Gliomatosis cerebri, imaging findings of 12 cases

Gliomatose cérébrale, imagerie de 12 cas

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Available online 23 March 2010

KEYWORDS
Gliomatosis cerebri; Magnetic resonance imaging; Magnetic resonance spectroscopy; Perfusion weighted images; Histology; PET-Scan

Summary
Background and purpose. — We report 12 cases of Gliomatosis cerebri (GC), a rare brain neoplasm, to define its semio logic criteria. Literature was reviewed to clarify its physiopathology.

Patients and methods. — From 1997 to 2008, 12 histologically proven cases with GC were retrospectively reviewed. Of the 12 patients, nine were male. The mean age was of 54 years. Were performed CT-Scan (n = 6), MRI (n = 12), diffusion and perfusion weighted images (n = 12 and n = 4), MR Spectroscopy (n = 3), a FDG and a Methionin PET-Scan (n = 2 and n = 3 respectively).

Results. — Primary diagnosis was missed in six cases. Most frequent clinical signs were seizure and mental changes. Imaging criteria were: area of high signal intensity on FLAIR and T2-weighted images, involving three or more contiguous lobes with conserved architecture. Frequently a bilateral widespread invasion with involvement of the corpus callosum or the anterior white commissure or both was observed. At diagnosis and in the classical form (type I) of GC, no significant contrast enhancement and decreased rCBV were observed. Focal enhancement and increased rCBV were observed in the focal mass in type II GC. MR Spectroscopy showed an increase of the Cho/Cr ratio and a decrease in the NAA/Cr one. FDG PET showed in type I a decreased avidity for the FDG whereas in type II a increased avidity was observed. MET-PET showed an increased avidity for the tracer in a GC type II and a slight avidity in a GC type I.

Conclusion. — GC is a rare brain entity. Primary diagnosis is often missed. The imaging findings of GC I, a WHO grade III tumor, should be known and include classical MRI but also PWI, MRS and scintigraphic findings.

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Gliomatosis cerebri (GC) is a rare and diffusely infiltrating glial tumor. The diagnosis is difficult and often missed because of nonspecific clinical manifestations and imaging findings. Nevin [1] was the first to describe GC in 1938 on the basis of pathological criteria. The definition and classification of this entity evolved over time. In 1993, the World Health Organisation (WHO) classified it as a neuroepithelial neoplasm of unknown origin. Later, in 2007, GC became a diffuse glioma (usually astrocytic) with a growth pattern consisting of exceptionally extensive infiltration of a large region of the central nervous system with involvement of at least three contiguous cerebral lobes. Usually, the involvement of a cerebral hemisphere and/or homolateral deep grey matter expands to the heterolateral hemisphere; more over, frequent extension to the brain stem, cerebellum and even to the spinal cord has been described [2]. Although GC seems to be radiologically a low-grade lesion, GC corresponds usually to a WHO grade III for the classical form (type I) without a focal mass. After the appearance of a focal mass (type II), it processes classically to a WHO grade IV. Before magnetic resonance imaging (MRI), GC was a postmortem diagnosis. In this study, we reviewed conventional MRI, magnetic resonance proton spectroscopy (H-MRS), Perfusion weighted images (PWI), positron emission tomography scan (PET-Scan) and pathological diagnostic criteria.

Patients and methods

Clinical material

We retrospectively reviewed 12 patients with GC from 1997 to 2008. All patients had a histopathologic confirmed GC. Of the 12 patients, nine were male. The mean age was of 54 years, ranging from 10 to 86 years. At diagnosis, the main clinical symptoms were seizure in six patients, mental and personality changes in five patients, dysarthria and aphasia in three patients, headache in two patients, diplopia in two patients and facial palsy in two patients. One patient, suffered from sensory deficit, mydriasis, visual hallucination, amenorrhea and subarachnoid haemorrhage. Three patients developed hemiparesis during follow-up.

Different erroneous diagnosis were proposed in six patients: Schilder disease, inflammatory disease, herpetic encephalitis, cerebral vasculitis, ischemia, metastasis and astrocytoma.

The study was carried out in compliance with our institutional ethic committee (CE Accred. No. 2008/24OCT/297).

Medical imaging

CT-Scans without contrast were performed in six patients and MRI without and with contrast agent were performed in all. MR imaging was performed using 1.5 T MR scanners from different brands (General Electric MS, Philips MS and Siemens MS). In all patients, the minimal study performed included axial T1-weighted sequences without and after administration of contrast agent, axial T2weighted sequence, fluid attenuated inversion recovery (FLAIR) sequence and diffusion weighted images (DWI). The apparent diffusion coefficient (ADC) values were calculated on 10 patients. Perfusion weighted images (PWI) study was performed on four patients. The ADC and the rCBV were measured in the involved white matter and in the normal white matter tissue on FLAIR and T2 sequences (usually in the contralateral side). Three patients underwent a H-MRS with a long TE; two a FDG PET-Scan (Siemens Pet Ecat Exact HR+, Knoxville, TN, USA) and three a Methionin PET (MET-PET) Scan (HR 961, CTI-Siemens, Knoxville, TN, USA).

Data were analyzed using different sequences for precise localization and extension of the lesion, for measurements of signal intensity volume, the presence of hemorrhagic, necrotic or cystic changes and for the enhancement characteristics. ADC, PWI, MRS and FDG and MET-PET were analyzed using dedicated post-processing platforms.

Results

Patient cohort and lesion topography overview are presented in Table 1. Table 2 presents main imaging features.

At the time of diagnosis, eight patients presented a GC type I (without a focal mass) (Fig. 1) and four with a type II (with a focal mass) (Fig. 2). During follow-up, one patient evolved to type II with development of a focal mass.

Two of the six patients who underwent initially a CT-Scan, had a negative examination. In the four positive cases, two patients showed a hypodense infiltrative pattern and two a slightly hyperdense pattern (Fig. 2). In all six CT-Scans, no calcification was observed. The extent of the involvement was typically underestimated in comparison with the MRI (Fig. 2).

All patients showed a low signal intensity area on T1-weighted images (T1-WI) and one patient had an additional focal area of high T1-weighted signal intensity. All patients had an infiltrative lesion with a high signal intensity on FLAIR and T2-WI. The abnormalities were better seen on FLAIR images. No contrast enhancement after Gadolinium intravenous injection was observed in five patients. A very slight enhancing area occurred in three patients with GC type I: two in one area and one in two area. All patients with GC type II showed one or more enhancement foci. Loss of grey-white matter distinction was seen in nine patients in large areas (Fig. 1) and in one patient in a focal area. The area of high signal intensity on FLAIR sequences was homogenous in seven patients and heterogeneous in five patients.

Lesions were bilateral in seven patients, on the left side in four patients and on the right side in one patient. All patient showed three or more involved lobes (including the limbic system): eight lobes were infiltrated in three patients, five lobes in four patients, four lobes in four patients and three lobes in one patient. The corpus callosum was involved in eight patients: the genu in seven patients and the splenium in one patient. The anterior white commissure was involved in six patients whereas the posterior white commissure only in one case. All patients with bilateral widespread invasion had an involvement of the corpus callosum or of the anterior white commissure, or both (Figs. 3 and 4) except in one patient where an involvement of the thalamus was found. All patients had an involvement of the basal ganglia and ten of at least one thalamus. The
<table>
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<th>Anterior commissure</th>
<th>Posterior commissure</th>
<th>Basal ganglia</th>
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''+'' indicates involved and ''−'' indicates not involved.
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<td>Signal T2-weighted imaging</td>
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<td>Decreased avidity</td>
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<td>MET PET</td>
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</table>

"+" indicates present and "−" indicates not present.
brainstem was involved in eight cases and the cerebellum only in one patient (Fig. 3).

The mean tumoral volume at diagnosis was of $514\, \text{cm}^3$ (ranging from 175 to $1075\, \text{cm}^3$). Despite an extensive involvement, architecture was well conserved (Fig. 4). Three patients showed no mass effect and eight showed a slight mass effect characterized by a slight impingement of the homolateral ventricle with or without a small shift of midline structures. Only one patient showed a significant mass effect on the homolateral ventricle with midline shift.

At the time of the first imaging, no necrosis was seen with GC type I. Only one patient, with a GC type II, presented a necrosis of the focal lesion. One patient developed a focal necrosis during follow-up. One patient presented a small haemorrhagic focus in the basal ganglia at diagnosis and one patient during follow-up. No hydrocephaly was found in any patient. One patient showed three small cysts of five millimetres.

DWI was performed on 12 patients and ADC measurements were obtained in 10 patients. Two patients had a diffusively high signal intensity whereas only a slight increase in signal was observed in three patients (Fig. 5). Three had a normal signal on DWI in the infiltrative area. In GC type II, two patients showed one or two foci of high signal intensity. The ADC values were only decreased in one case at 90% but with foci at 140%. The mean ADC value was of 120%.

Figure 1  Patient 3, a 10-old-year boy. A. Axial T2-weighted image shows the diffuse involvement (area of increased signal intensity) of the right hemisphere with extension to the left one. There is only a slight mass effect, in comparison with the abnormal high signal volume. B. Axial FLAIR shows the loss of grey-white matter distinction.

Figure 2  Patient 4, a 62-year-old man, with a Gliomatosis cerebri (GC) type II: focal left capsulo-lenticular mass. A. The CT-Scan without contrast injection shows a subtle capsulo-lenticular lesion with a small mass effect on the left ventricle without deviation of the midline. B. Axial T1-weighted image shows an area of low signal intensity of the left capsulo-lenticular lesion with inhomogeneity of the temporal lobe. C. Axial FLAIR shows more clearly the diffuse involvement and the focal mass.
Figure 3  Patient 4; A, B. Axial FLAIR weighted image shows the extension to the right lobe by the white anterior commissure (A) and involvement of the brainstem (B).

Figure 4  Patient 1, a 17-year-old man; A. Unenhanced CT-Scan shows a diffuse hypoattenuation in the left white matter with a significant mass effect on the left lateral ventricle. B. Axial FLAIR sequence shows an area of high signal intensity of the left white matter with involvement of the corpus callosum. Despite the extensive involvement, the architecture is well conserved.

Perfusion studies were performed on four patients. Two patients, with GC type I, had a rCBV max decreased to 46% (Fig. 6). The two other patients with GC type II had a rCVB max in the diffuse infiltration between 100 and 160% but within the focal nodular lesion a rCVB max of 300% (Fig. 7).

Three patients underwent a H-MRS, both showing an increase in the Cho/Cr ratio and a decrease in the NAA/Cr in one (Fig. 8).

Two patients had a FDG PET, in which a decreased avidity for the FDG was shown for GC type I (Fig. 6). The other one, a GC type II, showed an increased avidity for the tracer in the focal mass.

Three patients underwent MET-PET. One patient with GC type I showed a low activity of the white matter. The two other patients, GC type II, demonstrated an increased avidity for the tracer in the focal high-grade lesion.

Discussion

A recent study of Tallibert et al. [3] analyzing 296 individual cases showed that GC is more common in adults with an incidental peak at the age of 40–50 years (median age in our serie of 54), ranging from one month to 85 years [4]. The incidence of GC seems higher among men than women (sex ratio 1.31 for Tallibert and 3 in our study) although male population is younger (45 for Tallibert and 39 years old in our study).

The most common presenting symptoms described by Tallibert were in concordance with our results (mental status changes, seizures, corticospinal tract deficits and headaches) albeit he described cases of intracranial hypertension, which was not significant in our serie. Other neurological findings such as cranial or focal neu-
rological deficits, papilledemas, spinocerebellar deficits, sensory deficits, paraesthesias, visual disturbances, pain and myelopathy were described [5]. GC is a rare cause of medically resistant epilepsy that may be present in early life. [4].

GC has been divided by some authors into primary, appearing de novo, and secondary subtypes resulting from the spreading of a focal previously primary glioma [6]. Stricto sensu, secondary GC should be excluded from the definition of GC. A glioma localised in the junctional region of frontal, temporal and parietal lobes should be excluded from the GC entity [2]. Primary GC can be subdivided into two entities: type I is described as the classical diffusely infiltrating lesion without formation of an obvious tumor mass, whereas type II GC, that develops from type I, denotes the coexistence of the diffuse infiltrating lesion in association with a tumor mass formation, usually showing features of a malignant glioma. Sometimes this evolution of secondary malignant tumor areas within the diffuse low-grade tumor process can be seen on neuroradiological follow-up examinations [7,8] like in our patient 2. We advocate the use of the term ‘stage’ rather than ‘type’ because the type II seems to be a progression of the type I.

GC is classified by the WHO classification 2007 in the astrocytic tumors group, but it is still a matter of debate whether GC represents a separate entity or rather a subset of a diffuse glioma [8]. Morphometric analyses and a few genetic studies suggested that GC is an extensively infiltrating subform of a common glioma rather than a separate entity [2,13]. Furthermore, some other typical alterations of gliomas such as astrocytomas $EGFR$ gene amplification and PTEN mutations or oligodendroglioma $CDKN2A$ deletions, are rarely seen in GC [8,13].

They are two principal hypotheses for GC pathogenesis (Vates et al. [14]). First, GC results from the neoplastic transformations of all types of glial cells occurring simultaneously in various areas of the brain in a kind of a disease of the glia of the cerebrum (polyclonal origin hypothesis). Secondly, GC results from a single clone of cells and then spreads widely.
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Figure 7  Patient 4; A. post-contrast axial T1-weighted image demonstrating a small left capsulo-lenticular enhancement. B. Axial diffusion weighted images show no significant area of high signal intensity of the diffuse involvement but rather shows an area of high signal intensity of the left capsulo-lenticular focus. C. The perfusion map shows no significant increase of the rCBV max but shows an increased rCBV max to 300% in the left capsulo-lenticular lesion.

(monoclonal origin hypothesis). Even if it seems to have now better evidence that most GC have a monoclonal origin, no conclusive data has yet been reached [14,15].

The pathological diagnostic criteria were defined in 1943 by Scheinker and Evans [9]. GC induces a diffuse enlargement of affected regions with preservation of the general configuration [10]. GC involves the normal brain tissue by a proliferation of glial cells that frequently resemble astrocytes, with fusiform or oval and often hyperchromatic nuclei (Fig. 9). When they involve myelinated tracts, the cells often form parallel rows following axons reflecting local histochirchitecture. Myelin sheaths may be destroyed [11], but with only slight involvement of the axis cylinder and nerve cells [10]. They are no cellular or centrally necrotic center [12] and microvascular proliferation is usually absent in classical stage I GC. Mitotic activity is variable. Perivascular cuffs of inflammatory cells are usually absent. There is, therefore, any real specific signs of GC on pathological findings. An important missed data with biopsy is the fact that the architecture of the surrounding tissue is conserved. Although the stage I of GC usually demonstrates histomorphological features of a low-grade tumor, the overall biologic behavior corresponds at least to WHO grade III [2] and the progression to a secondary highly malignant tumor (stage II) regions may occur [13].

CT is not the adequate technique to analyze GC. The CT appearance is variable, and ranges from normal or subtle mass effect on ventricles to increase or decrease area density. These signs are important to recognize and a complete MRI workup is then mandatory.

Figure 8  The MR spectroscopy of patient 1 shows an increased Cho/Cr ratio, a decreased NAA/Cr ratio and an elevated Cho/NAA level. The Cr level is slightly increased.

Figure 9  Gliomatosis cerebri (GC) involves the normal brain tissue by proliferation of glial cells that frequently resemble astrocytes, with fusiform or oval and often hyperchromatic nuclei.
The extent of the involvement is always underestimated.

New imaging techniques combined with biopsy and pathological analysis are nowadays the gold standard [16]. MRI is the most commonly used imaging technique for evaluation and patients follow-up.

The main morphological characteristic of GC is its diffuse and contiguous growth pattern, which involves white matter of at least three cerebral lobes.

The most commonly involved areas, based on post-mortem studies [2], are the cerebrum (76%), the mesencephalon (52%), the pons (52%), the thalamus (43%), the basal ganglia (34%), the cerebellum (29%), the medulla oblongata (13%), the hypotalamus, the optic nerve and chiasma, and the spinal cord (each 9%). When the lesion involves the cerebral hemispheres, the centrum semi-oval is always affected, whereas the cerebral cortex is infiltrated only in 19% of such cases, with spread to the leptomeninges in 17%. In our study, the lesion was often located bilaterally with a predilection for the right side of the brain. The basal ganglia were always involved and the cerebellum only in one case. The right predilection of the lesion was not confirmed in our serie in which we had a global predilection for the left side, explaining the higher percentage of dysarthria and aphasia observed in our patients’ cohort. On the other hand, in bilateral lesions, there was always an involvement of the corpus callosum and/or the anterior white commissure or in one case the commissural thalamic fibres. In equivocal cases, corpus callosum infiltration helped us in differentiating GC case the commissural thalamic fibres. In equivocal cases, the spread of tumor along white matter tracts, such as corticospinal tract, when present, are therefore highly suggestive of GC [9,11]. The diffuse enlargement of the involved cerebral structures is also characteristic. The mass effect is minimal or absent compared with the extent of tumoral [10]. Hydrocephalus is rare.

On T1-WI, the involved areas are iso- or hypointense. Area of elevated signal on T2-WI most likely reflects tumoral spread but may also represent secondary destruction of myelin fibres [10]. The presence of asymmetrical or heterogeneous distribution of areas of high signal on T2-WI and overall on FLAIR together with a thickening of the corpus callosum and/or the absence of clear delineation between white and gray matter are often suggestive of GC [10]. The FLAIR sequences are the most helpful. We used this sequence to calculate the volume of the lesions, to see the distribution and the extent of the lesions. We used the T2-WI to clarifying some extensions and to analyze the posterior fossa.

Contrast enhancement is absent or seldom observed in the classical form of GC (stage I), but is usually present in the stage II. The relative preservation of the blood brain barrier is thought to be the underlying reason for the absence of contrast enhancement in GC. The focal enhancing lesions probably correspond to areas of anaplastic transformation [11]. Vascular proliferation, nodular enhancement and necrosis are typically absent of the GC stage I [18] but are malignant features that appear with GC stage II [19].

On DWI, they are no usually area of elevated signal, seldom an area of a slightly elevated signal may be depicted, like the signal found in the hypercellular tumors, but lower than the signal of an acute vascular cerebral ischemia. Thus, the elevated signal on DWI reflects the T2-weighting of the tumor and the shine through effect. The ADC is not decreased (in our serie, the mean ADC was about 120%).

The classical form of GC shows a very low rCBV on perfusion studies whereas a low-grade tumor or inflammatory lesion has rather a normal rCBV than a low rCBV. This low rCBV level is unusual for a lesion of this severity (WHO grade III). Those features are important to recognize for an eventual GC diagnosis. This low MR rCBV measurements seems to be in concordance with the lack of vascular hyperplasia found at histopathologic examination [18]. In our serie, the rCBV of the focal mass of patients with GC stage II was increased, probably due to a neoangiogenesis induced by the focal degeneration of the lesion. In GC stage II, perfusion studies are very useful for the analysis of high-grade malignant lesions.

MR spectroscopy (MRS) is a non-invasive diagnostic method that can be used for metabolic characterization of brain tumors [20]. The study is essentially based on the analysis of the choline (Cho), \( \nu \)-acetylaspartate (NAA) and creatin (Cr) peaks. In the classical form of GC, increased Cho/Cr and Cho/NAA ratios and variably decreased NAA/Cr ratio are found in the abnormal areas on T2-WI [12,21].

The Cho peak seems to be more related to tumor proliferation and high-grade tumors than the NAA level [20]. The increase of Cho/Cr and Cho/NAA ratios indicate malignant progression of a brain tumor. So, MR spectroscopy might be used to classify GC as a stable or a progressive disease with potential therapeutic relevance [23]. The area of maximum Cho/NAA increase may be used to assess the overall tumor grade and also to determine a target for stereotactic biopsy [23]. MRS should be helpful to distinguish GC from low-grade glioma. However, it has been reported that both GC and low-grade gliomas are characterized by elevated concentrations of Cho and reduced NAA. Normal to mildly elevated Cho/Cr ratios together with elevated Cho/NAA ratios might favour the diagnosis of GC rather than low-grade glioma [24]. A recent study also stated that creatin levels were elevated in patients with GC and reduced in those with low-grade gliomas [25]. Recent studies have reported a high level of myo-inositol (myo-In) in patients with GC [22].

FDG PET shows decreased uptake in the involved areas of GC, which is a non-specific findings to provide a definitive diagnosis [26].

Increased uptake on MET PET strongly suggests neoplasia and is present in GC area.

MET PET is valuable for differentiating GC from non-neoplastic diseases showing similar findings on T2-WI [26]. The usefulness of F\( \alpha \)-Methyl Tyrosine PET (FMT PET) seems to be, on preliminary study, valuable to differentiate GC from non-neoplastic diseases [26].

The differential diagnosis of GC includes all the lesions with diffuse involvement of the white matter. Like described by Yu A et al. [21], the most important alternative diagnosis for the GC stage II concerns the entity of low or intermediate grade tumors. Heterogeneous signal intensity, presence of necrotic, cystic and hemorrhagic changes and an irregular ring-like contrast enhancement zone are characteristic MRI findings of glioblastoma multiform and infiltrating malignant glioma, that are different from GC [21]. The difficulty arises when the differential diagnosis must be done between
a secondary glioblastoma multiform in the evolution of a GC [27,28] or in the case of a primary one. A distinction is made between GC and a multicentric glioma. GC refers to tumor with contiguous involvement of different regions, whereas a multicentric glioma is defined as distinct foci of tumor in different sites [18]. It can be extremely difficult to distinguish GC from diffuse glioma presenting with widespread contiguous tumor infiltration into adjacent brain tissue [10]. The glioma and more particularly oligodendroglioma show necrosis, cysts and calcifications but the main feature differentiating a conventional glioma from a GC is the presence of mass effect.

The second differential diagnosis for the stage I GC are white matter diseases and demyelinating lesions such as such as Marburg disease. Shin et al. [17] reported that involvement of the corpus callosum is helpful in differentiating GC from demyelinating diseases in equivocal cases. Finally, other alternative diagnosis for stage I GC are infections (eg. viral encephalitis, AIDS-associated progressive multifocal leukoencephalopathy), Behcet’s disease, ischemic cerebrovascular diseases, vasculitis, venous sinus thrombosis, post-treatment changes (eg. after irradiation) and some metabolic disorders.

The prognosis of GC is generally poor, the recent study of Tallibert et al. [3], which analyzed 296 individual cases, shows a median survival time of 14.5 months (between 25 days to 22 years). It is higher for patients younger than 42 years (17 months vs. 13 months), 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 GC and 11 months for astrocytic GC). The presence of an oligodendrogial component is predictive of a better outcome. Male population is usually younger (median 39 years vs. 45), has a higher incidence of oligodendroglial GC (22% vs. 13%), which may explain their better prognosis (median survival 17 months vs. 11.5 months) than female population. Age inferior to 10 years and contrast enhancement on MRI studies at diagnosis may be poor prognostic factors [16].

The combination of widespread tumor infiltration with minimal central nervous system destruction, which is frequently present in the classical GC makes an initial chemotherapy approach particularly attractive [29]. Some data suggest that chemotherapy is superior to supportive care and provides a benefit compared to radiotherapy in terms of benefit/ risk ratio [30]. Initial chemotherapy, by Procarbazine-CCNU-Vincristine (PCV) or by Temozolomide (TMZ) is clinically helpful for 33% of patients and produced an objective radiologic response in 26%, with an overall median survival of 29 months [30]. In this setting, TMZ is thus well tolerated and appears to be a valuable alternative to PCV, especially for slow-growing, low grade GC [6]. It should be noted that once chemotherapy fails, radiotherapy is still an option for these patients [29].

Conclusion

GC is a rare brain entity. The primary diagnosis is often missed. The stage I of GC is the classical form without focal mass and is generally a WHO grade III tumor. GC stage I can evolve in stage II with the appearance of at least one focal mass, increasing the GC in a WHO grade IV tumor with neoangiogenesis, necrosis and mitosis. GC has to be suspected when a patient with seizure or mental status changes present on FLAIR sequences a diffuse growth pattern with involvement of at least three contiguous cerebral lobes. The imaging findings have to be known and include classical MRI but also PWI, MRS and scintigraphic ones. Those additional findings permit to precise the diagnosis, to differentiate the stage I from the stage II, to determine a target for stereotactic biopsy and for are useful for follow-up.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgement

I would like also to thank the Professor B. Balériaux and the Doctors P. Borremans, P. Reginster, M. Ruelle for their help. I would like finally to thank my wife, Marie-Laure, for her help, her support and her comprehension.

References


