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EDITORIAL

Gliomatosis cerebri

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Abstract
Introduction: Gliomatosis cerebri (GC) is a rare, diffusely growing glial tumour characterised by extensive brain infiltration. The diversity of histological subtype and grade on presentation among different subjects, in addition to the usually poor response to treatment make GC an uncertain entity where many questions still remain unanswered. One article in this issue of NEUROLOGÍA describes a series of 22 patients with GC, where clinical, therapeutic and outcome results are detailed.
Development: Clinical presentation of GC is non-specific and, although the neuroimage is characteristic, the spectrum of differential diagnosis is wide. Despite the fact that known prognostic factors in glioma also seem to be involved in GC, the heterogeneity of pathology and molecular findings on biopsy samples makes it difficult to characterise GC correctly. Therefore, variability of outcome and response to therapy is the rule. Evidence on therapeutic strategies is based on case-series. According to this, the optimal treatment is not well established. Part of current research is focused on identifying molecular predictor factors of response to chemotherapy.
Conclusions: The addition of chemotherapy in the classic treatment schedule based on radiotherapy seems to produce better responses in GC patients. However, the outcome of these patients remains poor with low survival rates. Phase III multi-centre trials to evaluate different therapeutic strategies in GC are essential. Further knowledge on the histological profile and molecular prognostic factors is also required. Patients should be stratified according to the prognostic factors identified.

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Gliomatosis cerebri

Resumen
Introducción: La gliomatosis cerebri (GC) es un tumor glial difuso infrecuente, caracterizado por una gran capacidad infiltrativa. La variabilidad de características histológicas y de grado que presenta, junto con respuestas generalmente pobres a los tratamientos, convierte a la GC en un tumor poco conocido con diversas cuestiones por responder. En este volumen de NEUROLOGÍA se presenta un estudio sobre las características clínicas, evolución y respuestas al tratamiento en una serie de 22 pacientes con GC.
Desarrollo: La GC presenta una clínica poco distintiva, junto con una neuroimagen característica pero poco específica, lo que implica la realización de un diagnóstico diferencial amplio. Aunque en su evolución parecen estar implicados factores pronósticos similares a los de los otros gliomas, la heterogeneidad de sus hallazgos patológicos y moleculares dificulta su precisa caracterización. Así se explican sus variables comportamiento y respuesta al tratamiento. La evidencia sobre la eficacia de distintos abordajes terapéuticos se basa en series de casos clínicos; por lo tanto, el tratamiento no está bien establecido. Parte de la investigación actual se centra en identificar factores moleculares que puedan ser predictores de la respuesta a la quimioterapia.
Conclusiones: La incorporación de quimioterapia al tratamiento clásico basado en la radioterapia parece ofrecer mayores tasas de respuestas, aunque su impacto en la supervivencia sigue siendo escaso. Es necesaria la realización de estudios multicéntricos de fase III para evaluar las diferentes estrategias terapéuticas. Asimismo, hay que profundizar en el conocimiento sobre la histogénesis y los factores moleculares pronóstico para poder estratificar adecuadamente a los pacientes.

Introduction

Gliomatosis cerebri (GC) is a rare primary brain tumour; it probably represents less than 1%of all astrocytomas[1,2], with an intriguing histogenesis and natural history that are still undefined. In addition, GC has a poor, conflicting response to treatment. In this volume of NEUROLOGÍA, we present an article on a series of patients with GC, which helps to improve our understanding of the evolution and response to treatment of this problematic entity.

Definition

According to the criteria of the World Health Organization (WHO) Classification of Tumours, GC is a diffuse glioma with an exceptionally infiltrative and extensive growth pattern than generally preserves the architecture of surrounding neural tissues. It has to involve a minimum of 3 brain lobes and can infiltrate both cortical grey matter and basal ganglia, as well as extend along the brainstem and spine[2]. The cellular phenotype is usually of astrocyte type but it also admits the oligoastrocytoma and oligodendrocyte types[3]. GC has been divided into Type 1, when no tumour mass is observed in the infiltrative pattern, and Type 2, when there is a lesion with mass effect, usually small (<1cm in diameter) in addition to cerebral infiltration. When other types of gliomas present extensive progression with infiltrative characteristics, rather than growth of the tumour mass itself, these phenomena are called secondary GC[2,4,5].

Gliomatosis cerebri typically presents an aggressive biological behaviour, so the WHO classifies it as grade III malignancy. Since most of the pathological samples consist of biopsies due to the inoperability associated to its extension, these may not be representative of the entire tumour. For this reason, even if there are no features corresponding to cellular anaplasia, it is still regarded as a high-grade tumour.

Epidemiology, clinical manifestation and neuroimage

The incidence of GC is higher in males than in females (1.3:1), with a probable rate of about 0.6 to 8.2 cases/year[4,6]. Although the age interval at diagnosis ranges from the first months of life until old age, most patients are between 40 and 50 years old[4]. The clinical presentation is variable and is not a diagnostic aid; it is generally the unspecific changes in magnetic resonance imaging (MRI) that arouse the diagnostic suspicion. In addition to presenting extensive hyperintense signal changes on FLAIR and T2 sequences not present in T1 or computed tomography scan, the image can present some alterations that are indicative of, but not specific for GC. These would consist in a thickening of the corpus callosum, slight signs of collapse

of ventricular horns and hemispheric swelling, loss of differentiation between grey and white matter, thickening of the cortex or basal ganglia and, usually, preservation of the cerebellum even when there is brainstem involvement. Contrast uptake can also be observed, which may range from diffuse and patchy to very clear, present in up to half of patients; this finding is more common in Type 2 GC[7-9]. The lack of specificity of neuroimaging and the clinical presentation raise a differential diagnosis with Behçet's syndrome, Sjögren syndrome, ischemic, post-radiotherapy progressive multifocal or reversible posterior leukoencephalopathy, infectious or immune encephalitis, leukodystrophies, vasculitis, demyelinating diseases, certain forms of primary brain lymphoma and some types of stroke such as CADASIL (cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Assessment of the MRI, along with the appropriate clinical context, is what will determine the indication for a biopsy to confirm the diagnosis. Spectroscopy and the sequences of relative cerebral blood volume can be of great help in interpreting the lesions seen on the MRI as glial lineage tumours, as well as serving as a guide for the area in which to perform the biopsy[10-12].

Genetic and molecular alterations

Various questions about GC histogenesis have been raised, both because of its extension and by the fact that it presents heterogeneity in grade and histological subtype, as well as because of the absence of a clear specific histopathological finding. First, it may simply be a subtype of diffuse glioma with an exceptional infiltrative ability which, by acquiring a series of molecular changes similar to those that occur in transforming low-grade astrocytomas into anaplastic or secondary glioblastomas, would become malignant and would probably be observed as Type 2 GC. This hypothesis would be supported by the presence of p53 or PTEN mutations or by EGFR amplification. These alterations have been found in GC, but with a much less frequently than in conventional astrocytomas[13-19]. Other alterations have also been described in relation to cell cycle control mechanisms, such as decreased p27 expression in relation to GC progression[14-16], which would support the evolution of a tumour from low to high grade. On the other hand, an alternative hypothesis would argue that GC is an entity independent from diffuse glioma. Its arguments are based on finding chromosomal alterations and molecular markers other than those of astrocytomas[20]. Interestingly, some studies have identified, in GC samples, a high percentage of Nestin and Sox2-positive cells (which are markers of neural precursors)[21,22] and of CD34 (a marker of stem cells)[22]; this reflects a more primitive nature of GC with respect to astrocytomas. There is only more consensus about accepting that GC is a tumour of monoclonal origin, thus ruling out the possibility of neoplastic transformation of different brain regions that end up joining[14,16]. The main cause of the disparity in findings and interpretations is the shortage of good anatomopathological material for an adequate molecular analysis, since in most cases what is available is material from biopsies with a high presence of normal brain tissue.

Prognostic factors

With respect to GC evolution, the independent, good prognosis factors most firmly established in relation to survival are, as in other gliomas, the Karnofsky index (≥ 70-80) and histological grade of the analysed sample[4,7]. Age as a prognostic factor presents, in most studies, a trend toward significance but without reaching it; young patients have discreetly more prolonged survival[4,7,9]. Other good prognostic factors to consider are the histological subtype (oligodendrogliomas better than the others)[4], the absence of contrast uptake (probably related to histological grade)[6,9] and less grey matter infiltration as compared to white[12]. Non-replicated studies indicate that deletions in chromosomes 13q and 10q and gains in chromosome 7q, as well as p53 and PTEN mutations, correlate with poor survival[9,15]. In the molecular field, in a series dominated by the oligodendrocyte histological type, it appears that 1p19q deletions are associated with improved survival, as is the case with oligodendrogliomas[23]. In addition, there is also a significant correlation between the presence of this mutation and MGMT methylation; however, in these patients methylation absence is only associated with a non-significant trend toward a lower progression-free tumour interval[8].

Treatment

The treatment schedule for GC has not been defined yet. GC is an unresectable tumour, so surgery can only have a diagnostic role. The only evidence on the effectiveness of cancer treatment, chemotherapy (CT) and/or radiotherapy (RT), comes from series of clinical cases or retrospective reviews of individual cases (table 1)[4,6,8,13,24-26]. As in other gliomas, RT has been the mainstay of GC treatment for the last decade. Its relative and contradictory impact on survival, the lack of consensus about total dose, dose/fraction and irradiation type (focal or whole brain), as well as about potential adverse effects generated by irradiating large areas of the brain, do not dispel the doubts about its therapeutic benefit[2,4,7]. The administration of CT, together with RT or in isolation, is an increasingly widespread practice, although there is not a high level of evidence to back it up. The most commonly used chemotherapeutic agents are PCV schemes (procarbazine, lomustine, vincristine) and temozolomide (TMZ), with no significant differences in survival between the two, even though TMZ has shown a better adverse effect profile and allows prolonged administration[4,5,8,24-26]. Administering CT alone (especially using TMZ) has emerged as a possible first-line strategy for GC of oligodendroglial lineage or for tumours showing 1p19q deletion[4,23]; RT would then be reserved as a salvage therapy after progression from CT. This would enable a delay of the toxicity from radiation, maintaining a certain rate of response to this second-line treatment. Obviously, if the histology lineage of GC corresponded to a glioblastoma, the treatment recommended would be the Stupp regime[27]. Furthermore, the usefulness of antiangiogenic agents (bevacizumab, celecoxib) in GC is still to be established[28]. Finally, we emphasise the limited usefulness of steroids in GC, as there is only a small component of vasogenic oedema, especially in Type 1 GC.

Table 1 Summary of the most recent studies on treatment in gliomatosis cerebri

Author	Study period	Patients (n)	Histological type	Treatment	Responses, n (%)	Overall survival (months)
Levin et al.[24 a]	6 years	11	OII, 6; OIII, 1; AII, 1; GBM, 1; OAII, 2	CT (PCV/TMZ), n = 11	PR, 4 (36%); SD, 5 (45%); PRO, 2 (18%)	PFS 6 months, 73%; PFS 12 months, 55%; PFS 24 months, 23%
Taillibert et al.[4 b]	1985-2004	296	O, 54; GII, 100; A, 108; GIII, 81; OA, 17; GIV, 19; NR, 117; NR, 96	No treatment, n = 105; RT, n = 41; CT (PCV/TMZ), n = 71	NR	OS all the series: 14.5; OS No treatment: 11; OS QT: 11-36
Piccirilli et al.[25 c]	NR	11	GBM	RT + CT (TMZ), n = 11	NR	OS, 16.3 (13-22)
Armstrong et al.[6 d]	1982-2005	13	NR	CT (PCV), n = 1; RT, n = 4; RT + CT[e], n = 8	PR, 0; SD, 12 (92%); ND, 1 (8%)	OS 12 months: 92%; OS 24 months: 64%; OS 36 months: 21%
Kaloshi et al.[8]	2000-2006	25	O, 14; GII, 19; A + OA, 9; GIII, 6; NR, 2	CT (TMZ), n = 24; RT + CT (TMZ), n = 1	PR, 12 (48%); SD, 9 (36%); PRO, 4 (16%)	OS: 37.7 (15.2-66.8)
D'Urso et al.[15]	2000-2005	59	AII, 11; AIII, 23; OAII, 8; OAIII, 17	RT + CT (TMZ), n = 59	PR, 17 (29%); SD, 26 (44%); PRO, 16 (27%)	OS: 14.58-41.20
Park et al.[13]	1999-2005	33	GII, 21; GIII-IV, 12	No treatment, n = 5; RT, n = 17; RT + CT, n = 11	NR	OS: 16 (0-39)
Glas et al.[26]	2001-2006	12	AII, 10; OII, 2	CT (PC o PCV), n = 12	PR, 0; SD, 11 (92%); PRO, 1 (8%)	OS: 37 (33-41)
Novillo-López et al. (present work)	2003-2009	22	AII, 5; AIII, 8; OAII, 1; OII, 1; OAIII, 1; GBM, 4	No treatment, n = 4; RT, n = 2; CT (TMZ), n = 4; RT + CT, n = 11; NR, n = 1	PR + SD, 12 (70.6%)	OS all the series: 9.5; OS treated: 15

A: astrocytoma; CT: chemotherapy; GBM: glioblastoma; GII: Grade 2; GIII: Grade 3; MTX: methotrexate; NR: not reported; O: oligodendroglioma; OA: oligoastrocytoma; OS: overall survival; PC: procarbazine + lomustine; PCV: procarbazine + lomustine + vincristine; PFS: progression-free survival; PR: partial response (including minor response); PRO: progression; RT: radiotherapy; SD: stable disease; TMZ: temozolomide; VCR: vincristine.

[a] Exclusion of those who had received RT previously.

[b] Includes review of the 206 cases previously reported in the literature.

[c] All with age over 70 years.

[d] All patients are paediatric.

[e] Combinations with MTX, VCR, carboplatin, VCR, PCV, TMZ.

Conclusions

This study presented by Novillo-López and colleagues shows the histological heterogeneity of this tumour and its apparent response to treatment, although unfortunately with an evolution comparable to that of glioblastomas, even in their tendency to produce thrombotic events. The characterisation of GC has been hampered by the difficulty of diagnosing live patients before the advent of the MRI and the predominance of pathological biopsy material. This is reflected by the fact that it is the only brain tumour that, for its diagnostic criteria, requires neuroimaging indispensably and is even subclassified based on it, which does not necessarily correlate with its biological behaviour. A conclusion indicated by the heterogeneity of the histological and molecular findings, as well as by its natural history, is that this is a tumour of undetermined origin, with an, as yet, unidentified genomic instability that favours its rapid progression through various malignancy grades (III and IV) compared to classic astrocytomas. These circumstances explain the differences in survival and treatment response, making it advisable in future studies to separate patients with Type 2 GC or glioblastoma histology from other patients. Furthermore, this entity shows that the classic anatomopathological classification used to determine tumour aggressiveness is limited; it is necessary to identify individual genetic or molecular "signatures" that can determine the evolution of the different tumours more accurately. This would facilitate and even personalise the homogeneity of tests and treatments. Further insight into

GC knowledge will not only benefit these patients, it will probably also help to understand the mechanisms of infiltrative migration of secondary gliomatosis, which are more common today as a result of the use of angiogenesis in glioblastoma treatment.

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