



---

# **Gliomatosis Cerebri Type 1 Mimicking an Ischemic Stroke and Progressing to a Type 2: a Case Study and Literature Review**

**Siegfried H elage<sup>1\*</sup>, Samir Benadjaoud<sup>1</sup>, J er me Hodel<sup>1</sup>,  
Sophie Gerber<sup>1</sup> and Marc Zins<sup>1</sup>**

<sup>1</sup>*Department of Radiology, H opital Saint-Joseph, Paris, France.*

### **Authors' contributions**

*This work was carried out in collaboration between all authors. All authors were involved in the management of the patient discussed. Author SH wrote the first draft of the manuscript and managed the literature searches. All authors read and approved the final manuscript.*

**Case Study**

**Received 21<sup>st</sup> March 2013**  
**Accepted 13<sup>th</sup> June 2013**  
**Published 28<sup>th</sup> June 2013**

---

## **ABSTRACT**

**Aims:** To report a rare clinical case of gliomatosis cerebri, which presented with non-specific clinical, laboratory, and radiological findings. We provide images and stress the importance of differential diagnosis based on imaging, especially magnetic resonance (MR) spectroscopy.

**Case Presentation:** A 73-year-old woman developed a right hemiplegia suggestive of ischemic stroke. Cerebral magnetic resonance imaging (MRI) highlighted a diffuse tumor-related infiltration involving several lobes without contrast enhancement, corresponding to the specific description and definition of gliomatosis cerebri type 1. With the aid of MR spectroscopy, we correctly diagnosed the disease preoperatively, which was finally confirmed pathologically by stereotactic biopsy. During radiological follow-up, a contrast enhancement occurred on cerebral MRI, suggestive of progression to a gliomatosis cerebri type 2. Given a poor performance status, this elderly patient received palliative treatment.

**Discussion:** Gliomatosis cerebri is a relatively rare but well-known entity, which affects mostly middle aged patients. It often presents with confounding clinical and imaging features, thus additional examinations such as MR spectroscopy are almost always necessary before reaching the correct diagnosis before biopsy.

**Conclusion:** Contrast enhancement on cerebral MRI, which is usually absent, is found

---

\*Corresponding author: Email: [siegfriedhelage@yahoo.fr](mailto:siegfriedhelage@yahoo.fr);

in case of transformation from type 1 gliomatosis cerebri to type 2. Some features on MR spectroscopy are helpful for gliomatosis cerebri diagnosis: N-acetylaspartate levels are diminished, levels of myoinositol are significantly elevated, but Cho/Cr ratio may be normal.

**Keywords:** *Gliomatosis cerebri; type 1; type 2; contrast enhancement; MR spectroscopy; myoinositol; stroke.*

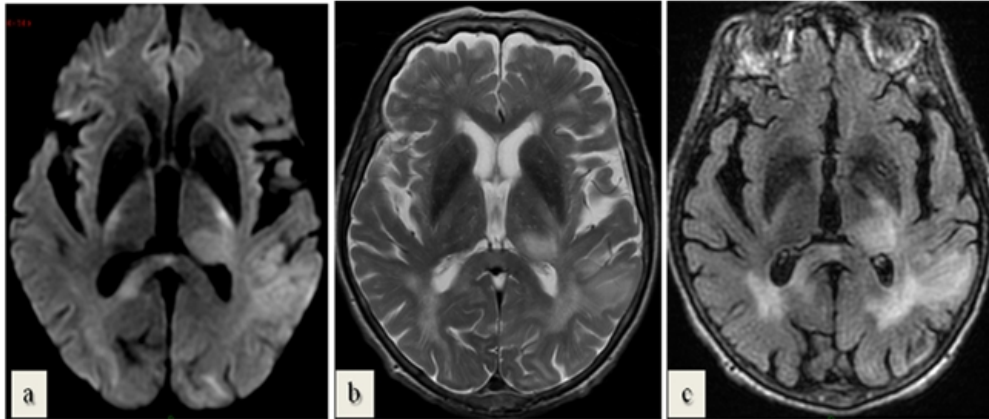
## 1. INTRODUCTION

Gliomatosis cerebri is a rare and severe central nervous system neoplasm. It is usually fatal due to its ability to infiltrate cerebral tissues, compromising efficacy of treatments. Gliomatosis cerebri is defined as a diffuse neoplasm of glial cells, involving more than two lobes and occasionally infiltrating infratentorial structures and spinal cord, with relative preservation of neuronal architecture [1]. Pathologists describe two types of gliomatosis cerebri: type 1 is the classic form characterized by diffuse overgrowth with neoplastic glial elements without a focal mass. Type 2 may stem from type 1 and is characterized by a diffuse brain infiltration with a focal mass, usually a high-grade glioma [2]. The diagnosis is usually made on the basis of both histology and neuroimaging. Conventional MR imaging shows a diffuse signal intensity abnormality with minimal or no mass effect and a lack of contrast enhancement. Although clinical and MR imaging findings may suggest infiltrative neoplasm, they are not specific, and the use of proton MR spectroscopy to help in classification of gliomatosis cerebri has been suggested [3]. This paper describes a case of gliomatosis cerebri, a very rare brain tumor seldom affecting the elderly, whose presentation mimicked an ischemic stroke.

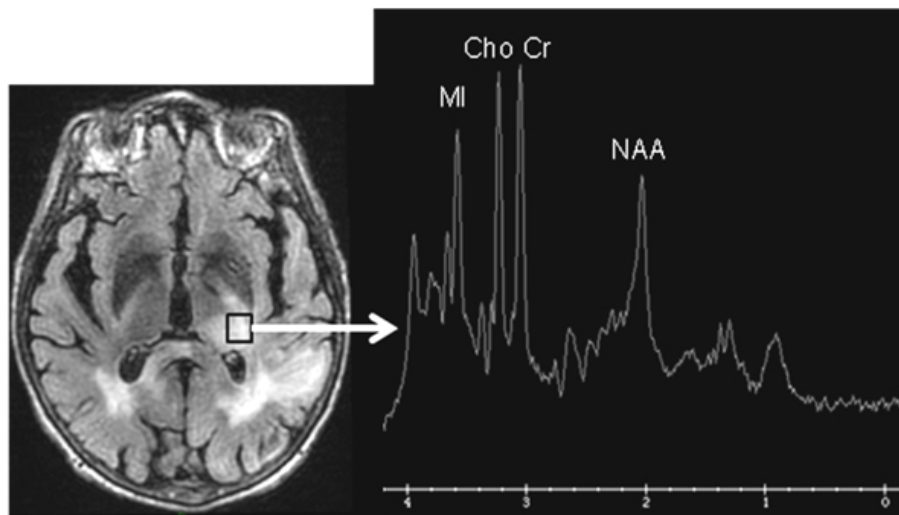
## 2. CASE PRESENTATION

A 73-year-old woman with a history of left superficial middle cerebral artery ischemic stroke was admitted to our hospital for behavioral disorder. A noncontrast computed tomography brain scan was considered normal. During surveillance a neurological worsening (right hemiplegia) occurred, suggestive of stroke recurrence. A magnetic resonance imaging (MRI) including diffusion-weighted (DWI) and fluid-attenuated inversion recovery (FLAIR) images revealed multiple hyperintense brain areas (left parietal and occipital lobe, left corticospinal tract, left thalamus, across the midline involving the splenium of corpus callosum, right occipital lobe), without Apparent Diffusion Coefficient (ADC) decrease or contrast enhancement or mass effect (Fig. 1). The involvement of corpus callosum led us to hypothesize several diagnoses: infection (progressive multifocal leukoencephalopathy - PML), inflammation (multiple sclerosis - MS, acute disseminated encephalomyelitis - ADEM), metabolic disorder (posterior reversible encephalopathy syndrome - PRES), neoplasia (primary brain lymphoma or lymphomatosis cerebri, low-grade glioma, brain metastases). Except for the T1 hypointense lesions, the lack of immunodepression invalidated PML. The advanced age of the patient, the morphology and topography of lesions invalidated multiple sclerosis. Absence of recent viral infection invalidated ADEM. Absence of contributing factor and asymmetric distribution of lesions invalidated PRES. The lack of enhancement and absence of ADC decrease combined with no signal in the lipid region on MR spectroscopy invalidated primitive lymphoma or lymphomatosis cerebri; moreover a full body scanner failed to show a primary tumor. MR spectroscopic imaging was subsequently performed (Fig. 2): spectrum was consistent with a neoplastic lesion since Choline/N-acetylaspartate ratio

was elevated and N-acetylaspartate/Creatine ratio was diminished; although Choline/Creatine ratio was not so elevated in this case, Choline/N-acetylaspartate ratio was abnormally elevated on long TE single voxel spectroscopy. Furthermore myoinositol (at 3.5 ppm) was elevated. This last finding led us to suggest a diagnosis of gliomatosis cerebri.



**Fig. 1. DWI(a), T2WI(b) and FLAIR(c) showing hyperintense brain areas: left parietal and occipital lobe, left corticospinal tract, left thalamus, splenium of corpus callosum, right occipital lobe. Postcontrast T1WI reveals no enhancement**



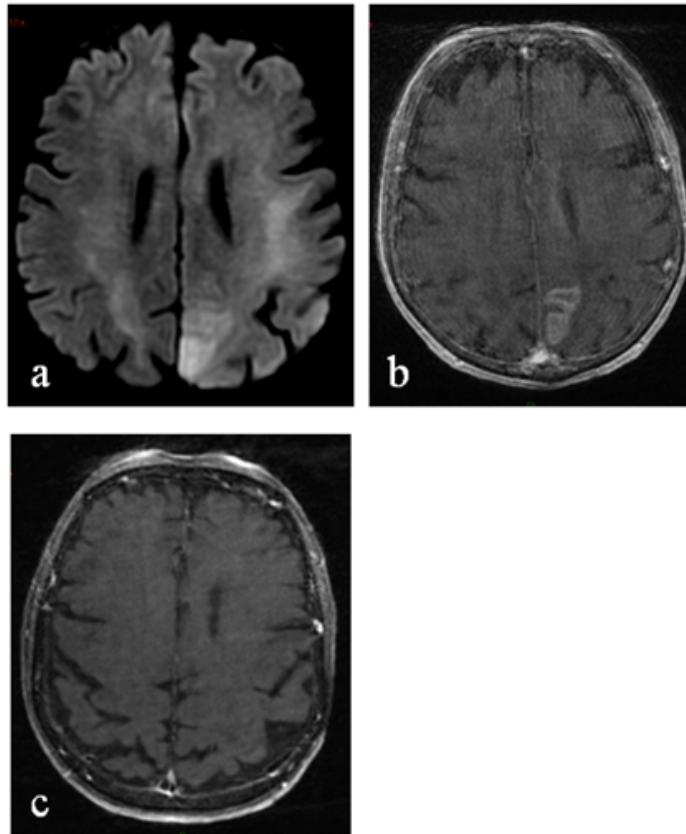
**Fig. 2. Single voxel MR spectroscopy (TE 144ms) of left thalamus showing an increase of the Cho/NAA ratio and a decrease of the NAA/Cr ratio (tumor profile), associated with a Myoinositol peak, suggesting gliomatosis cerebri. Cho: Choline, NAA: N-acetylaspartate, MI: Myoinositol**

A stereotactic biopsy of left thalamus was performed; pathological examination confirmed the diagnosis of gliomatosis cerebri. It revealed a moderately cellular neoplasm composed of

cells with round-to-oval nuclei, some of which displayed small eccentric cell bodies; mitoses were absent. Although glial fibrillary acidic protein (GFAP) immunoreactivity was intense, the small specimen size precluded further interpretation. The lesion was categorized as an infiltrating glioma of intermediate grade (grade II-III when using the WHO classification system, which grades astrocytomas on a scale of I to IV) [6].

The patient refused any treatment, in particular chemotherapy with Temozolomide.

Four months later, a rapidly progressive cognitive impairment prompted us to perform a MRI (Fig. 3) that showed a new location in left parietal lobe with focal nodular contrast enhancement, suggestive of progression to a type 2 gliomatosis cerebri (high-grade glioma).



**Fig. 3. DWI(a) showing a new location in left parietal lobe with focal nodular contrast enhancement on postcontrast T1WI(b), suggestive of progression to a type 2 gliomatosis cerebri (high-grade glioma). Four months earlier, postcontrast T1WI(c) revealed no enhancement in the same area**

Given a poor performance status, this elderly patient received palliative treatment, and subsequently died from the disease. Family members refused autopsy.

### **3. DISCUSSION**

Gliomatosis cerebri is a rare cerebral tumor, affecting more readily 40 to 50-year-old patients; some cases are reported in children. Incidence of gliomatosis cerebri seems higher among men than women. The most frequent symptoms are mental status changes, behavioral disorders, seizures, corticospinal tract deficits and headaches [4].

Gliomatosis cerebri has been divided into primary, occurring de novo, and secondary subtypes resulting from the spreading of a pre-existing focal glioma. Primary gliomatosis cerebri can be categorized into two groups: type 1 is described as a diffuse infiltrating lesion without obvious tumor mass, and type 2, originating from type 1, is described as the diffuse infiltrating lesion associated with a focal tumor mass, usually a high-grade glioma. Sometimes, as in our case report, the development of a high-grade glioma within the diffuse low-grade infiltrating tumor process can be seen during radiological follow-up.

Gliomatosis cerebri is included in the astrocytic tumor group (WHO 2007).

There are two principal hypotheses for pathogenesis:

- Polyclonal origin hypothesis: gliomatosis cerebri results from neoplastic transformation of glial cells, occurring simultaneously in various areas of brain.
- Monoclonal origin hypothesis: gliomatosis cerebri results from a single clone of cells and then spreads widely in brain. Most gliomatosis cerebri seems to have a monoclonal origin [5].

Histopathologically, gliomatosis cerebri induces a diffuse enlargement of affected regions with preservation of brain tissue architecture. The normal brain tissue is invaded by a proliferation of glial cells that frequently resemble astrocytes, with fusiform or oval and often hyperchromatic nuclei. These cells often follow axons, preserving local histoarchitecture [6]. Necrosis and microvascular proliferation is usually absent in type 1 gliomatosis cerebri. Mitotic activity is variable. There is no specific sign of gliomatosis cerebri on pathological findings. An important confounding factor with biopsy is the fact that architecture of the surrounding tissue is preserved, causing some sampling bias. Although type 1 gliomatosis cerebri usually demonstrates histopathological features of a low-grade tumor, the overall biologic behavior corresponds at least to WHO grade 3 and the subsequent secondary progression to a high-grade tumor (type 2) may occur, as in our case report.

CT scanner is not the appropriate technique to analyze gliomatosis cerebri. CT appearance is variable, and ranges from normal or subtle mass effect on ventricles to increased- or decreased-density areas [7]. These possible features lead to perform a MRI. The extent of tumor infiltration is often underestimated [8].

MRI combined with biopsy and pathological analysis is the gold standard [9]. The main morphological characteristic of gliomatosis cerebri is its diffuse and contiguous growth pattern, which involves white matter of at least three cerebral lobes; sometimes it may extend to infratentorial region [8]. The two hemispheres are usually involved due to tumor extension across corpus callosum. Most often the disease invades hemispheric white matter; however cortex may be involved too. Basal ganglia and thalamus are often affected, as in our case report. Lesions of brain stem, cerebellum and spinal cord are much rarer.

The most commonly involved areas are cerebrum (76%), mesencephalon (52%), pons (52%), thalamus (43%), basal ganglia (34%), cerebellum (29%), medulla oblongata (13%), hypothalamus (9%), optic nerve and chiasm (9%), spinal cord (9%). When the lesion involves cerebral hemispheres, centrum semiovale is always affected, whereas cerebral cortex is infiltrated only in 19% of such cases, with spread to the leptomeninges in 17% [2]. In equivocal cases, corpus callosum infiltration is helpful for differentiating gliomatosis cerebri from demyelinating diseases or vasogenic edema. Vasogenic edema involves peritumoral white matter but not corpus callosum or contralateral hemisphere. Tumor spread along corticospinal tract, when present, is highly suggestive of gliomatosis cerebri. The diffuse enlargement of the involved cerebral structures is also characteristic. Mass effect is minimal or absent compared with the diffuse tumor extension. Hydrocephalus is rare [10].

On T1-weighted images, the involved areas are iso- or hypointense. Areas of elevated signal on T2-weighted images most likely reflect tumor spread but may also represent secondary destruction of myelinated fibers. Asymmetrical or heterogeneous distribution of high-signal areas on T2-weighted or FLAIR images, together with a thickening of corpus callosum and/or a blurring of the limits between white and gray matter are often suggestive of gliomatosis cerebri. FLAIR sequence is the most helpful to evaluate tumor extent in supratentorial region while T2-weighted images are the most helpful to analyze posterior fossa [8].

Contrast enhancement is absent or rarely seen in type 1 gliomatosis cerebri, but is usually present in type 2. Relative preservation of the blood brain barrier is thought to be the underlying reason for the absence of contrast enhancement in type 1. The focal enhancements result from neoangiogenesis and probably correspond to areas of anaplastic transformation. Vascular proliferation, nodular enhancement and necrosis are typically absent in type 1 but are malignant features appearing during progression towards a type 2.

On Diffusion-weighted images, there are usually no high signal areas. The potential elevated signal results from the T2 shine-through effect. ADC is not decreased [11].

The low rCBV (relative cerebral blood volume) of type 1 gliomatosis cerebri on perfusion studies seems to be related to the lack of vascular hyperplasia found in histopathologic examination [11].

MR spectroscopy can be used for metabolic characterization of gliomatosis cerebri [12]. The study is based on analysis of choline (Cho), N-acetylaspartate (NAA) and creatine (Cr) peaks. Increased Cho/Cr and Cho/NAA ratios and variably decreased NAA/Cr ratio are found in the abnormal areas on T2-weighted images. Creatine levels may be elevated in gliomatosis cerebri and reduced in low-grade gliomas. A high level of myoinositol (MI) in gliomatosis cerebri is reported [13]. If Cho/Cr ratio or Cho/NAA ratio is not elevated, MR spectroscopy may still help narrow the differential diagnosis in favor of gliomatosis cerebri. Thus, results showing elevated Cho/NAA ratios should still be considered suspicious for gliomatosis cerebri, even when Cho/Cr ratio is normal. Cho/NAA ratio should be used to estimate tumor grade and target sites for biopsy [14]. In addition, MI/Cr and MI/NAA ratios should be measured because they can be elevated even when Cho/Cr ratio is normal.

In our case, the combination of clinical and MR findings is consistent with gliomatosis cerebri yet without marked elevation of Cho relative to Cr in the lesion, which distinguishes this case from previously reported series of gliomatosis cerebri evaluated with MR spectroscopic imaging [11,14].

FDG-PET shows decreased uptake in involved areas, which is insufficiently specific for diagnosis. Increased uptake on MET-PET strongly suggests neoplasia and is therefore valuable for differentiating gliomatosis cerebri from non-neoplastic diseases with similar features on T2-weighted images [15].

Differential diagnosis includes lesions with diffuse involvement of white matter. The major alternative diagnosis for type 1 gliomatosis cerebri is a low or intermediate-grade glioma. Heterogeneous signal intensity, presence of necrotic, cystic and hemorrhagic changes and an irregular ring-like contrast enhancement zone are characteristic MRI features of glioblastoma multiforme, which are different from those of gliomatosis cerebri. The difficulty arises when differential diagnosis must be done between a secondary glioblastoma multiforme during the course of a gliomatosis cerebri and a primary one. A distinction is made between gliomatosis cerebri and a multicentric glioma. Gliomatosis cerebri refers to a tumor with contiguous involvement of different regions, whereas a multicentric glioma is defined as distinct foci of tumor in different sites. It can be extremely difficult to distinguish gliomatosis cerebri from a diffuse glioma presenting with widespread contiguous tumor infiltration into adjacent brain regions. Oligodendroglioma shows necrosis, cysts and calcifications but the main feature differentiating a conventional glioma from gliomatosis cerebri is mass effect in case of conventional glioma.

Another alternative diagnosis is lymphomatosis cerebri. This entity is typically characterized by diffuse leukoencephalopathy. MRI findings include diffuse supra- and infra-tentorial white matter T2 hyperintensity and, most of the time, absence of contrast enhancement. On MR spectroscopy, a reduced NAA signal, an increased Cho signal, and increased Cho/NAA ratios are usually observed. Otherwise, elevated signals in the lipid region of the spectrum provide some clues to the diagnosis of lymphomatosis cerebri [16].

Another differential diagnosis for type 1 gliomatosis cerebri is white matter diseases and demyelinating lesions such as Marburg disease.

Finally, other alternative diagnoses for type 1 gliomatosis cerebri are infections (progressive multifocal leukoencephalopathy), metabolic disorders (posterior reversible encephalopathy syndrome), ischemic cerebrovascular diseases, vasculitis, post-treatment changes (brain radiotherapy) [8].

Gliomatosis cerebri is of poor prognosis. The median survival is 14.5 months. It is higher for younger patients (<40 years old), for low-grade gliomatosis (grade 2=20 months, grade 3=11.5 months, grade 4=8.5 months), oligodendroglial subtype (36 months compared to 14 months for mixed gliomatosis cerebri and 11 months for astrocytic subtype). An oligodendroglial component is predictive of better outcome. An age below 10 years and contrast enhancement on MRI studies at diagnosis may be poor prognostic factors [8].

The widespread tumor infiltration makes an initial chemotherapy approach particularly attractive in gliomatosis cerebri. Chemotherapy may be superior to supportive care and may provide a better risk-benefit balance compared to radiotherapy. Initial chemotherapy, by Procarbazine-CCNU-Vincristine (PCV) or by Temozolomide is clinically effective for 33% of patients and produced an objective radiologic response in 26%, with an overall median survival of 29 months. Temozolomide is well tolerated and appears to be a valuable alternative to PCV, especially for slow-growing, low-grade gliomatosis cerebri. Once chemotherapy fails, radiotherapy is still an option for these patients [17].

#### **4. CONCLUSION**

Gliomatosis cerebri is a neoplastic glial cell infiltration of brain tissue. It involves three or more contiguous lobes. It can simulate a stroke as in our case report. MRI shows a tumor infiltration within a preserved brain histoarchitecture, appearing hyperintense on T2- and FLAIR-weighted images, and iso- or hypointense on T1-weighted images. Contrast enhancement, which is usually absent, is found in case of transformation from type 1 gliomatosis cerebri to type 2 as in our case report. Some features on MRI spectroscopy are helpful for gliomatosis cerebri diagnosis: N-acetylaspartate levels are diminished, levels of myoinositol are significantly elevated, but Cho/Cr ratio may be normal as in our case report.

#### **CONSENT**

All authors declare that written informed consent was obtained for publication of this case report and accompanying images.

#### **ETHICAL APPROVAL**

Not applicable.

#### **ACKNOWLEDGEMENTS**

We thank Dr Éric Meary for his wise counsel and guidance throughout the preparation of this report.

#### **COMPETING INTERESTS**

The authors declare that they have no competing interests.

#### **REFERENCES**

1. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. WHO Classification of Tumors. WHO; 2007.
2. Fuller GN, Kros JM. Gliomatosis cerebri. In WHO Classification of Tumors of the Central Nervous System. Edited by Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. Lyon, IARC. 2007;50-52.
3. Galanaud D, Chinot O, Nicoli F, et al. Use of proton magnetic resonance spectroscopy of the brain to differentiate gliomatosis cerebri from low-grade glioma. J Neurosurg. 2003;98:269-276.
4. Taphoorn MJ, Klein M: Cognitive deficits in adult patients with brain tumors. Lancet Neurol. 2004;3:159-68.
5. Kros JM, Zheng P, Dinjens WN, Alers JC. Genetic aberrations in gliomatosis cerebri support monoclonal tumorigenesis. J Neuropathol Exp Neurol. 2002;61:806-814.
6. Lantos PL, Bruner JM. Gliomatosis cerebri in Tumors of the Nervous system. Kleihues and Cavenee Ed, IARC Lyon. 2000;92-93.
7. Del Carpio-O'Donovan R, Korah I, Salazar A, Melançon D. Gliomatosis cerebri. Radiology. 1996;198(3):831-5.
8. Sanson M, Napolitano M, Cartalat-Carel S, Taillibert S. La gliomatose cérébrale. Rev Neurol (Paris). 2005;161(2):173-181.



9. Peretti-Viton P, Brunel H, Chinot O, et al. Histological and MR correlations in Gliomatosis cerebri. *J Neurooncol.* 2002;59(3):249-259.
10. Yip M, Fisch C, Lamarche JB. AFIP archives: gliomatosis cerebri affecting the entire neuraxis. *Radiographics.* 2003;23(1):247-53.
11. Yang S, Wetzel S, Cha S. Dynamic contrast-enhanced T2\*-weighted MR imaging of gliomatosis cerebri. *AJNR Am J Neuroradiol.* 2002;23:350-355.
12. Guzmán-de-Villoria JA, Sánchez-González J, Muñoz L, Reig S, Benito C, García-Barreno P, Desco M. 1H MR spectroscopy in the assessment of gliomatosis cerebri. *AJR Am J Roentgenol.* 2007;188(3):710-4.
13. Levin N, Linetsky E, Siegal T. Gliomatosis cerebri: proton MR spectroscopy (1H-MRS) features. *Neurology.* 2004;62(suppl. 5):A470.
14. Bendszus M, Warmuth-Metz M, Klein R, et al. MR spectroscopy in gliomatosis cerebri. *AJNR Am J Neuroradiol.* 2000;21:375-380.
15. Juhasz C, Chugani D, Muzik O, et al. PET imaging of recurrent brain tumors using alpha (C-11) methyl-L-tryptophan. *Neurology.* 2004;62(suppl. 5):A470.
16. Raz E, Tinelli E, Antonelli M, et al. MRI findings in lymphomatosis cerebri: description of a case and revision of the literature. *J Neuroimaging* 2011;21(2):e183-6.
17. Sanson M, Cartalat-Carel S, Taillibert S, et al. Initial Chemotherapy in Gliomatosis Cerebri. *Neurology.* 2004;63:270-275.

---

© 2013 Héléage et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Peer-review history:*

*The peer review history for this paper can be accessed here:*  
<http://www.sciencedomain.org/review-history.php?iid=205&id=12&aid=1569>