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Thalamic Gliomas: A Clinicopathologic Analysis of 20 Cases with Reference to Patient Age

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Summary

Twenty patients (M 11, F 9; ranging from 1–77 years old) with histologically proven glial tumours in the thalamic region, treated from 1979 until 1994 at Kyushu University Hospital were retrospectively reviewed and analysed in order to elucidate their clinical and neuropathological characteristics. The initial common clinical manifestations were those of increased intracranial pressure or motor weakness. The histological diagnosis of the tumour was pilocytic astrocytoma in 2 patients, fibrillary astrocytoma in 7, anaplastic astrocytoma in 7, and glioblastoma multiforme in 4. The initial treatment was surgery alone in 4 patients, surgery followed by radiation therapy in 5, surgery followed by radiation therapy and chemotherapy in 9, and conventional radiation therapy alone in 2 patients. The 3-year overall actuarial survival rate for all patients was 20% but was related to both the histological type and the age of the patients: As a result, the rate was 44% for patients with low-grade astrocytoma compared to 0% for those with high-grade astrocytoma. While 5 out of 11 patients under the age of 25 years at their initial presentation have survived for from 2–16 years after the diagnosis, all patients presenting after the age of 25 years died within 3 years after treatment. Thalamic glial tumours are not a homogeneous group of tumours in terms of clinical behaviour and histopathological features, and the poor overall results, especially in adult tumours, thus emphasise the need for continued research in the treatment of these tumours.

Keywords: Glioma; thalamus; treatment.

Introduction

The rostral end of the brain stem, the thalamus, is relatively small and constitutes less than 2% of the neuraxis. Glial tumours which arise primarily in this region are rare, and only represent approximately 1% to 5% of all brain tumours [6, 24, 29]. These lesions are usually not the object of surgical treatment due to their deep seated, midline location [18, 23, 31], and they have been treated with radiation and adjuvant chemotherapy, either with or without a tissue diagnosis [6, 17, 22, 24, 29]. In this study, we have reviewed our experiences with 20 histologically verified glial tumours which originated in the thalamus in the hope that more light may be shed on the biological, clinical and pathological characteristics of the tumours in this area.

Report

Between the years 1979 and 1994, 438 patients with cerebral gliomas were treated at our institution. Gliomas which arose primarily in the thalamus were thus selected from these cases based on the CT and/or MRI findings and histopathological diagnosis. While tumours also secondarily involving the surrounding structures were included, tumours which primarily arose in the epithalamus, opticohypothalamic region, midbrain, basal ganglia, adjacent white matter, or the third and lateral ventricles were excluded. As a result, a total of 20 patients (age at diagnosis: 1–77 years; median 24.5 years; male: 11; female: 9) were selected and form the basis of this retrospective study.

Symptoms and Signs

The clinical duration of the symptoms before diagnosis ranged from 2 weeks to 13 years (median 2 months, average 13.1 months). Two patients had a long history; one child had a 5-year history of hemiparesis, while another adolescent with a pilocytic astrocytoma had a 13-year history of epilepsy. Except for these 2 patients, no apparent difference in the pre-operative duration of symptoms among paediatric (15 years old or younger), adolescent (16–25 years old), and adult (26 years old and older) patients was noted (Table 1).

The most common symptoms and signs were those related to increased intracranial pressure and hemiparesis. While behavioural and/or mental disturbances, including confusion, apathy, and disorientation, were found in only 2 out of 6 adolescent patients, they were found in 7 out of 9 adult patients; while no such disturbances were found in any children.

Treatments

All patients were treated immediately after diagnosis, although no uniform policy was in place during the 15-year study period

Table 1. *Symptoms and Signs at Diagnosis in 20 Patients with Thalamic Tumours According to the Age of the Patients*

	Age at diagnosis		
	≤ 15 years old (cases)	16–25 years old (6 cases)	26 years old ≤ (9 cases)
Pre-operative duration of symptoms	3 wks – 5 yrs (average: 14.4 mo; median 3 mo)	3wks – 13 yrs (average: 27.3 mo; median 1.5 mo)	2 wks – 8 mos (average: 3 mo; median 2 mo)
Symptoms present			
headache, nausea, vomiting	2	2	6
behavioural and/or mental change	0	2	7
seizures	0	3	0
homonymous hemianopsia	2	0	0
ocular movement disturbances (diplopia, squinting, nystagmus)	0	1	2
motor weakness (hemiparesis)	4	1	5
sensory deficit	1	0	1

Table 2. *Summary of the Initial Treatment for the 20 Patients with Thalamic Gliomas*

	Age at diagnosis		
	≤ 15 years old	16–25 years old	26 years old ≤
Surgery (partial removal)			
alone	3[a]	0	0
+ irradiation + chemotherapy	0	2	1
Biopsy			
alone	0	1	0
+ irradiation	1	1	3
+ irradiation + chemotherapy	1	1	4
Irradiation (alone)	0	1	1

[a] 1 total removal.

Table 3. *Pathological Diagnosis of the 20 Thalamic Tumours*

	Age at diagnosis		
	≤ 15 years old (5 cases)	16–25 years old (6 cases)	26 years old ≤ (9 cases)
Pilocytic astrocytoma	1	1	0
Fibrillary astrocytoma	1	2	4
Anaplastic astrocytoma	2	2	3
Glioblastoma	1	1	2

regarding treatment (Table 2). Two patients initially received radiation therapy without undergoing a tissue diagnosis, and both had their first operation after the initial radiation therapy had failed. The remaining 18 patients initially underwent a surgical procedure; 12 underwent a biopsy (2 open, 9 stereotactic needle, 1 neuro-endoscopic), 5 had a partial resection, and 1 had total resection. After surgery 4 patients received no further treatment: 2 patients because of low-grade astrocytomas, the third because of a poor postoperative neurological condition, and the fourth because after total removal of the tumour his parents refused any further treatment. The remaining 14 patients received radiation therapy and/or adjuvant chemotherapy.

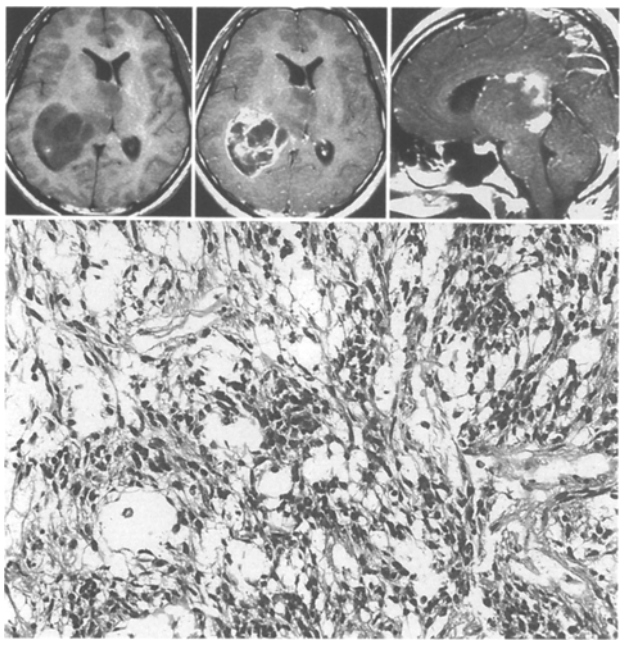

Fig. 1. MRI scans, plain (upper left) and enhanced (upper, center and right), of a 19-year-old man with a headache for 3 weeks prior to admission and a recent onset of somnolence. A large mass in the right thalamus extends into the lateral ventricle. The margin of the tumour within the thalamus is obscure, and the intraventricular part of the tumour is enhanced. At surgery, the tumour occupying the right lateral ventricle was removed. Lower: a histological section of the tumour shows a moderately cellular tumour with pleomorphic elongated cells and scant cytoplasm. The diagnosis is anaplastic astrocytoma. H & E, × 150

After completion of initial treatment, 3 patients received tumour removal at recurrence, and 17 received no further treatment other than palliative even when the tumours became space occupying lesions.

Pathology

Pilocytic astrocytomas were found in two girls aged 9 and 16, while none were found in the adult patients (Table 3). Among the 5 children, 3 had high-grade tumours, and 2 of them were under the age of 3 years. A histological feature of one thalamic high-grade tumour in an adolescent was distinctive in that it was composed of atypical elongated hyperchromatic cells, which morphologically resembled the tumour cells of pilocytic astrocytoma (Fig. 1).

Results of Treatment and Various Factors Influencing the Outcome

Age of the patients: Survival of adult patients, although not statistically significant ($p = 0.16$) was shorter than that of children or adolescents (Fig. 2). Among 5 children, 2 died 2 and 20 months after diagnosis, respectively. The remaining 3 patients have survived for from 2–11 years. Among the 6 adolescent patients, 4 have died after a median survival of

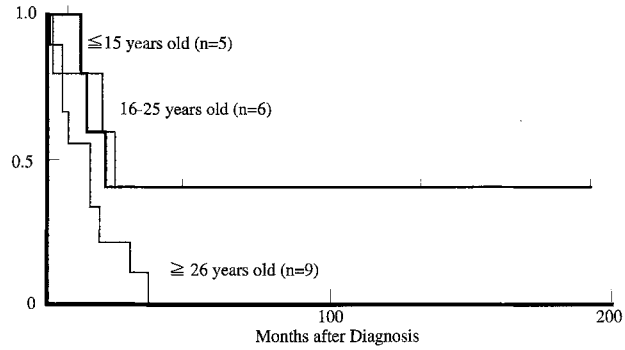

Fig. 2. A graph showing Kaplan-Meier survival curves for children (≤ 15 years old), adolescents (16 years–25 years), and adult patients (≥ 26 years old). Younger patients survived longer than older patients

13 months (range from 8 to 21 months) while the remaining 2 patients have survived for 4 and 16 years, respectively; the former had a stable minute fibrillary astrocytoma at the primary site, and the latter had a stable pilocytic astrocytoma. All 9 adult patients died after a median survival of 15 months (range from 1 to 36 months, average 15 months).

Clinical duration of symptoms: Two patients, who had a 5-year history of hemiparesis or a 13-year history of epileptic seizures before diagnosis, have survived with tumours for 11 and 16 years after diagnosis, respectively. Except for these 2 patients, no apparent differences were noted in the survival between those with either a short or long duration of symptoms before diagnosis.

Symptoms and signs: Two children and 2 adolescents, who had initially presented with symptoms and signs of increased intracranial pressure, died between 2 and 20 months after diagnosis (median 13 months; average 12 months). Among the 3 adolescents with a history of epileptic seizure, one has survived for 16 years after diagnosis while 2 died 8 and 21 months after diagnosis, respectively. Three children, who had initially presented with motor weakness of the extremities, survived for from 2–11 years (median 6.5 years; average 8 years). In contrast, all 9 adult patients died between 5 and 36 months after diagnosis irrespective of the nature of the initial symptoms and signs.

Histology: The survival rate for patients significantly differed based on the histological type of the tumour (Fig. 3). While 10 patients with high-grade tumours died with a mean survival time of 12.4 months after diagnosis (range from 2 to 30 months; median 10 months), one infant with a high-grade

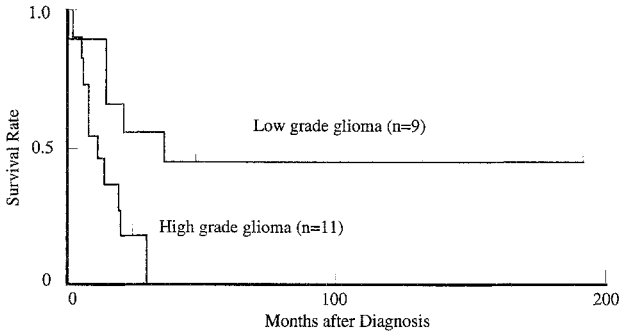

Fig. 3. A graph showing Kaplan-Meier survival curves for low-grade and high-grade gliomas. The histological grade of malignancy correlated with the outcome (Wilcoxon test, $p < 0.05$)

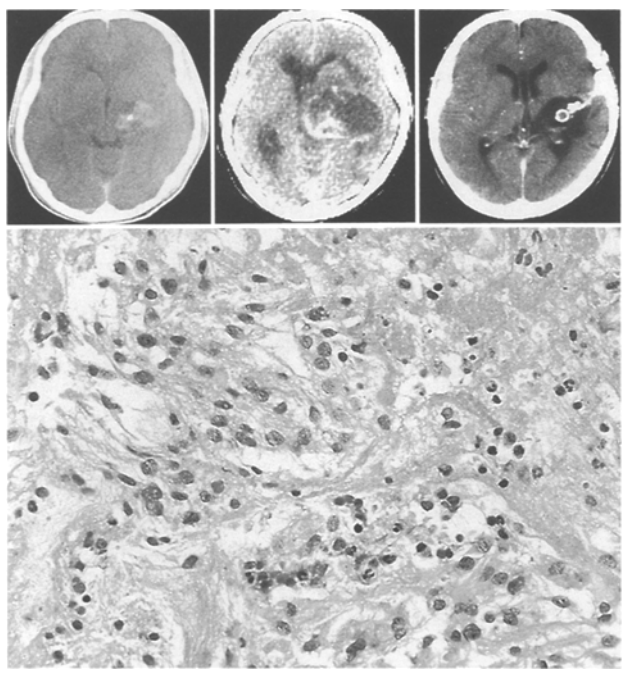

Fig. 4. Neuro-imaging and histological features of a 13-year-old boy. Upper left: before treatment. A CT scan shows an irregularly enhanced tumour in the left thalamus and basal ganglia. Upper center: six months after biopsy and irradiation. A large low density mass is associated with an irregularly enhanced rim. Upper right: eleven years after the partial resection and chemotherapy. No tumour is seen. Lower: a histological section of the tumour obtained at the second operation shows moderate cellularity with pleomorphism. The diagnosis is fibrillary astrocytoma. H & E, × 190

tumour has survived for 24 months after treatment. Of the 9 patients with low-grade tumours, 5 with fibrillary astrocytoma died with a mean survival time of 17.6 months (median 15 months), while 2 with fibrillary astrocytoma and 2 with pilocytic astrocytoma have survived a mean period of 10.5 years (median 11 years) since diagnosis.

Treatment: In relation to the various modalities of treatment, no differences in the clinical improvement or survival were evident. However, 2 children were remarkable in that a resection of the tumour was performed with relatively good results; the first was a 13-year-old boy with a 5-month history of progressive right-sided motor weakness and headache (Fig. 4). A stereotactic needle biopsy revealed the thalamic tumour to be a fibrillary astrocytoma. He received radiation therapy with a total dose of 56 Gy. A CT scan obtained 6 months after the completion of radiation therapy, however, showed a recurrent tumour. At the second operation, the tumour was partially removed by the trans-sylvian route, and an Ommaya reservoir system was placed into the cyst cavity. Postoperatively, adriamycin was administrated locally through the subcutaneous Ommaya reservoir (total dose: 40 mg) and interferon α-2 was given for 2 years (total dose: 367 × 106 unit). After these treatments, the tumour disappeared and the patient is now 25 years old and doing well with mild right hemiparesis.

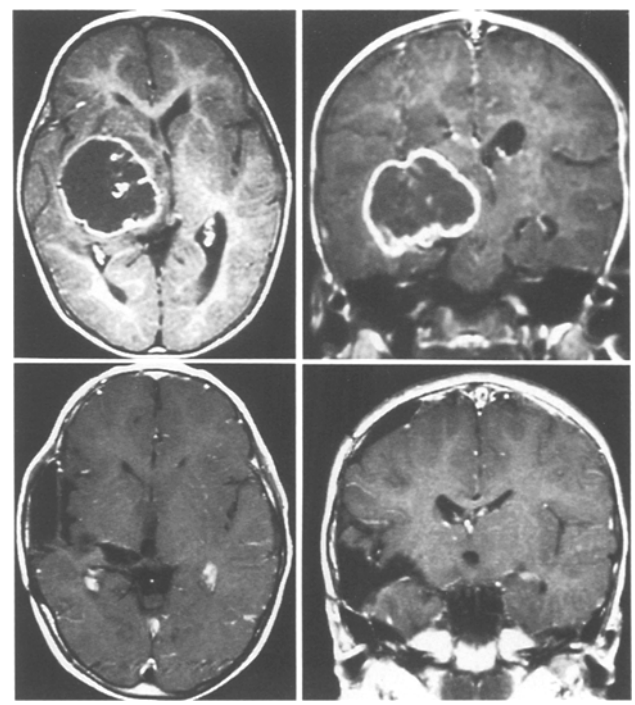

Fig. 5. A 1-year-old boy with a 5-month history of progressive right-sided motor weakness and headache. MR images with Gd-DTPA show a large hypo-intensity mass with an irregularly enhanced rim in the left thalamus and basal ganglia (upper row). MR images with Gd-DTPA obtained 2 years after an extensive removal of the tumour show no evidence of tumour recurrence (lower row)

The second child with an anaplastic astrocytoma underwent an extensive removal of the tumour at the age of 1 year, and he is now 3 years old with no tumour at the primary site on neuro-imaging studies (Fig. 5). In this series, no apparent postoperative speech disorders were encountered in any patient.

Quality of life in 5 survivors: Of the 5 surviving patients, 3 are associated with moderate hemiparesis, but they can all walk independently (Karnofsky performance score 70%). A moderate intellectual deficit was noted in one patient, who also received local radiation therapy at the age of 16 years and had a residual thalamic mass (Karnofsky performance score 80%). One adolescent, who has survived for 4 years after diagnosis remains in good neurological condition (Karnofsky performance score 90%).

Discussion

Midline intra-axial tumours involving the thalamus are usually gliomas, predominantly of the astrocytic series. They cause progressive neurological deterioration either by infiltrating and disrupting the normal nuclei and tracts or by causing obstructive hydrocephalus [1, 28]. Although a preponderance of thalamic gliomas in children and adolescents has been reported by several authors [6, 17, 24, 29], they can occur in any age group as illustrated herein. In this retrospective study, the clinical and pathological characteristics of thalamic gliomas and their differences according to the age of the patients were investigated.

The clinical manifestations of our patients were similar to those previously reported [11, 22, 27, 28, 31]. Although the presenting symptoms and their durations in adults are generally similar to those in children and adolescents [10, 14], the incidence of personality alterations, behavioural and/or memory disturbances was higher in adult patients than in younger patients. Symptoms of intracranial hypertension as the first clinical manifestation of the disease were predictive of poor prognosis, and similar findings have also been reported by several other authors [5, 11].

There have been a few reports in which the survival of the patient with thalamic gliomas correlated with the degree of anaplasia of the tumour [4, 6, 25, 29, 31, 32]. In Albright's series, the median survival time of children with low-grade gliomas was 4.8 years, while that of children with malignant tumours was 0.5 year [2]. In Kelly's review of 72 thalamic tumours, the mean survival times were 23, 13.6, and 5.4 months after a stereotactic biopsy for patients with Kernohan Grades 2, 3, or 4 astrocytomas, respectively [19]. In a recent series of Krouwer and Prados, the mean survival time in patients with thalamic glioblastoma was 25.6 months [22]. Except for the last series, the survival rates for patients with malignant lesions are fairly similar to ours, in which all patients but one with high-grade gliomas died with a mean survival time of 12.4 months.

Although Hoffman *et al.* [18] claimed that pilocytic axial tumours are more aggressive than fibrillary astrocytomas, this was not the case in the present series; our 2 patients with pilocytic astrocytoma have survived with tumours for 11 and 16 years, respectively, whereas 5 out of 7 patients with fibrillary astrocytoma died within 3 years after diagnosis. Furthermore, a malignant transformation of pilocytic astrocytomas, even though there have been some reports, remains a rare occurrence [7, 26]. Regarding the above mentioned "Hoffman" experience, one of our high-grade tumours had the distinctive features that the anaplastic astrocytes of this tumour had some morphological resemblance to tumour cells of pilocytic astrocytoma (Fig. 1). "Pilocytic" astrocytomas of Hoffmann *et al.* may include this kind of high-grade astrocytomas.

As with most gliomas, younger patients with thalamic tumours do better than older patients [1, 11, 22, 28]. In our series 5 out of 11 patients under the age of 25 years at their initial presentation have survived for 2–16 years, whereas all 9 patients above 26 years old died within 3 years after diagnosis. Furthermore, even for the same low-grade tumours, the outcome has been better for younger patients than for adult patients; 2 out of 3 young patients with fibrillary astrocytoma have survived for 4 and 11 years, respectively, whereas all 4 adult patients with the same tumour died within 36 months after diagnosis. The biological behaviour of an astrocytoma of adult patients may thus be "one grade more aggressive" than tumours of similar histology in young patients.

The management of thalamic gliomas presents special problems [4]. Several recent authors have described radical resections of these tumours based on improved surgical techniques, such as computer-assisted stereotactic open microsurgical techniques [8, 19–21, 23, 30]. Such aggressiveness, however, has not yet to become widely accepted [3, 4, 9, 13, 18]; thalamic tumours are rarely completely excised, and there have been many patients who experienced a permanent worsening of their neurological status after

either a total or subtotal removal. Furthermore, a significant improvement in survival after an extensive resection has yet to be obtained, and there seems little to be gained from an extensive tumour resection in patients with high-grade gliomas [14]. Nevertheless, we think that a tumour resection may be indicated in some cases to reduce intracranial pressure [3]. In our series, one somnolent adolescent with anaplastic astrocytoma obtained temporary relief after a partial removal of the tumour, and he also tolerated the course of radiation and chemotherapy (Fig. 1). In addition, 2 children with hemiparesis underwent tumour removal without an additional neurological deficit and have survived 2 and 11 years after diagnosis, respectively. Although a partial or subtotal resection may be performed on thalamic tumours in selected cases, and it may enhance the effectiveness of postoperative adjuvant treatments [1, 4, 18], the benefits of an extensive resection, especially of high-grade tumours, still await further evaluation in a prospective study [8, 19, 22].

With regard to postoperative adjuvant therapy, a course of cranial radiation therapy may be considered for all patients with high-grade tumours [4, 12, 14–16, 19, 22]. For small thalamic gliomas, focal radiation therapy, either with the Gamma Knife, Linac or eventually brachytherapy, seems to be the primary treatment of choice. The use of conventional radiation therapy for low grade gliomas in children, however, is not without controversy. Besides the well known side effects of radiation on the developing brain, there is also a subpopulation of low-grade astrocytomas that behave in a very benign manner [4, 28], as illustrated by our 2 pilocytic astrocytomas, which have remained dormant for over 10 years. It would thus be reasonable not to irradiate young patients with low-grade astrocytomas, especially pilocytic astrocytomas, but to follow these patients and reserve radiation therapy for any documented tumour progression [4, 31].

The prognosis of patients with thalamic gliomas has been generally poor regardless of the type of treatment, and the overall guidelines with respect to treatment for progressive gliomas remain obscure. Although the tumour's biological behaviour following treatment is uncertain and the management decisions for each case are difficult, it should be noted that several patients in our series have responded well to treatment. Any future improvement in the survival of patients, however, especially those with high-grade tumours, awaits a new therapeutic breakthrough.

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Comments

Gliomas involving the thalamic area are not routine lesions to deal with and therefore a collection of these gliomas with reference to outcome is a valuable contribution for careful decision making. As the study is well composed and the evaluation of the data carefully performed, this paper enhances the knowledge of the fate of patients with thalamic gliomas.

G. Pendl

This is a retrospective series report comprising 20 cases collected from a 15 years period. It is meticulously compiled, carefully analysed and illustrated; the material is nevertheless very heterogeneous and taken from too few cases to obtain conclusive remarks. Overall guidelines with respect to the treatment of these tumours still remain obscure and the limited number of cases in this paper cannot give more evidence to the reader regarding progress and outcome.

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