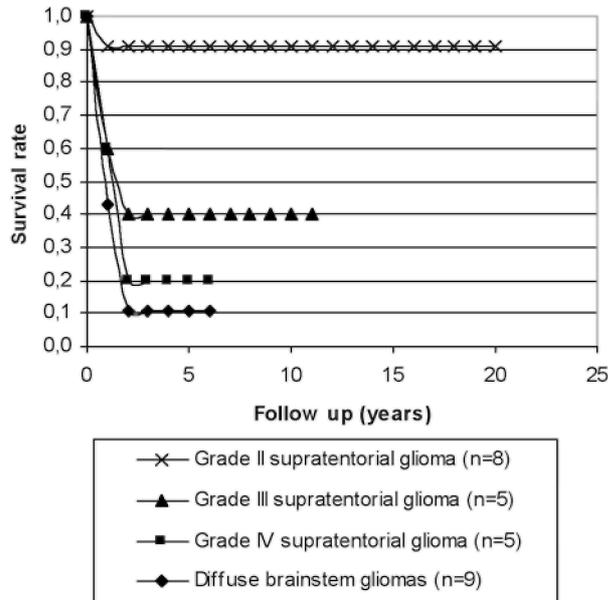


FIG. 3. — Brainstem grade III astrocytoma of the left part of the protuberance, with partial contrast enhancement (patient 24).

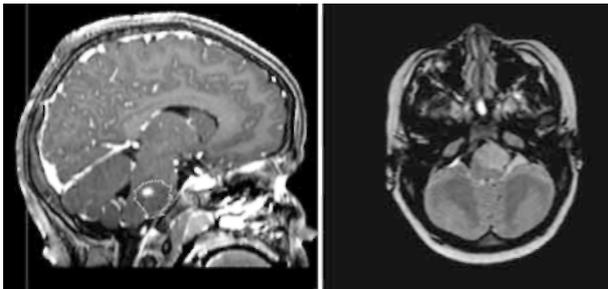
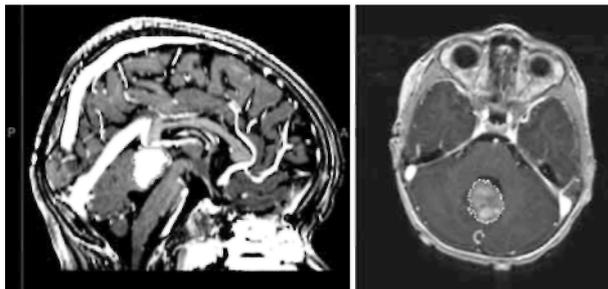


FIG. 4. — Tectal grade II fibrillary astrocytoma (patient 2).



Grade III and IV supratentorial gliomas ($n = 10$)

For grade III tumours, the 5-year survival was 40% (2/5) (Fig. 2), with a follow up respectively of 8.5 and 10.7 years for the two survivors (cases 9 and 10). The two patients who achieved prolonged complete remission were those who benefited from complete surgical resection. In the other cases, only an open or stereotactic biopsy (patients number 11 and 13) or a partial surgical excision could be performed (patient number 12) and death ensued within two years following diagnosis despite adjuvant radio- or chemotherapy.

For glioblastoma, the 5-year survival was 20% (1/5) (Fig. 2), with a follow up of 5.7 years for the survivor. Only one patient benefited from macroscopically complete resection but he died rapidly due to tumour recurrence (patient 16). In the other four cases, surgery was only partial. Three patients (cases 14, 15 and 18) died within two years following diagnosis. A 6-year old girl with left parietal glioblastoma achieved prolonged complete remission with radio- and chemotherapy (patient 17). This girl presented with a 5 week history of asthenia, vomiting and right hemiparesis. Total resection was obtained in two steps and followed by radiotherapy (60 Gy). After two months, the patient developed headache, vomiting and right hemiparesis. Control MRI showed recurrence of a mainly cystic tumour which was drained. Temozolomide was then given for 4 years, leading to complete tumour regression and prolonged second complete remission (5.7 years). Unfortunately, the patient kept sequellae with right hemiparesis and dysarthria.

As expected, the time interval between onset and diagnosis was of prognostic significance. Indeed, all patients with a delay before diagnosis > 1.5 years died, while 3/5 patients with a delay < 1.5 years are alive. For patients with complete remission, diagnosis was always made during the first 18 months of evolution.

Finally, in this series, age at diagnosis was not predictive of outcome. In larger studies, younger age has been shown to be of better prognosis (Finlay *et al*, 1995 ; Wisoff *et al*, 1998) but these data are still debated.

Brainstem glioma ($n = 9$)

Eight patients died shortly after the onset of symptoms and the mean survival was 0.7 years (Fig. 2). All had received radiotherapy and 5 of them were also treated with chemotherapy (3 with temozolomide alone, 1 with fotemustine and 8-in-1 regimen and one with vincristine and carboplatine). One patient (case 27) with a grade II glioma achieved partial remission at 5 years, after biopsy and chemotherapy. This 14-years-old boy, with Chiari malformation, presented with a one year history of left hemifacial spasm, cerebellar signs and left inferior hemihypoesthesia. MRI showed an expansive lesion of the left part of brainstem, without contrast enhancement. Histology was made on open biopsy and showed a grade II glioma. Treatment by chemotherapy following Packer (vincristine, carboplatine) was given leading to prolonged partial remission.

Table 2 Patients Characteristics See "Diffuse gliomas Table 2"

Case	Gender	Age (years)	Year	Localisation	Histology	WHO grade	Ki 67 and p53 index (a)	Presenting symptoms	Neurological examination	Interval before diagnosis (months)	Diagnosis	Surgery	Radiotherapy	Chemotherapy	Follow up (years)
1	f	15	2002	Temporal, right	Oligodendroglioma	II		Convulsion	Normal	0,0	Surgical specimen	Complete	No	No	Complete remission (4.5)
2	m	4	2004	Tectum	Fibrillary astrocytoma	II	Ki67 : 1 p53 : 1	Headache, vomiting	Normal	3,6	Surgical specimen	Complete, in two times	No	No	Complete remission (2.3)
3	f	5	2004	Cerebellar vermis	Astrocytoma	II	Ki67 : 1	Ophthalmic manifestations, headache	Strabism	6,4	Surgical specimen	Complete	No	No	Complete remission (2.3)
4	f	12	1997	Thalamus, right	Astrocytoma	II	Ki67 : 0	Headache, ophthalmic manifestations, ataxia.	Bilateral pyramidal syndrome	4,5	Stereotactic biopsy	Biopsy	No	No	Partial remission (10.1)
5	m	15	1999	Thalamus, left	Astrocytoma	II	Ki67 : 1 p53 : 0	Ophthalmic manifestations, ataxia	Right pyramidal syndrome	3,1	Stereotactic biopsy	Biopsy	Yes	No	Progression. Tumour related death (0.3)
6	f	6	1999	Parietal, left	Astrocytoma	II		Convulsion	Normal	5,4	Surgical specimen	Complete	No	No	Complete remission (7.5)
7	f	12	2005	Fronto-temporal, left	Pleomorphic xanthoastrocytoma	II	Ki67 : 1 p53 : 1	Headache, vomiting	Normal	1,0	Surgical specimen	Complete, in two times	No	No	Complete remission (1.6)
8	m	1	1985	Fronto-parietal, left	Astrocytoma	II	Ki 67 : 3	Convulsion	Right hemiparesis	5,0	Open biopsy	Open biopsy	Yes	BB SFOP (b)	Progression. Tumour related death (20.2)
9	f	4	1996	Thalamus, left	Astrocytoma	III	Ki67 : 0	Right hemiparesis	Right hemiparesis with no involvement of the face, right pyramidal syndrome.	0,5	Surgical specimen	Complete, in two times	No	BB SFOP (b)	Complete remission (8.5)
10	f	1	1996	Fronto-temporo-parietal, left	Astrocytoma	III		Ophthalmic manifestations, vomiting, apathy	Fever, bulging fontanelle, left ptosis, lethargy	0,3	Surgical specimen	Complete, in two times	No	BB SFOP (b)	Complete remission (10.7)
11	f	0	1996	Diencephalon	Astrocytoma	III		Anorexy	Macrocephaly, bulging fontanelle	2,6	Open biopsy	Biopsy	No	No	Progression. Tumour related death (0)
12	f	15	1998	Temporal, left	Astrocytoma	III		Ophthalmic manifestations, headache, vomiting	Normal	0,6	Surgical specimen	Incomplete	Yes	Vincristine	Progression. Tumour related death (0.2)

13	m	7	1999	Diencephalon	Astrocytoma	III	Ki 67 : 2 p53 : 2	Headache, vomiting, ophthalmic manifestations	Lethargy, right facial hemiparesis bilateral 6th cranial nerve palsies.	24,0	Open biopsy	Biopsy	No	BB SFOP (b)	Progression. Tumour related death (1.8)
14	f	7	1994	Frontal, right	Glioblastoma	IV		Acute intracranial hypertension	Left hemiparesis	0,0	Surgical specimen	Incomplete	Yes	HIT 89 (c) Carboplatinum Vincristine	Progression. Tumour related death (1.9)
15	f	9	1998	Thalamus, right	Glioblastoma	IV	Ki67 : 3	Acute intracranial hypertension	Left babinski	1,5	Surgical specimen	Incomplete	Yes	Temozolomide	Progression. Tumour related death (1.4)
16	m	4	2000	Temporal, right	Glioblastoma	IV		Behavioural changes, vomiting, headache, photophobia	Normal	12,1	Surgical specimen	Complete	No	BB SFOP (b)	Relapse (after 5 months). Palliative treatment. Tumour related death (0.5)
17	f	7	2001	Parietal, left	Glioblastoma	IV	Ki67 : 3 p53 : 2	Asthenia, vomiting, right hemiparesis	Right hemiparesis involving the face, right facial hemiparesis	1,3	Surgical specimen	Complete	Yes	No	Relapse (after 2 months) treated with temozolomide. Complete remission (5.7)
18	f	6	2005	Right hemisphere	Glioblastoma	IV	Ki67 : 3 p53 : 3	Ataxia, headache, asthenia, vomiting, convulsion	Left pyramidal syndrom, left cerebellar syndrom	6,2	Surgical specimen	Incomplete	Yes	Temozolomide	Progression. Tumour related death (0.1)
19	f	10	1996	Brainstem	Astrocytoma	III	Ki67 : 3	Ataxia, vomiting	Dysphagia, right hemipresis.	1,1	Stereotactic biopsy	Biopsy	Yes	No	Progression. Tumour related death (0.9)
20	f	4	1997	Brainstem	Astrocytoma	III	Ki67 : 2	Ataxia, asthenia, dysphagia	Dysarthrie, intermittent strabism, cerebellar ataxia, Parinaud syndrome, left preeminent pyramidal syndrome, central left 7th cranial nerve palsy.	0,3	Stereotactic biopsy	Biopsy	Yes	No	Progression. Tumour related death (0.6)
21	f	5	1999	Brainstem	Astrocytoma	II	Ki67 : 2	Headache, vomiting, ophthalmic manifestations	Cranial nerve palsies (VI)		Open biopsy	Biopsy	Yes	Temozolomide	Progression. Tumour related death (0.3)
22	m	15	1999	Brainstem	Astrocytoma	II		Ataxia, dysarthria, dysphagia	Right pyramidal syndrome, right hemihypoesthesia, cranial nerve palsies (V, VIII, IX, X, XI), left cerebellar syndrome.	1,0	Stereotactic biopsy	Biopsy	Yes	No	Progression. Tumour related death (1.1)

23	f	14	1999	Brainstem	Fibrillary astrocytoma	II		Headache, vomiting, dysphagia, ataxia	Cerebellar syndrome	30,1	Open biopsy	Open biopsy	Yes	Fotemustine and 8-in-1 regimen	Progression. Tumour related death (1.1)
24	f	7	2004	Brainstem	Astrocytoma	III	Ki67 : 3 p53 :3	Diplopia	Strabism	1,3	Stereotactic biopsy	Stereotactic biopsy	Yes	Temozolomide	Progression. Tumour related death (1.2)
25	f	5	2005	Brainstem	No biopsy	No biopsy		Headache, diplopia, left hemiparesis, ataxia, dysphagia, dysarthria	Strabism, left hemiparesis involving the face, left pyramidal syndrom, ataxia.	3,0	Radiologic	No surgery	Yes	Temozolomide	Progression. Tumour related death (0.5)
26	m	9	2004	Brainstem	Astrocytoma	III	Ki67 : 3 p53 :3	Acute intracranial hypertension	Bilateral myosis, left hemiparesis, left inferior limb myoclonia. Glasgow 9/15.	0,1	Open biopsy	Open biopsy	Yes	No	Progression. Tumour related death (0.9)
27	m	14	2001	Brainstem	Astrocytoma	II	Ki67 : 1 p53 : 1	Left facial hemispasm	Left facial hemispasm, left dysmetria, hemi-hypoesthesia of the left inferior limb. Romberg sign.	12,0	Open biopsy	Open biopsy	No	Vincristine, carboplatine	Partial remission (5.1)

a. 1 = low, 2 = moderate, 3 = high

b. BB SFOP protocol : carboplatin, procarbazine, etoposide, cisplatin, vincristin and cyclophosphamide

c. HIT-GBM 89 : CCNU, vincristin and prednisolone.

Table 3 Characteristics of tumour groups

	Diffuse astrocytoma (WHO grade II)	Anaplastic astrocytoma (WHO grade III)	Glioblastoma (WHO grade IV)	Brainstem gliomas	Total
Number of patients	8	5	5	9	27
Age, years					
Mean	8.9	5.5	6.5	9.2	7.9
Range	1.3-14.9	0.2-15.3	4.5-9.2	3.7-15.2	0.2-15.3
Sex					
Male	3	1	1	3	8
Female	5	4	4	6	19
Diagnosis delay, months					
Mean	3.6	6	4	5	5
Range	0-5	0-24	0-12	0-30	0-30
Surgery					
None	-	-	-	1	1
Open biopsy	1	2	-	4	9
Stereotactic biopsy	2	-	-	4	4
Subtotal resection	-	1	4	-	5
Total resection	5	2	1	-	8
Chemotherapy	1	4	5	5	15 (51%)
Radiotherapy	2	1	4	8	15 (51%)
5-year survival	90%	40%	20%	10%	44%
Follow up of survivors, years					
Mean	4.7	9	5.7	5.1	5.4
Range	1.6-10	8.5-10.7	-	-	1.6-10.7

Table 4 Symptoms at onset

	Supratentorial infiltrative gliomas	Diffuse brainstem gliomas
Headache	6	1
Convulsion	5	
Ophthalmic manifestations	2	5
Paresis	2	
Ataxia	1	
HTIC	1	
Anorexia	1	
ENT symptoms		3

Table 5 Symptoms at diagnosis

	Diffuse astrocytoma (WHO grade II)	Anaplastic astrocytoma (WHO grade III)	Glioblastoma (WHO grade IV)	Diffuse brainstem gliomas	Total
Ophthalmic manifestations	3	3	-	6	12
Headache	4	2	2	3	11
Hemiparesis	1	3	2	4	10
Acute intracranial hypertension	-	3	5	1	9
Ataxia	2	-	-	6	8
Nausea, vomiting	2	1	1	3	7
Convulsions	3	1	1	-	5
ENT symptoms	-	-	-	5	5
Asthenia	-	-	1	2	3
Behavioural changes	-	-	1	-	1
Photophobia	1	-	1	-	2
Hemihypoesthesia	-	-	-	2	2
Anorexia	-	1	-	-	1

Discussion

We have reviewed 27 consecutive cases of paediatric infiltrative gliomas and we have described their clinical presentation, treatment and outcome. Pilocytic astrocytoma, although it is the most common glioma in children, was not included in this review. This tumour typically occurs in the first two decades of life and affects midline structures, such as the cerebellum, the walls of the third ventricle and the anterior optic pathway. They are often well delineated and have a low proliferative rate. Unlike diffuse astrocytoma, progression to anaplasia is distinctly rare in these tumours. Complete surgical excision, when amenable, offers an excellent prognosis to patients. Therefore the diagnostic features and therapy of these tumours are relatively straightforward. On the contrary, the less frequent diffuse astrocytomas are much more controversial in terms of clinical features and therapy protocol.

The aim of this work is to illustrate the specificities of diffuse gliomas in children and report the experience of a large referral paediatric department in Belgium between 1985 and 2005. The small number of patients included in this cohort prevents a meaningful statistical treatment of data. However, some trends are worth mentioning.

Gender analysis shows a strong female predominance (F/M : 2.4/1) in our cohort of children. This distribution is particularly obvious for brainstem glioma and supra-tentorial high-grade tumours. However, these ratios may be biased by the small size of the cohort studied. Larger series of the literature suggest that the incidence of astrocytoma is the same in boys and girls under 15 years (Greenberg *et al.*, 1985 ; Peris-Bonet *et al.*, 2006). In adults, diffuse astrocytoma is slightly more common in men than women (Fleury *et al.*, 1997 ; Guthrie *et al.*, 1990 ; Salzman *et al.*, 1994).

The age distribution of our cases of brainstem glioma is comparable with the reported peak of tumour prevalence between 6 and 10 y (Packer *et al.*, 1992 ; Pierre-Kahn *et al.*, 1993). In our group of supratentorial diffuse glioma, grades III and IV seem to occur in younger patients than grade II tumours. An extensive review of brain tumours in children under 4 years of age reports a higher rate of malignancy in the first year of age (Rickert *et al.*, 1997). Data are conflicting regarding the impact of gender and age on prognosis. However, suggestions have been made that female gender and younger age may affect outcome favourably (Finlay *et al.*, 1995 ; Wisoff *et al.*, 1998).

In this cohort, headache is the most frequent symptom of supra-tentorial high grade astrocytoma and sometimes the sole complaint, delaying the diagnosis. Isolated headache in a child, even with normal clinical examination, should always be explored and brain imaging considered. Nausea and vomiting never occurred in isolation but were always accompanied by headache, visual disturbance, paresis and ataxia. Any of these associations should also direct explorations towards an intracranial mass. Finally it is important to note that a normal neurological examination does not rule out the presence of an intracranial tumour, particularly with temporal and frontal location, as for 5 patients with temporal tumour in this study.

Survival rates are comparable with larger series (Brada *et al.*, 2003 ; Broniscer *et al.*, 2004 ; Spoto *et al.*, 1989) with 5-year survival depending on grade and location : 90% in grade II, 40% in grade III and 20% in grade IV supra-tentorial glioma. In the group of brainstem glioma, one patient with grade II glioma uncommonly survived for 5 years, after biopsy and chemotherapy associating vincristine and carboplatine. The other patients rapidly died, with a mean survival of 0.7 years, as expected from published large studies (Freeman *et al.*, 2000 ; Packer *et al.*, 1996).

In supratentorial infiltrative gliomas, we observed that complete resection seems to be associated with a better prognosis. This observation is confirmed by larger studies (Campbell *et al.*, 1996) ; (Wisoff *et al.*, 1998) ; (Kramm *et al.*, 2006). Fisher *et al.* (Fisher *et al.*, 2001) showed that, once the patients with complete resection were excluded from the analysis, the extent of surgical resection lost its significance as a prognostic factor. In several series, the tumour location is an independent prognostic factor as well, and deep midline tumours show a much poorer survival than hemispheric ones but this obviously relates, at least partly, to the ability of conducting a complete surgical resection (Finlay *et al.*, 1995). Two patients with complete remission had an oligodendroglioma (case 1) and a pleomorphic xanthoastrocytoma (case 7), which both show a longer evolution than astrocytomas (Ohgaki *et al.*, 2005). Little information is available on the role of biological markers but it seems that overexpression of p53, high proliferation index, PTEN (phosphatase and tensin homology) mutation and overexpression of basic fibroblast growth factor protein (bFGF) are associated with a worse outcome in high grade gliomas (Broniscer *et al.*, 2004). In contrast with adult tumours, deletions in chromosomes 1p and 19q are not associated with a survival advantage in pediatric high grade gliomas (Rutka *et al.*, 2004). Unfortunately, these genetic studies were not performed in this series of cases.

In brainstem glioma, high morbidity and mortality rates are the rule and are independent of the extent of resection or histology and grade. For this reason, surgical resection or biopsy of a brainstem glioma is no longer advocated (Hargrave *et al.*, 2006). Nevertheless, with development of targeted therapies, some study groups readdress the interest of stereotactic or open biopsies to correlate biological findings with drug activity (Hargrave *et al.*, 2006). Moreover, occasional patients with atypical tumours in this region may benefit from a tissue diagnosis and partial resection (Rutka *et al.*, 2004). This series illustrates the specific management of paediatric infiltrative gliomas. These tumours are much rarer in children than in adults, accounting for the few randomised studies specifically directed towards paediatric treatments. It is hoped that future studies will identify specific genetic patterns acting in paediatric glioma, allowing for the development of new targeted therapies in this population.

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