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Brainstem gliomas— Retrospective analysis of 86 patients

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ABSTRACT

Brainstem gliomas constitute 10% of brain tumors in children and less than 2% in adults. Since therapeutic options are limited and brainstem gliomas are associated with a high morbidity and mortality, we sought to analyze the prognostic factors associated with a better outcome.

We reviewed the records of 86 patients with brainstem gliomas treated between 1996 and 2006. We recorded demographic and clinical variables as well as radiological findings and survival. Patients were divided in two groups regarding overall survival: late progressors (survival ≥12 months) or early progressors (survival<12 months). Of 86 patients with brainstem gliomas, 55.8% were females. The mean age at diagnosis was 14.2 years (range 1 to 52 years). Twenty-four (27.9%) patients were adults. Lesions were located at pons in 75.6% of patients, midbrain in 15.1% and medulla in 9.3%. There was no difference between early and late progressors concerning gender, age at onset, location at pons, presence of necrosis or contrast enhancement observed at MRI or surgical resection. In both univariate and multivariate analysis, only a short duration of symptoms before diagnosis (<3 months) was associated with a worst prognosis (odds ratio 5.59, 95% CI 1.94 to 16, $p = 0.0014$). A short duration of symptoms, which may imply a more aggressive tumor, was associated with a worst prognosis in patients with brainstem gliomas. This information may be useful in the selection of patients for future therapeutic trials.

1. Introduction

Brainstem gliomas constitute 10% to 20% of the brain tumors in children [1,2] and less than 2% in adults [3]. The median age at onset is six to seven years and there is no gender predominance [4]. Once considered a single entity associated with a poor prognosis, new imaging techniques demonstrated subsets with different evolutions and outcomes [5]. Several grading systems have been developed taking into consideration location, growth pattern and resectability [6], but they can be subdivided in diffuse pontine gliomas, tectal and cervicomedullary gliomas [7]. Pontine gliomas represent 80% of the brainstem gliomas [8]. They are usually infiltrative, have an aggressive course and are associated with a dismal prognosis [9]. On the other hand, midbrain and cervicomedullary gliomas follow an indolent course, usually are well defined, have a growth pattern of low grade glial tumors and portray a better survival [7].

Conventional external beam, local field radiation has been the cornerstone of the treatment [4]. Chemotherapy efficacy is not proven and resection is not feasible in the diffuse infiltrative pontine lesions [4,10]. Since therapeutic options are limited and brainstem gliomas are associated with high morbidity and mortality rates, it is important to have a better understanding of the prognostic factors associated with a favorable outcome.

In this study, we sought to describe the demographic and clinical characteristics of a large series of Brazilian patients diagnosed with brainstem gliomas and determine possible prognostic factors associated with survival.

2. Methods

We reviewed the medical records of patients with brainstem gliomas treated at The National Institute of Cancer, Rio de Janeiro, Brazil, between 1996 and 2006. Clinical variables as well as radiological findings (gender, age at onset, duration of symptoms ≥3months [7], initial symptoms and signs location, the presence of necrosis or contrast enhancement observed at MRI), treatment modalities and survival were recorded. All patients underwent magnetic resonance imaging (MRI). The participants were divided into two groups regarding survival: individuals who survived ≥12 months were considered late progressors and those who survived <12 months were considered early progressors.

Fisher exact test was used to compare possible factors related to survival. In addition, we performed multivariate analysis using SPSS 13.0 for Windows (SPSS, Chicago, IL) with logistic regression to control for possible confounding variables. We also created Kaplan–

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Table 1
Initial symptoms and signs.

Symptoms and signs	*N* (%)
Headache	25 (29.1)
Motor deficit	21 (24.4)
Visual complaints	17 (19.8)
Ataxia	11 (12.8)
Sensory deficit	6 (7)
Vomiting	2 (2.3)
Seizures	2 (2.3)
Confusion	1 (1.2)
Hypoacusia	1 (1.2)

Meyer curves to demonstrate survival in the study population. All p values were two sided and an $\alpha = 0.05$ was employed.

3. Results

Of 86 patients with brainstem gliomas, 48 (55.8%) were females. The mean age at diagnosis was 14.2 years (SD ± 11.2, range 1 to 52 years). Twenty-four (27.9%) patients were adults (≥18 years). Headache (29.1%) and motor complaints (24.4%) were the most prevalent symptoms at onset (Table 1). The duration of the symptoms preceding the diagnosis was <3 months in 51 patients (59.3%) and ≥3 months in 35 (40.7%).

The pons was the most common site of the lesions (75.6%), followed by the midbrain in 15.1% and the medulla in 9.3%. The MRI revealed contrast enhancement in 48.8% of the cases and the presence of necrosis in 12.8%. Hydrocephalus was detected in 31 individuals (36%), more often in association with midbrain lesions (69.2%) when compared to lesions at other locations (43.1%) ($p = 0.011$).

The diagnosis was confirmed by biopsy in 37 patients (43%), while in 49 individuals with pontine gliomas, the diagnosis was established by the typical appearance on brain MRI (Fig. 1). The remaining eight patients died before starting treatment or were selected just for clinical observation. Among the cases with histological diagnosis, Grade II glioma was observed in 40.5%, anaplastic astrocytoma in 29.7%, pylocitic astrocytoma in 18.9% and glioblastoma multiforme in 10.8%. Low grade tumors (OMS Grades I and II) were observed more often in adults (46.1%) when compared to children (16.7%).

Seventy-eight patients (90.7%) underwent radiation therapy. Only four patients (4.7%) underwent chemotherapy. Partial or total resection was performed in 17 individuals (19.8%). Lesions were resected partially or completely in 6/8 patients (75%) with medullary

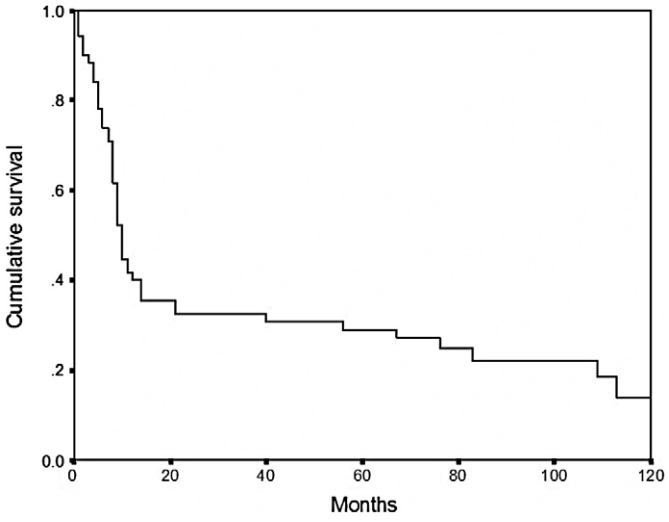

Fig. 2. The Kaplan–Meyer survival curve for patients in the study.

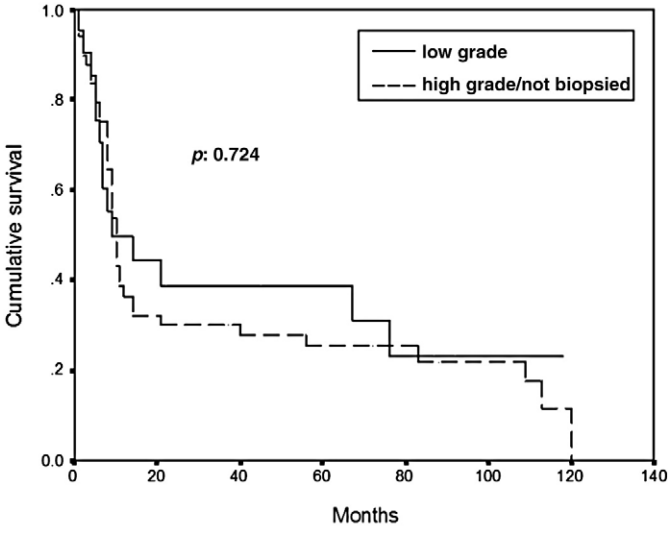

Fig. 3. The survival curve for patients according to tumor grade.

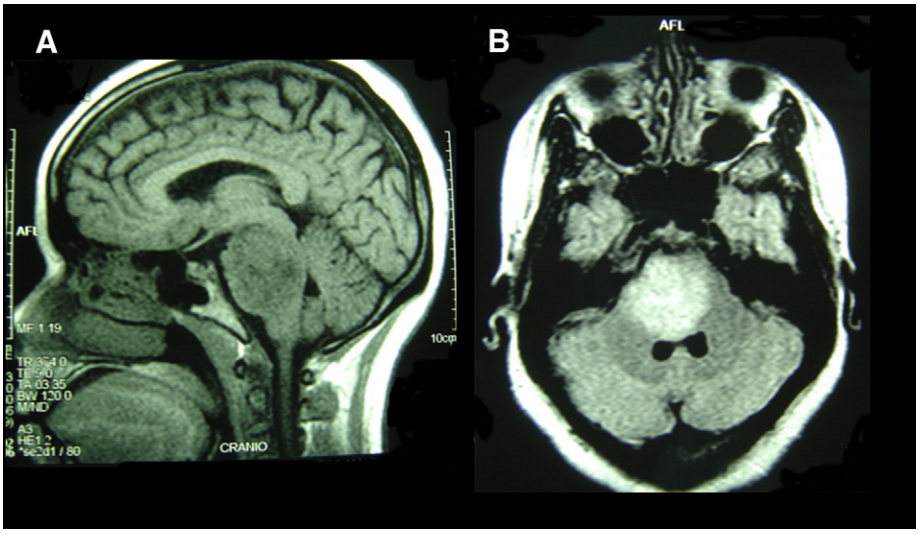

Fig. 1. MRI of a 26 year-old patient with a diffuse infiltrative pontine glioma. (A) Sagittal T1— weighted. (B) Axial FLAIR image.

lesions, in 4/13 (30.7%) patients with midbrain lesions and only 7/65 (10.7%) with pontine lesions.

The median survival was 9 months (range 1–120 months) (Fig. 2). Six recently diagnosed patients were excluded from the prognostic factor analysis. We also analyzed the survival according to tumor grade (low grade histology versus high grade and patients not biopsied) and any significant difference was found (Fig. 3). There was also no significant difference between early and late progressors concerning gender, age at onset, location at pons, presence of necrosis or contrast enhancement observed at MRI or surgical resection. In both univariate and multivariate analysis, only a short duration of symptoms before diagnosis (<3 months) was associated with survival <12 months (odds ratio 5.59, 95% CI 1.94 to 16, $p = 0.0014$) (Table 2).

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4. Discussion

In our study, the clinical and the epidemiologic characteristics of the study group were similar to those observed in previous series [7,11–13]. Most patients were in the pediatric group and there was no clear gender predilection. Headache, cranial nerve palsies and long tract signs dominated the clinical picture.

Conventional brain MRI has become invaluable in the diagnosis and management of brainstem gliomas [5,6]. In particular, the characteristic aspect of the diffuse infiltrative pontine gliomas warrants therapy, avoiding invasive procedures to obtain histological confirmation [14]. While some studies have shown an association between the presence of contrast enhancement and survival [7,15], in our study, contrast enhancement was observed in approximately half of the cases, but this was not related to a worse outcome. Different from supratentorial gliomas, where contrast enhancement usually represents a higher tumor grade and shorter survival, diffuse pontine gliomas frequently do not enhance but still can be highly aggressive [9].

Previous studies have shown a better prognosis in adults with brainstem gliomas [12]. It is likely that brainstem tumors of a lower grade and a less striking preferential location at pons in adults explain the longer survival in this population [12]. Guillamo et al. have shown that adult brainstem gliomas have a different behavior than childhood tumors and resemble supratentorial gliomas in adults [7]. However, we have not observed a difference between children and adults concerning the one-year survival. Some patients in the adult group had less than twenty years of age and tumors that might have a behavior closer to that observed in children.

The only factor associated with a longer survival in both univariate and multivariate analysis was the duration of symptoms ≥3 months. An association between duration of symptoms >1 month and a better outcome was observed in a previous series of 119 pediatric patients [16]. Similarly, symptoms lasting more than three months were a favorable prognostic factor in a study with 48 adults [7]. Several factors have been implicated in the outcome of brainstem gliomas in other series such as the necrosis or contrast enhancement [7], diffuse aspect of the tumor [9] the presence of cranial neuropathy or long tract signs [17] and the histological grade of the tumor [7]. Since most patients have not undergone biopsy, we can speculate that a longer duration of symptoms before diagnosis may reflect a less aggressive nature of the tumor.

There was a trend to a longer survival in patients who underwent surgery at the univariate analysis. Probably, this reflects a selection bias, since most of the patients in the surgical group had midbrain or medullary tumors which are usually well delimitated, have a more benign histology and are associated with a better outcome [7]. Due to their growth pattern, there is no role for surgery in treatment of the diffuse pontine gliomas [4].

Only a small proportion of the individuals in the present study underwent chemotherapy. While several drugs have been incorporated in the treatment of tumors in other brain locations, their benefit in brainstem gliomas remains elusive. A recent study has shown a longer survival in patients who were treated with intense chemotherapy using multiple drugs following irradiation when compared to irradiation alone [10]. Nevertheless, several other studies have evaluated the use of chemotherapy either before or after radiation with no clear benefits [4].

In conclusion, a shorter duration of symptoms, which may imply a more aggressive nature of tumor, was associated with survival <12 months in patients with brainstem gliomas. Since there is no effective therapy to date, this information might be useful in the selection of patients for future therapeutic trials.

Table 2
Univariate and multivariate analysis of factors associated with survival.

	Survival		Univariate analysis		Multivariate analysis	
	<12 months *n* (%)	≥12 months *n* (%)	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value
Gender						
Male	22 (51.1)	13 (35.2)	0.52 (0.2–1.27)	0.15	0.52 (0.19–1.48)	0.22
Female	21 (48.9)	24 (64.8)				
Age at onset						
<18 years	30 (69.7)	26 (70.2)	1.02 (0.39–2.67)	0.96	1.44 (0.46–4.48)	0.52
≥18 years	13 (30.3)	11 (29.8)				
Duration of symptoms						
<3months	33 (76.7)	14 (37.9)	5.42 (2.05–14.3)	0.0006	5.59 (1.94–16)	0.0014
≥3months	10 (23.3)	23 (62.1)				
Location at pons						
Yes	35 (81.4)	25 (67.5)	0.47 (0.17–1.33)	0.16	0.68 (0.1–2.4)	0.55
No	8 (18.6)	12 (32.5)				
Enhancement						
Yes	22 (51.1)	19 (51.3)	1 (0.41–2.42)	0.98	0.64 (0.2–1.97)	0.44
No	21 (48.9)	18 (48.7)				
Necrosis						
Yes	5 (11.6)	6 (16.3)	1.47 (0.4–5.28)	0.55	2.5 (0.5–12.25)	0.25
No	38 (88.4)	31 (83.7)				
Surgical resection						
Yes	6 (14)	11 (29.7)	2.6 (0.85–7.94)	0.09	2.13 (0.55–8.27)	0.27
No	37 (86)	26 (70.3)				

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