Neurología. 2010;**25(3)**:168-173

NEUROLOGÍA

www.elsevier.es/neurologia

ORIGINAL ARTICLE

Gliomatosis cerebri: review of 22 patients

M.E. Novillo López [a], A. Gómez-Ibáñez [b], M. Rosenfeld [c] and J. Dalmau [c,*]

[a] *Servicio de Neurología, Hospital Nuestra Señora de Sonsoles, Complejo Hospitalario de Ávila, Ávila, Spain*
[b] *Servicio de Neurología, Clínica Universidad de Navarra, Pamplona, Spain*
[c] *División de Neuro-oncología de la Universidad de Pensilvania, Philadelphia, USA*

Received on 5th January 2009; accepted on 20th January 2010

KEYWORDS
Gliomatosis cerebri;
Treatment;
Survival

Abstract
Introduction: Gliomatosis cerebri is a diffuse astrocytic neoplasm that involves more than two lobes of the brain. Treatment is not well defined and the prognosis is considered poor.
Methods: Retrospective analysis of 22 patients with gliomatosis cerebri.
Results: We identified 17 men and 5 women (median age 54 years) seen in a Division of Neuro-oncology over a 6 year period. Patients presented with focal sensorimotor or visual deficits (86.4%), seizures (36.4%), cognitive dysfunction (27.3%), or headache (27.3%), suggesting in some cases stroke, migraine, or limbic encephalitis. All patients had bilateral involvement; the regions involved included, temporal (19), basal ganglia (18), frontal (17), parietal (17), corpus callosum (10), and occipital (9). The most frequent pathological findings were Grade III astrocytoma (36.4%), Grade II astrocytoma (22.7%), and Grade IV astrocytoma (18.3%). Nine patients were diagnosed within the first month of symptom development, 11 between the first month and 1 year, and 2 after one year. Seventeen patients received treatment with chemotherapy, radiotherapy or both, and 12 patients (70.6%) had a clinical or radiological response. The median follow-up was 13 months, median progression free survival 6 months, and median survival 9.5 months (15 months if the patients received treatment). Eight patients had thromboembolic events.
Conclusions: Gliomatosis cerebri has a variable clinical course. Treatment often results in clinical responses. In this study de median survival of patients who received treatment was similar to that reported in series of glioblastoma multiforme.

*Author for correspondence.
E-mail: josep.dalmau@uphs.upenn.edu (J. Dalmau).

PALABRAS CLAVE
Gliomatosis cerebral;
Tratamiento;
Supervivencia

Gliomatosis cerebral: estudio de 22 pacientes

Resumen
Introducción: La gliomatosis cerebral es un tumor astrocítico difuso que afecta a más de dos lóbulos cerebrales. El tratamiento no está bien definido y el pronóstico es malo.
Métodos: Estudio retrospectivo clínico-radiológico de 22 pacientes diagnosticados de gliomatosis cerebral en una unidad de neurooncología.
Resultados: En un periodo de 6 años, identificamos a 17 varones y 5 mujeres (media de edad, 54 años). Los síntomas iniciales fueron déficits focales sensitivo-motores o visuales (86,4%), crisis epilépticas (36,4%), deterioro cognitivo (27,3%) y cefalea (27,3%); en algunos casos los síntomas semejaban ictus, migraña o encefalitis límbica. Todos los pacientes tenían afectación radiológica bilateral; las regiones más afectadas fueron: temporal (19 pacientes), ganglios basales (18), frontal (17), parietal (17), cuerpo calloso (10) y occipital (9). Los diagnósticos histológicos más frecuentes fueron astrocitoma de grado III (36,4%), astrocitoma de grado II (22,7%) y astrocitoma de grado IV (18,3%). Nueve pacientes fueron diagnosticados en el primer mes del desarrollo de los síntomas; 11, entre el primer mes y 1 año, y 2, después de 1 año. Diecisiete pacientes recibieron quimioterapia, radioterapia o ambas, de los que 12 (70,6%) tuvieron respuesta clínica o radiológica. La media de seguimiento fue 13 meses; el tiempo libre de progresión, 6 meses, y el tiempo de supervivencia, 9,5 meses (15 meses cuando los pacientes recibieron tratamiento); 8 pacientes desarrollaron complicaciones tromboembólicas.
Conclusiones: La gliomatosis cerebral tiene un curso clínico variable. Los pacientes generalmente responden al tratamiento. En este estudio la media de supervivencia de los pacientes tratados es similar a la de las series de glioblastoma multiforme.

Introduction

Gliomatosis cerebri (GC) is a diffuse cerebral infiltration of neoplastic glial cells that preserves the architecture of the brain tissue. Since Nevin[1] first described it in 1938, there have been about 300 cases, mainly in retrospective studies[2]. The clinical manifestations are non-specific, so it can be confused with other neurological entities, thus delaying its diagnosis. The aim of this study was to describe the clinical characteristics, treatment and outcome of 22 patients with GC.

Patients and methods

We reviewed the databases and medical records of patients diagnosed with GC between January 2003 and September 2009 in the Neuro-Oncology Unit at the Hospital of the University of Pennsylvania. According to the World Health Organization, the diagnostic criterion for GC is a diffuse cerebral infiltration of neoplastic glial cells, which preserves the normal architecture of the brain tissue, affects more than two brain lobes and, occasionally, infratentorial structures or the spine[3]. We define primary GC as that which appears without a prior history of brain tumour, and secondary GC as that which arises from a prior brain tumour[3]. We divide the primary GC into Type 1, a diffuse infiltration without adjacent tumour mass, and Type 2, with a tumour mass adjacent to the infiltration[4]. According to these criteria, all patients underwent magnetic resonance imaging (MRI) studies and histological confirmation of the tumour.

We define diagnostic delay time as the time elapsed from the initial symptom until diagnosis (value 0 represents a delay of less than 1 month). Follow-up time represents the months elapsed between diagnosis and September 2009 or death. Therapeutic response is defined as clinical-radiological improvement, clinical improvement with radiological stability or clinical-radiological stability. Lack of response is defined as clinical or radiological worsening. Progression-free time is that elapsed from the administration of treatment until evidence of progression.

Results

In total, we identified 22 patients diagnosed with GC, 17 males (77.2%) and 5 females (22.8%) (table 1). The average age was 54 years (51 in males and 54 in females; range 23-81 years). The initial clinical manifestations were focal sensory-motor or visual deficits (86.4%), epileptic crises (36.4%), mild cognitive impairment (27.3%) and headache (27.3%). All patients had bilateral radiological involvement (figs. 1 and 2), with deterioration of more than 2 brain lobes, involving the temporal (86.4%), frontal (77.2%), parietal (77.2%) and occipital (40.9%); other structures

Table 1 Clinical characteristics, treatment and outcome

No.	Gender, age	Symptoms	Duration of symptoms (months)	Regions affected (n)	Type of GC	Disease-grade	Treatment	PFT (months)	ST/ state
1	M, 51	Cognitive	3	FL, PL, TL (2)	2	O-II	CT	10	36/ D
2	F, 52	Headache, epilepsy	1	FL, PL (1)	2	O-III	CT	6	34/ D
3	F, 52	Motor and language deficit	0	FL, PL, TL, OL (2)	1	A-IV	RT/ CT + CT	10	15/ D
4	M, 67	Headache	3	FL, PL, TL, OL (2)	1	OA-II	N	U	U
5	M, 69	Language and cognitive alteration	7	FL, PL, TL (1)	1	A-II	N	0	1/ D
6	M, 49	Visual deficit, headache	2	FL, PL, TL, OL (1)	1	A-II	CT	38	38/ alive
7	M, 54	Motor and language deficit, epilepsy	8	PL, TL (2)	1	A-IV	RT/ CT + CT	3	24/ alive
8	F, 65	Motor deficit	1	PL, TL (1)	2	A-III	RT/ CT	0	3/ D
9	M, 54	Epilepsy	0	FL, TL (2)	2	A-IV	RT/ CT + CT	6	16/ D
10	M, 36	Sensory, motor and visual deficit	2	TL, OL (3)	1	A-III	RT/ CT	0	6/ D
11	M, 42	Motor deficit	0	FL, PL (1)	1	A-II	CT	5	15/ D
12	M, 69	Cognitive	0	FL, PL, TL, OL (2)	1	A-III	RT/ CT	0	U
13	M, 81	Motor deficit, language, epilepsy	0	FL, PL, TL, OL (0)	1	A-III	N	0	1/ D
14	M, 51	Sensory deficit, headache	1	FL, PL, TL (2)	2	A-III	RT/ CT	15	15/ alive
15	M, 49	Epilepsy	0	FL, PL, TL (2)	1	A-III	N	0	4/ D
16	M, 46	Epilepsy	0	FL, PL (0)	1	OA-III	RT/ CT + CT	15	15/ alive
17	M, 23	Headache, cognitive	1	FL, PL, TL, OL (3)	2	A-IV	N	0	1/ D
18	M, 78	Epilepsy	0	TL, OL (1)	1	A-II	RT + CT + BVZ	5	10/ alive
19	M, 60	Cognitive	0	FL, TL (0)	1	A-III	RT/ CT + CT	0	9/ D
20	F, 56	Motor deficit, language, epilepsy, headache	11	FL, PL, TL (4)	1	A-II	RT	6	8/ alive
21	F, 46	Headache, visual deficit	12	TL, OL (3)	1	A-III	RT/ CT	0	1/ D
22	M, 44	Cognitive	24	FL, PL, TL (0)	1	OA-III	RT	4	6/ alive

A: astrocytoma; BVZ: bevacizumab; CT: chemotherapy; D: deceased; F: female; FL: frontal lobe; GC: Gliomatosis cerebri; M: male; N: no treatment; O: oligodendroglioma; OA: oligoastrocytoma; OL: occipital lobe; PFT: progression-free time; PL: parietal lobe; RT: radiotherapy; ST: survival time; TL: temporal lobe; U: unknown.

affected were the basal ganglia (81.8%), corpus callosum (45.4%), brainstem (22.7%), insula (13.6%), cerebellum (9.1%), spinal cord (4.5%), cranial nerves, (4.5%) and leptomeninges (4,5%). All cases corresponded to primary GC: 16 patients presented Type 1 and 6 presented Type 2, most of the latter with concomitant mass effect. The anatomical pathology showed Grade III astrocytoma in 8 patients (36.4%), Grade II astrocytoma in 5 (22.7%), astrocytoma with characteristics of Grade IV in 4 (18.3%), Grade III oligoastrocytoma in 2 (9.1%), Grade II

Figure 1 Magnetic resonance image with FLAIR sequences of 4 patients diagnosed with gliomatosis cerebri. Diffuse, bilateral hyperintensity with hemispheric and diencephalic predominance can be observed.

Figure 2 Magnetic resonance image with FLAIR sequences and T1 after administration of contrast (intravenous gadolinium) that shows different degrees of uptake by the lesions. A and B: Images of a single patient in whom the infiltration does not take up contrast despite the widespread condition. C and D: Images of another patient in whom the lesion takes up contrast diffusely.

oligoastrocytoma in 1 (4.5%), Grade II oligodendroglioma in 1 (4.5%) and Grade III oligodendroglioma in 1 patient (4.5%) (table 2). The average diagnostic delay time was 1 month; 9 patients (40.9%) were diagnosed during the first month after onset of symptoms; 6 (27.3%) during the second month; 5 (22.7%) between the second month and the first year, and 2 (9.1%) after 1 year from onset of symptoms. In these last 2 patients, the symptoms were attributed to migraine in one case and to limbic encephalitis with unknown origin in the other[5]. In 4 patients, the initial diagnosis considered was an acute cerebrovascular process.

Seventeen patients had regular follow-up, 4 died soon after diagnosis and 1 patient did not return to consultation. The treatments administered were chemoradiation (RT/CT) with 75 mg/m^2/day of oral temozolomide (TMZ) and standard fractionated radiotherapy (RT) followed by cycles of TMZ (150-200 mg/m^2/day for 5 days, every 28 days) in 5 patients; RT/CT in another 5; TMZ alone in 4; RT alone in 2; and RT followed by TMZ plus bevacizumab (BVZ) in 1. Of the 7 patients with low grade tumours, 5 were treated and all of them responded to treatment. Nine of the 11 patients with Grade III tumours were treated: 4 (44.4%) responded and 5 did not. Three of the 4 patients with Grade IV areas received treatment and all responded. In total, 70.6%of patients treated responded to treatment. Nine patients (75%) suffered tumour progression, with a progression-free time of 6 months; 8 patients received treatment (4, TMZ at daily doses of 75 mg/m^2; 2, RT/QT; 1, procarbazine/lomustine/vincristine, and 1, BVZ / irinotecan; 2 patients required surgical resection of the area of progression). Of these 8 treated patients, 7 (87.5%) presented a therapeutic response. Six patients (85.7%) showed a second progression and were treated with TMZ (2), BVZ (1), irinotecan (1), BVZ /

Table 2 Histological tumour grade

Tumour type and grade	Patients, n (%)
Astrocytoma type III	8 (36.3)
Astrocytoma type II	5 (22.7)
Astrocytoma type IV	4 (18.3)
Oligoastrocytoma type III	2 (9.1)
Oligoastrocytoma type II	1 (4.5)
Oligodendroglioma type II	1 (4.5)
Oligodendroglioma type III	1 (4.5)

irinotecan (1) or RT plus etoposide / erlotinib (1); 3 of these patients (50%) responded to the treatment.

Of the 22 study patients, 13 have died, 7 are alive and 2 have not been tracked. The average follow-up time was 13 months. Eight patients (36.3%) developed thromboembolic complications (6, deep vein thrombosis; 5, pulmonary embolism; and 2, cerebral venous thrombosis). One patient developed both epidural and subdural haematoma. Overall survival was 9.5 months, which increased to 15 months in treated patients.

Discussion

The longest GC series was published by Taillibert et al.[2] in 2006 and included 296 patients. Most were male (56.8%) and the average patient age was 39 years (39 years for males and 45 for females), with isolated cases of newborns and elderly patients. In our series, the proportion of males was also higher (77.2%) and average age was 54 years (51 years for males and 54 for females). Because ours is a centre for adults, there are no paediatric patients. In the series of Taillibert et al.[2], 31.1% of patients started with epileptic crises (36.4% in our series), 18.6% with cognitive impairment (27.3% in our series) and 16.9% with focal deficits (86.4% in our series). The difference in focal deficits may be due to the fact that the Taillibert study did not include initial symptoms for all patients and in some of our patients the medical history listed several symptoms as the first, without really differentiating which one was the original. In our series, most patients suffered from Type 1 primary GC (72.7%); this contrasts with a series of 33 patients presented by Park et al.[6], in which Type 2 GC was the most common (54.5%). In our series, Type 2 GC could be underestimated because it was sometimes difficult to differentiate the tumour mass *per se* from the infiltration. Radiological involvement was predominantly hemispheric, although the diencephalic involvement in 81.8% of patients is notable. This is similar to other studies such as that by Vates et al.[7] with diencephalic involvement in 21 of 22 patients (95%). In the study by Taillibert et al.[2], 60.3% of tumours were astrocytomas (67.2% in ours), 50% were Grade II tumours (31.7% in our series), 40.5% were Grade III (49.9% in our series) and 9.5% presented areas of Grade IV (18.3% in our series), indicating a more aggressive histology in our patients. Although in 2 patients the symptoms were attributed to other neurological conditions, which delayed diagnosis by over 1 year, the overall average time of diagnosis was 1 month, significantly less than the 3 months mentioned in the study by Vates et al.[7]. Differential GC diagnosis often includes infectious or autoimmune encephalitis, demyelinating diseases, vasculitis and other brain tumours such as primary brain lymphoma[2,3,7]. In our patients, the most frequently considered initial diagnosis was acute cerebrovascular process.

The treatment of GC is not well established; the treatments administered to the patients therefore did not follow any particular protocol. The surgery was diagnostic and palliative. Neurological symptoms were improved by RT, but improvements were limited by its toxicity when applied to a large brain volume, and its effect on survival differs according to the study[8-10]. Chemotherapy, mainly TMZ, has shown clinical and radiological response, as well as an improvement in survival[11-13].

We did not find any studies evaluating the effect of RT/CT in GC, with or without adjuvant CT. In our study group, 70.6% of patients initially responded to the treatment, although 75% subsequently progressed after an average of 6 months. 87.5% responded to treatment of the first tumour recurrence and 50% responded to treatment of a second relapse. The survival of treated patients was of 15 months, which is 5.5 months higher than the overall sample survival (9.5 months). It is also higher than that of patients with glioblastoma treated in the standard form with RT/CT and adjuvant CT, following the protocol of Stupp et al.[14] (14.5 months). We highlight the case of a patient with stable hemianopsia and low histological grade astrocytoma who received TMZ and remains without progression 38 months after diagnosis. The most frequent complications were haematic, mainly thromboembolic, possibly due to systemic coagulation activation by the tumour itself.

Our study and those of other researchers indicate that patients with GC often respond to treatment[2,7-13], even after 1 or 2 relapses, with a survival similar to that of patients with glioblastomas[14].

Conflict of interests

The authors declare no conflict of interests.

References

1. Nevin S. Gliomatosis cerebri. Brain. 1938;61:170-91.
2. Taillibert S, Chodkiewicz C, Laigle-Donadey F, Napolitano M, Cartalat-Carel S, Sanson M. Gliomatosis cerebri: a review of 296 cases from the ANOCEF database and the literature. J Neurooncol. 2006;76:201-5.
3. Lantos PL, Bruner JM. Gliomatosis cerebri in tumours of the nervous system. In: Kleihues P, Cavence WK, editors. Pathology and genetics of tumours of the nervous system. Lyon: IARC; 2000. p. 92-3.
4. Fuller GN, Kros JM. Gliomatosis cerebri. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, editors. WHO Classification of Tumours of the Central Nervous System. Lyon: IARC; 2007. p. 50-2.
5. Simó M, Dalmau J. Gliomatosis cerebral simulando una encefalitis límbica. Neurología. 2009;24:498-510.
6. Park S, Suh YL, Nam DH, Kim ST. Gliomatosis cerebri: clinicopathologic study of 33 cases and comparison of mass forming and diffuse types. Clin Neuropathol. 2009;28:73-82.
7. Vates GE, Chang S, Lamborn KL, Prados M, Berger MS. Gliomatosis cerebri: a review of 22 cases. Neurosurgery. 2003; 53:261-71.
8. Elshaikh MA, Stevens GH, Peereboom DM, Cohen BH, Prayson RA, Lee SY, et al. Gliomatosis cerebri. Treatment results with radiotherapy alone. Cancer. 2002;95:2027-31.
9. Mena IX, Olivares DA, Del Brutto OH, Leone-Stay G. Gliomatosis cerebri: características clínico-patológicas, de neuroimagen y resultados del tratamiento con radioterapia. Rev Neurol. 2000; 31:101-6.

10. Cozad SC, Townsend P, Morantz RA, et al. Gliomatosis cerebri. Results with radiation therapy. Cancer. 1996;78:1789-93.
11. Levin N, Gomori JM, Siegal T. Chemotherapy as initial treatment in gliomatosis cerebri. Results with Temozolomide. Neurology. 2004;63:354-6.
12. Sanson M, Cartalat-Carel S, Taillibert S, Napolitano M, Djafari L, Cougnard J, et al. Initial chemotherapy in gliomatosis cerebri. Neurology. 2004;63:270-5.
13. Lodi R, Setola E, Tonon C, Ambrosetto P, Franceschi E, Crino L, et al. Gliomatosis cerebri: clinical, neurochemical and neuroradiological response to temozolamide administration. Magn Reson Imaging. 2003;21:1003-7.
14. Stupp R, Mason WP, Van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus concomitant and adjuvant Temozolomide for glioblastoma. N Engl J Med. 2005; 352:987-96.