

Gliomatosis cerebri in young patients' report of three cases and review of the literature

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Abstract Gliomatosis cerebri (GC) is a rare disease, defined as a diffuse neoplastic glial cell infiltration of the brain. Diagnosis and management of GC are difficult.

Method The authors report a literature review and their experience based on three patients, two male, and one female, all younger than 10 years, who were treated for GC.

Results Our series of three patients were combined for the purposes of survival assessment together with the 22 patients from the literature review yielding 25 evaluable patients with diagnosis of GC. We compared the patients treated (16) with chemo, RT, or both combined, with untreated patients (7) to evaluate the median survival. Even though, as expected, the number is too small to show a statistically significant increase of survival ($p=0.08$ log rank test), we still demonstrated a slight increase in survival in the group of patients treated (26.6 vs 14.8 months). We also compared the overall survival according to treatment. The comparison between the group of five patients treated with radiotherapy only, ten treated with chemotherapy with TMZ and ten with chemo and RT combined, showed a slight increase in mean survival, although not statistically significant, in the second and third groups ($p=0.6$ log rank test).

Conclusion The optimal treatment in children under 10 years with GC is still obscure and absolutely not clear because total surgical resection is impossible to perform for the diffuse nature of the disease; CHT with TMZ seems to be the best treatment for children because it demonstrates a little reduction of the extension tumoral mass, but the responsivity of this treatment is extremely variable from case to case.

Keywords Gliomatosis cerebri · Young patients · Neurosurgery · Stereotaxic biopsy · Chemotherapy · Radiotherapy

Introduction

Gliomatosis cerebri (GC) is a rare tumor of the central nervous system (CNS) characterized by diffuse neoplastic proliferation of glial cells and myelin sheath destruction. Only slight damage to neurons and axons and relative preservation of anatomical architecture have been observed. It can be difficult to diagnose clinically as it tends to present with non-specific progressive neurological symptoms [1] or personality changes and often obscure, non-specific changes on computerized tomogram (CT). Magnetic resonance imaging (MRI), however, may suggest the diagnosis, especially on T2-weighted images [2–4], where gliomatosis cerebri may be shown as areas of high signal change. In spite of advances in neuroimaging, GC still remains difficult to diagnose during life. According to the current World Health Organization (WHO) classification of brain tumors, the involvement of more than two lobes by an extensively infiltrating glioma is mandatory to establish the diagnosis of GC. It is a malignancy that has usually been found in adult patients,

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and the finding in children is very rare. In the literature, single cases or short series of GC have been reported, almost always with reference to adult patients. All age groups may be affected, but GC presents a peak of incidence in the second and fifth decades of life, without gender predominance; the cases reported in children are very few [5–13]. The authors report a literature review and their experience based on three patients, two male, and one female, all younger than 10 years, who were treated for GC.

Materials and methods

Case 1 An 8-year-old male child was admitted to our hospital with a 3-year clinical history of generalized Jacksonian convulsion. MRI showed a diffuse progressive white matter changes involving fronto-temporo-parietal left lobes and fronto-temporal right lobes. On T2-weighted images, there was a diffuse hyperintensity. Then, the patient underwent brain stereotaxic biopsy. The examination of the histological specimen revealed a diffusely infiltrating grade II astrocytoma according to WHO. The neoplastic cells were variably differentiated. Immunohistochemically, tumor cells were positive for glial fibrillary acidic protein (GFAP). A diagnosis of gliomatosis cerebri was made. Therefore, we adopted a wait-and-see policy, performing a MRI every 3 months. After 2 years of neuroradiological and clinical stability, the patient presented in a new MRI, an enhancement of the left frontal and temporal part of the lesion, after gadolinium administration. This patient was treated by chemotherapy (CHT) with temozolomide (TMZ) 75 mg/m²/day for 21 days for 12 cycles of 28 days. The patient showed disease stabilization for 3 years. After this period, the patient presented a tumor regrowth pointed out by a MRI and spectroscopy, which revealed a new multifocal enhancement with deep structures involvement. He was treated with WBRT. The patient had an overall survival of 5 years and 7 months. Karnofsky Performance Score (KPS) was over 70 until 20 days before exitus.

Case 2 A 6-year-old male child was admitted to our institute with an 8-month clinical history of seizures. MRI was performed and showed typical neuroradiological aspects of IV WHO glioblastoma, which involved diffusely both cerebral hemispheres. The patient underwent brain stereotaxic biopsy; histological data confirmed the suspects of MRI and showed a grade IV WHO glioblastoma, allowing the diagnosis of gliomatosis cerebri. This patient was treated by chemotherapy with TMZ 75 mg/m²/day for 21 days for 12 cycles of 28 days. The patient showed absence of seizures for almost 4 months until those begun again. He underwent MRI and spectroscopy, which showed

a tumor regrowth. The patient underwent a stereotactic radiotherapy on the hyperintensive lesions at a dose of 16 Gy in two fractions. The patient died after 9 months from the beginning of radiotherapy. Karnofsky Performance Score (KPS) was 80 until 15 days before exitus. The patient's overall survival was 13 months.

Case 3 An 8-year-old female child was admitted to our hospital with a 1-year clinical history of prolonged secondary generalized seizures. MRI showed typical aspects of diffuse gliomatosis cerebri involving the entire right hemisphere, fronto-temporal left lobe, with diffuse cerebellar localization. The patient underwent brain stereotaxic biopsy, and the histological patterns showed a grade III WHO astrocytoma. The patient underwent a chemotherapy treatment with TMZ 75 mg/m²/day for 21 days for 12 cycles of 28 days. The patient showed disease stabilization for 6 months. After this period, the patient showed seizures again and underwent MRI and spectroscopy, which showed a little reduction of the tumor's volume. She was treated with a stereotactic radiotherapy on the hyperintensive lesions at a dose of 16 Gy in two fractions. The patient died after 11 months. Karnofsky Performance Score (KPS) was 70 until 25 days before exitus. Her overall survival was 17 months.

A review of the literature was conducted using PubMed, an internet medical literature search engine. The search was undertaken using the terms “gliomatosis cerebri”, “child”. These terms were linked using the combinations of “gliomatosis cerebri” plus “child” or “young patients”. References from the retrieved reports were checked to identify other possible reports. We selected manuscripts reporting young patient from the age of 0 to 10 years affected by gliomatosis cerebri. Data extracted included, number of patients, male/female ratio, age distribution, location of the lesions, treatment, mortality, and for some of them histochemical and immuno-histochemical stainings (Table 1). Twenty-two cases of young patients that were found in literature all had histologic confirmation by either biopsy (13) or autopsy (5). Details of therapeutic intervention were available for 16 patients. Radiation therapy was done in ten patients with doses ranged from 2700 cGy to 7265 cGy and in conjunction with chemotherapy in seven patients. Chemotherapy alone was used in three cases, and three patients received symptomatic medical care only.

Results

Our series of three patients were combined for the purposes of survival assessment together with the 22 patients from the literature review yielding 25 evaluable patients with diagnosis of GC. From this cohort study, we excluded two

Table 1 Historic cohort: treatment, localization and survival

Reference	Age (year)	Diagnosis	Localization	Treatment	LOS, months	Alive
Armstrong et al. 2006 [5]	8	Biopsy	B. thalamus, upper brain stem	5,700 (IF)cGy	17.5	No
Armstrong et al. 2006 [5]	4	Biopsy	B.T., B. thalamus, corpus callosum, pons	2,700 (WB)cGy, VCR	6.5	No
Armstrong et al. 2006 [5]	9	Biopsy	B.F., R.T.	2,500 (WB), 2,800 (IF),TMZ	20	No
Armstrong et al. 2006 [5]	1.6	Biopsy	L.P., L.T., L. occipital	PCV	22	Yes
Armstrong et al. 2006 [5]	8	Biopsy	R.P., R.T., B. thalamus, basal ganglia	5,800 (IF), TMZ	16	Yes
Barth et al. 1988 [6]	0	Autopsy	B. hemispheres, brainstem, cerebellum	None	0,25	No
Caroli et al. 2005 [7]	8	Biopsy	L.F., corpus callosum, L.P., L. occipital	None	11	No
Cummings et al. 1999 [31]	7	Autopsy	B. hemispheres, brainstem, cerebellum, leptomeninges, spinal cord	7,265 cGy	5	No
Filho et al, 2008 [12]	3	Biopsy	Subarachnoid space,FCP	VCR, Carboplatin, TMZ	82	Yes
Geremia et al. 1988 [32]	9	Autopsy	B.F.	Corticotrophi, imuran	156	No
Jayawant et al. 2001 [8]	10	Autopsy	Brain and spinal cord	None	3	No
Jennings et al. 1995 [9]	0	Biopsy	L.F.	Corticotropin	13	No
Jennings et al. 1995 [9]	0.66	Biopsy	L.F. white matter, cortex, leptomeninges	Corticotropin	15	Yes
Jennings et al. 1995 [9]	6	Biopsy	R.F.	None	10	Yes
Maton et al., 2007	0	Biopsy	R. hemisphere	None	48	Yes
Maton et al., 2007	1	Biopsy	R.T., basal ganglia, insula, thalamus	Chemo, RT	48	Yes
Maton et al., 2007	8	Biopsy	L.F.T.P., basal ganglia, thalamus, midbrain	VCR, carbaplatin, RT	48	Yes
Ross et al. 1991 [33]	7	Autopsy		None	276	No
Shahar et al. 2002 [11]	5	Biopsy	R.F.	RT	18	Yes
Shahar et al. 2002 [11]	10	Biopsy	R.T.	Chemo	24	No
Vates et al. 2003 [13]	6	Biopsy		3,000 cGy, TMZ, thalidomide	9	No
Yip et al. 2004 [34]	7	Autopsy	Brainstem, cerebellum, cerebral hemispheres	4,500 cGy, carboplatin	13	No

LOS indicates length of survival, B bilateral, R right, L left, F frontal, T temporal, P parietal, RT radiation therapy, cGY centigrays, TMZ temozolomide, PCV procarbazine, lomustine, and vincristine, VCR vincristina

patients because their prolonged survival (greater than 150 months) could be related to an erroneous initial diagnosis of GC. We compared the patients treated (16) with chemo, RT, or both combined, with untreated patients (7) to evaluate the median survival (Fig. 1). Even though, as expected, the number is too small to show a statistically significant increase of survival ($p=0.08$ log rank test) we still demonstrated a slight increase in survival in the group of patients treated (26.6 vs 14.8 months). We also compared the overall survival according to treatment. The comparison between the group of five patients treated with radiotherapy only, ten treated with chemotherapy with TMZ, and ten with chemo and RT combined, showed a slight increase in mean survival, although not statistically significant ($p=0.6$ log rank test), in the second and third groups (Fig. 2).

Discussion

Gliomatosis cerebri is a rare primary brain malignancy, initially described by Nevin [14] in 1938 and then by Scheinker and Evans in 1943 on the basis of pathological criteria during autopsy. They defined GC as “diffuse enlargements of the affected regions, with intactness of their general configuration; widespread extension of the process; absence of demarcation between normal and affected areas corresponding to a glial proliferation associated to myelinolysis with only slight involvement of the axis cylinders and nerve cells” [4]. Nowadays, diagnosis of

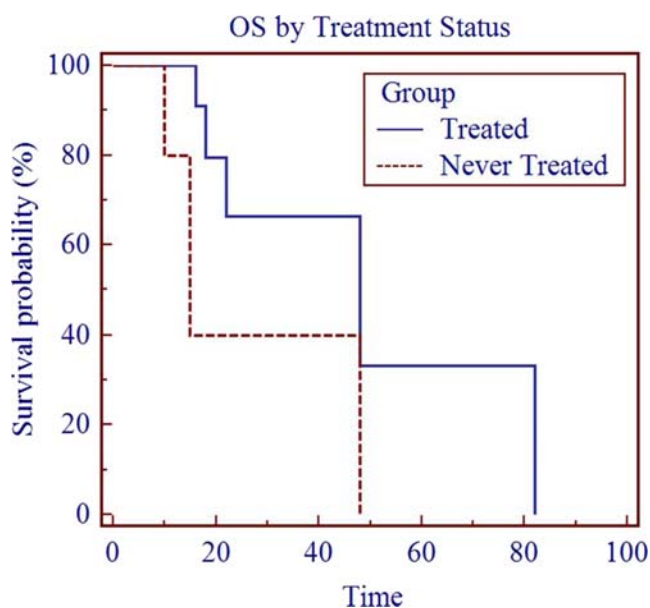


Fig. 1 Kaplan–Meier curves. Comparison between a group of patients treated with chemo, RT, or both combined and untreated patients. We can see a slight increase in survival in the treated patients (26.6 vs 14.8 months)

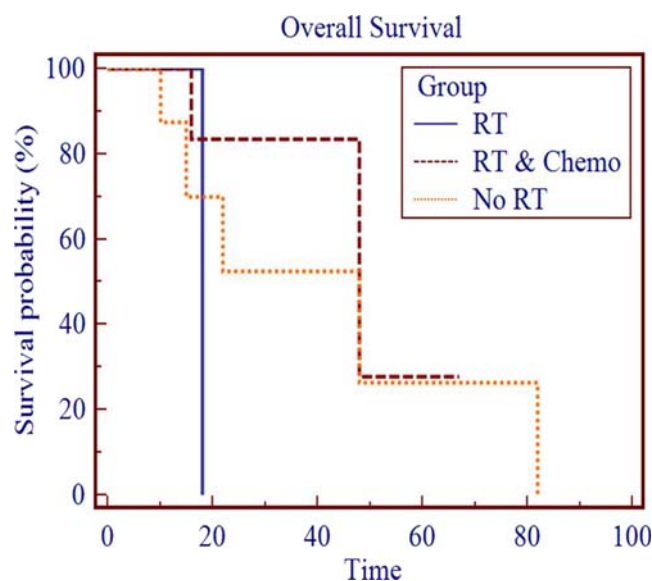


Fig. 2 Kaplan–Meier curves. Comparison between a group of five patients treated with RT only, ten treated with TMZ, and ten with both combined. The curve show a slight increase in mean survival although not statistically significant ($p=0.6$ log rank test) in the second and third groups

GC in children can be established using improved neuro-imaging (MRI and TC techniques), and it is histologically defined by stereotaxic brain biopsy [15]. Actually, GC is defined as a diffuse glial tumor infiltrating the brain extensively, involving more than two lobes, frequently bilaterally and often extending to infratentorial structures and even to the spinal cord. It is usually considered to be a malignant lesion usually corresponding to a WHO grade III [4, 16]. A congenital predisposition has been also proposed for the association with von Recklinghausens disease [17], but the fact that GC affects all age groups suggests that this pathology arises as a de novo tumor. MRI data are an important help for a correct diagnosis. The characteristic hallmarks of the lesion on MRI are hypointensity in T1-weighted sequences and hyperintensity in T2-weighted sequences and Flair. T2-weighted images are now considered the gold standard imaging technique for the diagnosis of GC [2–4, 18, 19]. A typical finding in MRI is diffuse infiltration of the cortex with an enlargement of the cortical sulci and poor demarcation of the gray and white matter. MRI with fluid attenuated inversion recovery images (FLAIR) has a better definition of lesion extent and delineation of callosal infiltration and cortical spread. The diffuse extensive contiguous involvement, mainly central, with preservation of overall cerebral structures, represents the key to the diagnosis of GC. Neurosurgical stereotaxic biopsy is necessarily for histological data, to establish a correct stadiation of the disease.

Response to the treatment, outcome, and survival time reported by different authors are extremely variable.

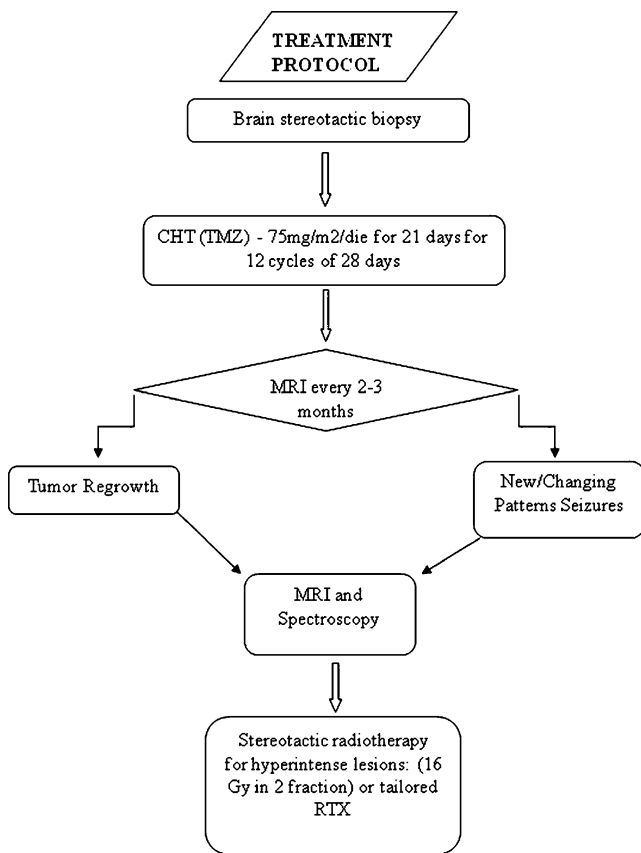


Fig. 3 A protocol treatment that we used to treat our patients

Although radiation therapy and different chemotherapy regimens have been attempted, the prognosis of GC is still poor. In our study, one patient died after 13 months, one had an overall survival of 5 years and 7 months and after 3 years showed a regrowth of the disease, and one had a little reduction of the neuroradiological aspects. The duration of survival from the beginning of the symptoms to death is quite variable, ranging from weeks to years. This phenomenon is explained by the fact that low-grade glioma may be misdiagnosed as GC [20].

Because almost all the cases have been diagnosed postmortem, there is little evidence regarding the best treatment option. It is impossible to perform a surgical resection for the diffuse infiltrative nature of GC. At the moment, stereotaxic biopsy is the treatment of choice for a diagnosis.

The optimal treatment for GC is unclear: surgery is an important point of treatment only in adults; in children,

surgery is only an important point for the histological diagnosis, which was obtained through a brain biopsy, performed in all of them by a frameless stereotactic way with the neuronavigator (Stealth Mach 3-Sofamor Danek). When the biopsy shows a high grade of malignancy, the radiological examinations as MRI in T1-weighted sequences and in T2-weighted sequences, spectroscopy [21–23], diffusion, and perfusion help us to understand the glial nature of the lesion.

The value of radiotherapy is difficult to establish because the beneficial effects are still anecdotal: WBRT is dangerous because the disease is widespread; and therefore, it involves a dangerous brain exposition to radiations. So, we believe that the first line treatment is chemotherapy with TMZ [24–26]. Temozolomide is an alkylating imidazotetrazine, which undergoes spontaneous conversion to the active alkylating agent and penetrates the blood-brain barrier that remains stable even under the acid conditions peculiar to the human stomach, meaning that it can be administered orally in capsules, without the need for a hospital regimen. Moreover, among all the chemotherapeutic drugs, temozolomide has the most favorable toxicity profile, and its bio-availability after oral administration is about 100% [27]. It has been used in the treatment of primary malignant brain tumors including glioblastoma multiforme, anaplastic astrocytoma, and oligodendroglioma [25]. In these malignant brain tumors, therapy with TMZ has demonstrated a little evidence of radiologic tumor regression associated with a little improved quality of life and survival. In our study, chemotherapy with TMZ 75 mg/m²/day for 21 days for 12 cycles of 28 days demonstrates a little reduction of the disease only in one case.

We also used WBRT and stereotactic RT as a second line therapy with the hope to succeed in stopping the evolution of the pathology [28]. Because of the large volume that requires treatment, our dose recommendation reflects a balance between the clinical benefit and the possible toxicity. In our study, we show that clinical aspects in children with gliomatosis cerebri were a little similar: all of them presented epilepsy, with different types of crises, but anyone presented headache, weakness, behavioral changes, and hemiparesis, typical aspects of gliomatosis cerebri in adults and elderly [29, 30].

We adopted a protocol treatment (Fig. 3) that considered chemotherapy (TMZ 75 mg/m²/day for 21 days for 12 cycles of 28 days) as a gold standard after brain stereotaxic

Table 2 Patient characteristics, treatments, and length of survival for the study population

Patient	Age at diagnosis, years	Gender	Diagnosis	Treatment	LOS, months	Alive
1	8	M	Biopsy	TMZ, WBRT	67	No
2	6	M	Biopsy	TMZ, RT	13	No
3	8	F	Biopsy	TMZ, RT	17	No

TMZ temozolomide, RT radiotherapy

biopsy for diagnosis of GC. As a second line treatment, we used RT if the patients had a progressive symptoms seen at the follow-up (MRI every 2–3 months) or RT on the hyperintensive lesions seen on the spectroscopy images using a different dose tailored for each patient. WBRT is used as the last line treatment when there is a worsening of the symptoms (Table 2).

Conclusions

In conclusion, we think that the optimal treatment in children under 10 years with GC is still obscure and absolutely not clear because total surgical resection is impossible to perform for the diffuse nature of the disease; WBRT is dangerous for the extensive brain exposition from the radiations; CHT with TMZ seems to be the best treatment for children because it demonstrates a little reduction of the extension tumoral mass, but the responsiveness of this treatment is extremely variable from case to case.

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