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Clinical profile and outcomes in brainstem glioma: An institutional experience

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ABSTRACT

Aim of the Study: This study was to analyze the clinical outcomes of brain stem glioma treated with radiation therapy (RT) in our institution.

Material and Methods: Records of 48 patients with brainstem glioma treated between January 2007 and January 2013 were reviewed. Demographic variables, clinical variables, radiological findings and treatment details with respect to age, sex, location of tumor (pontine Vs non pontine), signs and symptoms, RT dose, follow up period and outcomes were recorded. Patients were subdivided into two groups based on their age, age <15 years (Group I) and age ≥15 yrs (Group II).

Results: The median age at diagnosis was 10 years (range 4-50). Male to female ratio was 11:10. Of the 48 cases analyzed, 27 patients (56%) were in group I and 21 (44%) were in group II. Radiologically, 90.5% had involvement of pons. 10 (21%) patients received RT dose >60 Gy and 38 (79 %) patients received RT dose of 54-60 Gy. Median overall survival was 7months (range 3-44 months). Median overall survival in Group I and Group II was 4 months and 10 months respectively ($P = 0.042$).

Conclusions: Brain stem glioma in pediatric age group is associated with worse outcomes than in adults.

Key words: Brain stem glioma, pediatric brain tumor, radiotherapy

Introduction

In children, brainstem gliomas constitute 10% of brain tumors, and these are usually classified into three main groups.^[1-3] The largest subgroup is diffuse intrinsic pontine glioma, which is characterized by a striking diffuse enlargement of the brainstem on magnetic resonance imaging (MRI) with or without heterogeneous contrast enhancement, an aspect that obviates the need for biopsy according to many authors.^[4,5] These tumors carry the worst prognosis of any brain tumor in childhood, with a median survival of <1-year.^[6,7]

The second subgroup (10%) comprises slow-growing low-grade gliomas arising at the cervico medullary junction or from the

floor of the fourth ventricle.^[8,9] These tumors most often have a posterior contrast-enhancing exophytic development that may be amenable to surgical resection.^[5,10,11] Long survival is common and the median survival time is over 5 years. The third subgroup consists of indolent local tectal gliomas, which are often heralded by hydrocephalus.^[12,13]

In contrast, brainstem gliomas in adults are poorly understood because they are uncommon, accounting for <2% of gliomas.^[14] Most reported studies belong to an era when MRI was not available at diagnosis.^[15,16] However, some data suggest that survival is much longer in adults than in children.^[16-18]

To improve our understanding of the natural history of these tumors, to identify prognostic factors and to propose a scheme of classification for them, this retrospective study of brainstem gliomas was undertaken.

Patients and Methods

Inclusion criteria

Patients were included if they met the following criteria: (i) The epicenter of the tumor, defined as the center of the tumor bulk, was located in the brainstem (midbrain, pons and medulla oblongata) (this criterion excluded tumors originating in the thalamus, the cerebellar peduncles or the cervical spinal cord); (ii) the diagnosis was based on histological confirmation

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or on clinical history with characteristic MRI appearance, consisting an infiltrative expansive process, with or without contrast enhancement and (iii) a complete medical record, including clinical data, repeated MRI, and detailed treatment data, was available.

Data collection

The following clinical data were collected from treated cases of brain stem glioma at our institute including (i) patient demographic data (ii) at the time of diagnosis: Age, sex, time between the date of the first symptom and the date of the diagnosis (i.e., duration of symptoms), main symptoms and signs, Karnofsky performance status, description of the tumor on MRI (T1 and T2-weighted images in at least two planes before and after gadolinium contrast enhancement), and pathological reports when available; (iii) treatment administered at diagnosis of the tumor; (iv) during follow-up: Clinical and radiological course, complications (hydrocephalus, hemorrhage, leptomeningeal dissemination, bulbar involvement with swallowing impairment), treatment at recurrence, and date and cause of death or date of the last visit if the patient was alive.

The radiological response to radiotherapy (RT) and chemotherapy was reported as: (i) A complete response, that is, disappearance of all visible tumor; (ii) a partial response, that is, a decrease of $>50\%$ in the axial cross-section of the greatest surface area (contrast enhancement or T2-weighted hyper-signal for nonenhancing tumors); (iii) progressive disease, that is, $>25\%$ increase in axial cross-section of the greatest surface area; or (iv) stable disease, that is, all other situations.^[19,20] The response was evaluated while the patients were receiving stable or decreasing dose of corticosteroids.

Statistical analysis

Survival time was measured from the date of symptom onset to the date of last follow-up or death. Survival was estimated by the Kaplan–Meier method and its 95% confidence interval (CI) by the Rothman method. Survival curves were compared with the log-rank test. The following parameters were evaluated for their association with survival, age of onset, sex, duration of symptoms, motor impairment, Karnofsky performance status, location of the epicenter of the tumor, contrast enhancement on MRI after gadolinium infusion, MRI evidence of necrosis, histological grade and RT dose. Patients were subdivided into two groups based on their age, age <15 years (Group I) and age ≥ 15 years (Group II). The Cox proportional hazards model was used to test the prognostic factors in multivariate analysis. Results are expressed with a relative risk and its 95% CI.

Results

Patient population

Between January 2007 and January 2013, 48 patients treated at our institute who fulfilled the criteria described above were included.

Duration of symptoms

Overall survival and general characteristics of the patients including mean follow-up was 4 years (range: 3 months to 6 years). The mean age at diagnosis was 10 years (range: 4–50) there was a trend toward a biphasic; age distribution, with a first peak in the first decade and a second peak in the third decade. There was a predominance of males (33 males/15 females) but was not related to survival ($P > 0.42$). Overall median survival for the entire group was 7 months (range: 3–44 months). Median overall survival in Group I and Group II was 4 months and 10 months, respectively ($P = 0.042$).

The medical histories revealed that one patient with brainstem glioma had received cranial RT (54 Gy) 18 years earlier (at the age of 10 years) for medulloblastoma.

Clinical presentation

Median Karnofsky performance status at diagnosis was 80 (range: 50–100). Performance status <70 was associated with a shorter survival time ($P = 0.002$). The median symptom duration before diagnosis was 4 months (range: 1-week to 7 years). The onset of the disease was sudden for five patients and was related in three of them to intratumoral hemorrhage. Among the other patients: 20 (42%) had a short duration of symptoms (<3 months) and 23 (48%) had a long duration of symptoms (>3 months) before diagnosis, a feature strongly related to survival ($P < 0.0001$). At initial presentation 62% had features of raised intracranial tension, 71% had cranial nerve defects, and 57% had cerebellar signs.

Magnetic resonance imaging features at diagnosis

In an attempt to simplify the anatomical classification of these infiltrating tumors, their location was defined according to the site of the tumor epicenter. Using this criterion, 90% of tumors were located in the pons and 10% in medulla. Most tumors extended outside their main location and were most frequently pontomedullary (77%).

Four patterns were identified on MRI, namely patterns representing nonenhancing diffusely infiltrative tumors (65%), contrast-enhancing localized masses (31%), isolated tectal tumors (4%). Forty-six percent of tumors had contrast enhancement that was associated with a shorter survival time ($P = 0.001$). Presumed necrosis on MRI, defined as a zone of irregularly shaped T1-weighted hypo signal surrounded by contrast enhancement, was found in 20% of cases and was strongly associated with shorter survival ($P < 0.0001$).

Surgical procedures

Only two patients had craniotomy and biopsy. Infiltration of the metencephalon was a constant feature in patients who developed symptomatic hydrocephalus that required a shunt at diagnosis or during follow-up.

Pathology

Among the two, one is anaplastic astrocytoma, and the other one is oligodendroglioma.

Radiotherapy

All patients received RT. 10 (21%) patients received RT dose >60 Gy and 38 (79%) patients received RT dose of 54–60 Gy in conventional fractionation. Survival did not seem to be affected by the radiation dose. Durable symptomatic clinical improvement (defined as regression of cranial nerve palsies or weakness of the limbs or cerebellar syndrome for >6 months) was observed in 40% of patients after RT. After RT, a partial radiological response was noted in 8 patients (18%), stable disease in 27 (64%) and progressive disease in 8 (18%). The best response time was 14 ± 10 months (mean standard deviation), with great variation between cases, ranging from 5 to 36 months after completion of the RT. Tolerance of RT was generally good, although one patient died before the end of treatment, and eight others required increased doses of corticosteroids because of transient worsening of their symptoms during RT.

Evolution and complications

During the follow-up, hydrocephalus occurred in 8 patients (16%); it required a shunt placement in 6 patients (13%). Tumor progression was characterized either by steady deterioration or by rapid clinical worsening following a long period of stable disease, a finding that we observed in 6 patients (13%), associated with the appearance of an enlarging, contrast-enhancing lesion on MRI suggestive of anaplastic transformation.

Tumor extension was either intra- or extra-parenchymatous. Intra-axial progression (particularly in the medulla oblongata, with swallowing difficulties) in 42% of patients leading to severe aspiration pneumonia in 15% eventually extended outside the brainstem in 12 (24%) patients, involving the diencephalon (5 patients), the cerebellum (4 patients) and cervical spinal cord (3 patients). Extra-parenchymatous dissemination was due to leptomeningeal dissemination, a finding observed in 6 (13%) patients and characterized on MRI by multiple disseminated contrast-enhancing nodules in the ventricles and subarachnoid spaces. Two patients had spontaneous intratumoral hemorrhage that was rapidly fatal in both cases. These tumors were anaplastic oligodendrogliomas. Death was related to glioma in 92% patients.

Classification of adult brainstem gliomas

Using univariate analysis, four favorable prognostic factors were identified:

- Young age (<40 years)
- Duration of symptoms >3 months
- Karnofsky performance status >70
- Absence of contrast enhancement or “necrosis” on MRI.

Of the three clinical factors, duration of symptoms was the only one to be significant on multivariate analysis ($P < 0.001$). Of the paraclinical factors, MRI “necrosis” was significant

prognostic factor ($P < 0.05$) but contrast enhancement was not. When the duration of symptoms and MRI “necrosis” were introduced into multivariate analysis, the relative risks of these factors were similar but MRI; “necrosis” was the only one to be significant ($P < 0.03$).

According to these variables and the clinical and radiological patterns, we classified these tumors into three main categories with significant survival differences between them ($P < 0.0001$).

Diffuse intrinsic low-grade brainstem glioma

This group comprised of 22 patients (46%). Onset occurred in young adults in their third decade (19 out of 22 were; aged <40 years). Symptom duration was >3 months and symptoms sometimes appeared several years before diagnosis. In seven cases, the presentation was remarkable and was characterized by prolonged isolated facial palsy with facial hemi spasm in five cases. Most of the gliomas appeared as infiltrative, diffuse, pontomedullary tumors without contrast enhancement and necrosis on MRI. RT significantly improved the clinical neurological status in 13 out of 22 cases and four partial radiological responses. A presumed anaplastic transformation, characterized by contrast enhancement after a long period of stable disease, occurred in 27% of patients. The overall median survival time of this group was 7.3 years.

Malignant brainstem glioma

Fifteen cases (31%) were in this group, whose results contrasted with those for the previous group in most respects. The majority of patients were aged >40 years. Onset was rapidly progressive, and there was altered performance status. At diagnosis, contrast enhancement and necrosis were found on MRI. These tumors were highly resistant to treatment (after RT only two patients had clinical and radiological improvement). Evolution was always rapidly fatal, with a median survival time of 11.2 months.

Focal tectal brainstem glioma

We identified four cases (8%) of pure focal tectal tumors characterized by an indolent course. Hydrocephalus was the only presenting syndrome in two of them. Pathological examination was performed in two patients, one is an astrocytoma and the other is oligodendroglioma. All the patients survived (>5 years in one case and 8 years in three cases).

Other tumors

Three tumors (15%) could not be included in the three previous groups: One atypical extensively calcified oligodendroglioma, one radiation-induced oligodendroglioma and one dorsal exophytic contrast-enhancing glioma.

Discussion

This study confirms that adult brainstem gliomas are different from the childhood subtypes, identifies prognostic factors and

proposes a classification of these tumors. Overall, brainstem gliomas are less aggressive in adults than in children. Analysis of this series indicates that brainstem gliomas in adults can be divided into at least three groups diffuse, intrinsic, low-grade brainstem gliomas: Malignant brainstem gliomas; and other gliomas (in particular tectal gliomas) whose main characteristics are detailed below.

Diffuse intrinsic low-grade brainstem glioma

Interestingly, the most frequent type of brainstem glioma in adults (representing 48% of the patients in this series) resembles the childhood diffuse gliomas of the pons in terms of clinical and radiological presentation but is radically different in course and survival. In both adults and children, the clinical picture is of a combination of cranial nerve and long tract signs.^[21,22] However, while the onset is rapid in children, the duration of symptoms is often long in adults, as illustrated by our seven patients who experienced either long-lasting, isolated, discrete facial paresis or facial hemispasm.

In both children and adults, MRI at presentation reveals a diffuse infiltration of the pons, often increasing the size of the brainstem considerably. There is high signal on T2-weighted and low signal on T1-weighted images, which usually do not show contrast enhancement.^[23,24] It is worth noting that preferential location in the pons is less striking in adults than in children since the epicenter of the tumor was located in the pons in 15 out of 22 patients and in the medulla in seven out of 22 patients in the study.

Malignant brainstem gliomas

The other common tumor type identified in this adult series is clearly different from those discussed above. It occurs later than the diffuse, intrinsic, low-grade type and affects mainly older adults (most of them in their sixth decade). The clinical picture is characterized by the rapid onset of cranial nerve palsies and long tract signs leading to an early alteration in performance status. MRI reveals a brainstem mass that enhances after gadolinium infusion, often in a ring-like fashion. In our series, contrast enhancement was a pejorative factor (particularly when the area of enhancement surrounded a low-signal area suggestive of necrosis) in contrast with children, in whom the prognostic value of contrast enhancement remains controversial.^[23,25] Thus, the clinical-radiological pattern, pathology and course closely resemble the common malignant supratentorial gliomas in adults, and we suggest that this group be designated “malignant brainstem gliomas.”

Focal tectal gliomas

Focal tectal gliomas represent the third type of adult brainstem glioma and constitute a small subgroup that also exists in children. The clinical picture is dominated by hydrocephalus.

All our patients received RT and experienced long-term survival of good quality. Nevertheless, the benefit of RT can be questioned since pediatric patients with similar clinical and radiological features have been managed with ventricular shunt or observation alone for long periods.

Other types

Other types of brainstem glioma can be observed in adults. Interestingly, we observed only one exophytic contrast-enhancing glioma arising from the floor of the fourth ventricle; this entity, which is associated with a good prognosis, is well-described in children (representing up to 10% of brainstem gliomas). A likely explanation for this discrepancy between the two age-groups is that most of the exophytic gliomas correspond to pilocytic astrocytoma, a very rare type of tumor in adults.

Complications

Except for locoregional progression, two main complications were observed during the course of adult brainstem gliomas, namely hydrocephalus. Hydrocephalus was observed in 16% of cases. Whereas some pontine tumors may have an important mass effect on the fourth ventricle, hydrocephalus was always associated with mesencephalic involvement and blockage of the cerebrospinal fluid at the level of the sylvian aqueduct. Leptomeningeal dissemination was not reported in our case series.

The role of biopsy

Finally, this classification may help in the selection of patients for biopsy. In children, MRI has become the reference for the diagnosis of brainstem glioma and is advised for the current classification of these tumors. MRI has replaced biopsy in the diagnosis of pediatric diffuse brainstem gliomas, for which most authors agree that anticancer treatments can be administered without pathological confirmation if the clinical course is rapid. However, we believe that the biopsy is not useful in the diagnosis of intrinsic, diffuse, low-grade brainstem gliomas in adults when the clinical and radiological criteria described above are met. The issue is different in contrast-enhancing lesions because several reports have underlined the limits of MRI in differentiating tumors from infectious diseases. In this setting, a surgical approach is probably indicated.

Yamasaki *et al.*; studied clinical, conventional magnetic resonance (MR), and MR spectroscopic (MRS) findings predictive of the prognosis of patients with brainstem glioma. Total of 23 patients with diffuse intrinsic pontine or diffuse medullary brainstem glioma were studied. The MRS detection of lactate is a prognostic factor in patients with diffuse intrinsic pontine glioma. Patients with a lactate presence had a progression-free survival overall survival were 6.3 and 10.9 months whereas 20.1 and 33.3 months in patients with absent lactate on MRS ($P = 0.0061$ and $P = 0.0065$).^[26]

Summary

Brain stem glioma patients present with gait disturbance (61%), headache (44%), weakness of the limbs (42%), and diplopia (10%). Treatment consisted of partial biopsy in two cases and definitive RT for the rest. Overall median survival for the entire group was 7 months (range: 3–44 months). On univariate analysis, the following favorable prognostic factors were identified ($P < 0.01$): Age of onset < 40 years, duration of symptoms before diagnosis > 3 months, Karnofsky performance status > 70 , absence of contrast enhancement and “necrosis” on MRI. On multivariate analysis, the duration of symptoms and the appearance of “necrosis” on MRI remained significant and independent prognostic factors ($P < 0.05$).

Conclusion

Adult brainstem gliomas are different from the childhood forms and resemble supratentorial gliomas in adults. Low-grade tumors have a clinicoradiological pattern that is so characteristic that the need for a potentially harmful biopsy is debatable. The optimum timing of treatment for supratentorial low-grade tumors remains unclear. In high-grade gliomas, the prognosis remains extremely poor despite aggressive treatment with RT and chemotherapy.

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