"GLIOMATOSIS CEREBRI" SIMULATING AN ACUTE DIFFUSE ENCEPHALOMYELITIS

CASE REPORT

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ABSTRACT - Neuroradiologic, neuropathologic and immunohistochemical features are reported in a young man with a impairment of the central nervous system mimicking an acute diffuse encephalomyelitis. A white male, 17 years old, healthy till 4 months before, when developed a right hemiparesis and after 2 months a bilateral hemiparesis with a progressive impairment of several cranial nerves. Magnetic resonance imaging showed multiple lesions without a mass effect that suggested myelin loss. He remained unconscious for almost one month before dying of pneumonia. The neuropathologic examination showed a heavy brain (1505 g) with herniations and a large right midbrain. There were several soft and pink areas mainly at the right midbrain, left cerebellum and in the white matter of the left cerebral hemisphere. The histopathologic sections showed diffuse blastomatous proliferation without total replacement or destruction of the original tissue. The tumor cells had astrocytic, oligodendrocytic and spongioblastic phenotypes, some of them with a GFAP-positive reactivity. There were focal anaplastic changes. The diagnosis of "gliomatosis cerebri" was only possible by the autopsy.

KEY WORDS: Gliomatosis cerebri, neuroradiology, neuropathology, brain, tumour.

"Gliomatosis cerebri" simulando encefalomielite disseminada aguda: relato de caso

RESUMO - São relatados os aspectos neurorradiológicos, neuropatológicos e imuno-histoquímicos em um paciente jovem com comprometimento do sistema nervoso central simulando encefalomielite aguda disseminada. Paciente masculino branco, com 17 anos de idade, hígido até há 4 meses, quando desenvolveu hemiparesia direita e, após 2 meses, hemiparesia bilateral com comprometimento progressivo de vários nervos cranianos. A imagem de ressonância magnética mostrou lesões múltiplas, sem efeito de massa, sugerindo perda da mielina. Permaneceu inconsciente durante quase 1 mês, com óbito decorrente de pneumonia. Na autópsia o encéfalo pesou 1505 g, com hérnias e tumefação do hemitronco direito. Havia várias áreas moles e rôseas principalmente ao nível do hemitronco direito, cerebelo esquerdo e substância branca do hemisfério cerebral esquerdo. A histopatologia evidenciou proliferação blastomatosa difusa sem substituição ou destruição do tecido original. As células neoplásicas apresentavam fenotipos astrociticos, oligodendrociticos e espongioblasticos, algumas delas com reatividade positiva para GFAP. Havia transformação focal anaplásica. O diagnóstico de "gliomatosis cerebri" apenas foi possível com a autópsia.

PALAVRAS-CHAVE: gliomatosis cerebri, neuroradiologia, neuropatologia, cérebro, tumor.

"Gliomatosis cerebri" (GC) is a rare disease whose diagnosis for certain is very difficult during life. Nevin17 in 1938 introduced the denomination GC, postulating that the neoplastic changes should originate from different areas of the brain and were not the result of dissemination by continuity.


The object of this report is to present a case of GC in a young adult with symptoms of central and peripheral nervous system involvement, with rapidly progressive course, whose initial diagnosis was acute disseminated encephalomyelitis (ADEM). The confirmation of the diagnosis was possible only by the post mortem examination.

CASE REPORT

EA, male, white, 17 years old, seen on June 6, 1995 with a one month history of slowly progressive numbness on the left side of the face, dizziness and unbalance on walking, jumbled speech and blurred vision. There were no relevant familial and personal antecedents. He denied infections and contact with toxic compounds. He had been admitted to another hospital with the diagnosis of multiple sclerosis and treated with Solumedrol 500 mg/day, for 4 days without improvement. The neurologic examination showed mild tetraparesis, with a slight left predominance, ataxia of the four limbs and on walking. Generalized increase in reflexes. Normal sensibility. Cranial nerves: peripheral left facial paralysis. The examination of the fundus of the eye showed mild bilateral pallor of the temporal edges. He was treated with prednisone, 60 mg/day. Laboratory tests: blood count, glicemia, urine, creatinine, electrophoresis of proteins, ESR, mucoproteins, liver function tests, LE cells and anti-HIV were normal. The cerebrospinal fluid (CSF) examination was normal, with normal IgG. The magnetic resonance imaging (MRI) showed focal images in midbrain, middle cerebellar peduncle and left semi-oval substance, with mild hyperintensity in T1, without contrast, and faint hyperintensity in T2.

On July 25, 1995 the patient was re-admitted in the hospital because his symptoms had worsened. The neurologic examination showed tetraparesis, more pronounced on the right, disphasia, paralysis of the conjugated lateral gaze to the right, peripheral left facial paralysis and ataxia. He was treated with intravenous metilprednisolone, 500 mg/day and on the third day developed bronchopneumonia with respiratory failure, being removed to the ICU, where he remained for 15 days. He was transferred back to his room with tracheostomy. He deteriorated gradually, progressed to coma and died of bronchopneumonia on September 16, 1995. The laboratory tests were normal, including the CSF with normal IgG. The brain MRI (Fig 1) showed enlargement of the previous lesions and new lesions affecting the depth of the left cerebral hemisphere, including the lentiform

![Fig 1. MRI shows hyperintensity in T2 at basal ganglia and at left frontoparietal semi-oval substance(A). Identical aspect in midbrain, bilateral middle cerebellar peduncles and left cerebellar hemisphere (B).](image-url)
nucleus and the internal capsule, besides the cerebellar middle peduncle on both sides. The electroneuromyography was consistent with peripheral neurologic process.

The *post mortem* neuropathological study showed edema of the brain (weight: 1505 g), swelling of the right cerebelar amygdala and of the uncus, bilaterally. Externally the volume of the right midbrain was increased, with edematous aspect, and the left cerebellar hemisphere was mollified. The sections presented several pink mollified areas, without neat limits with the surrounding parenchyma, in the right midbrain, left cerebellum and left frontoparietal cerebral hemisphere (Fig 2). The histopathologic study showed neoplastic proliferation in

![Image of brain sections](image)

*Fig 2. Mollified pink area in the left frontoparietal cerebral hemisphere (A). Another area with identical aspect at pons, cerebral peduncles and at left cerebellar hemisphere (B).*
Fig 3. Cerebellar cortex permeated with neoplastic cells. HE X200 (A). Medulla oblongata with neoplastic cells permeating bundles of fibers. HE X200 (B). Brain stem showing neoplastic cells ressembling astrocytes and oligodendrocytes. HE X400 (C).

several focuses, many permeating bundles of fibers, without substitution of the organ structure, with hypercellularity formed by cells sometimes elongated with fascicular arrangement in several directions, othertimes round, ressembling astrocytes and oligodendrocytes (Fig 3). The neoplastic cells were diffusely positive to S-100 protein and many were positive to GFAP (glial fibrillary acid protein). Many bizarre giant cells were also present and there were scattered foci of micronecrosis surrounded by glomeruloid endothelial proliferation. The midbrain was severely affected, as well as the cerebellum, wherein the permeative aspect of the dissemination was apparent, without total destruction of the structure. There was also neoplastic dissemination on the surface of the molecular layer of the cortex on the adjacency of the brain and cerebellum lesions, and a subependymal area of neoplastic dissemination. In the spinal cord there was only subarachnoid dissemination. The peripheral nerves had no changes at the optical microscopy. The other organs were not examined at the family's request.
DISCUSSION

"Gliomatosis cerebri" corresponds to an extreme form of diffusely infiltrative glioma affecting extensive areas, and sometimes, the most part of the brain. It is a rare disease, whose diagnosis is presumed in lifetime and only confirmed by histology and, in general, by autopsy.

Nevin in 1938 introduced in the literature the denomination GC, considering it a disgenetic abnormality of the neural system, postulating that the neoplastic changes should origin from different points of the brain and should not be a product of dissemination by continuity. Eversince more than a hundred cases have been reported.

Sheinker and Evans, in 1943, established the pathological criteria to be fulfilled: 1) diffuse enlargement of the affected areas; 2) dissemination and large extension of the process; 3) absence of demarcation between normal and affected areas; 4) microscopic proliferation of glial neoplastic cells that infiltrate the nervous system along the "intersticial paths of the connective tissue"; 5) partial damage of the nervous system characterized by destruction of myelin but with mild involvement of the axons and nervous cells. These criteria are still valid, although its differentiation with diffusely infiltrative solitary gliomas and multicentric gliomas is not well established.

In our case the clinical picture, the CSF and the brain MRI suggested that the patient had acute disseminated encephalomyelitis, despite the absence of immediate antecedents of viral infection.

The diagnosis of multiple sclerosis must not be defined as an initial monophasic feature. The CSF examination in patients with multiple sclerosis shows increased IgG. In the present case the normality of CSF IgG (in two occasions), the electromyography showing peripheral changes of the nervous system and the rapidly progressive clinical course seemed to confirm the clinical suspicion of ADEM.

The literature reports that the clinical diagnosis of GC is difficult due to the diversity of symptoms and the negativity of the majority of the laboratory tests and radiologic examinations. In the late stages of the disease appear neurologic focal signs that are, in general, profound mental impairment, changes of personality, convulsive seizures and intracranial hypertension, the clinical features being disproportional to the extension of the brain involvement. The duration is extremely variable, can be slowly progressive, and the course can vary from weeks to 20 years after the first symptoms, with two peaks of incidence, in the second and in the fifth decades. There are cases reported of children under 1 year of age, with uncontrolled epilepsy. The CSF analysis in GC is in general normal. There is only 1 report of cytologic diagnosis in the spinal fluid.

Russell and Rubinstein observed the majority of their cases in the 1st and 2nd decade, with macroscopic and microscopic aspects very similar to the diffuse brain astrocytoma. Incidentally, the majority of the cases reported in the literature are macroscopically and microscopically similar to diffuse brain astrocytomas.

As to the neuroradiological aspects, the imaging studies frequently underestimated the extension of the disease. Koslov et al. correlated, in their case, the computed tomography (CT) and MRI aspects before and after death, suggesting that a poor demarcation between the white and gray matter in the MRI may indicate neoplastic infiltration. Tomographic studies by positron emission (PET) with carbon 11-L-methionine showed an accurate correlation in the areas of diffuse tumoral infiltration, more evident and larger than the images detected by TC and MRI. Recently Shin et al. compared the findings on TC and MRI in 9 patients, with neuropathological confirmation, and concluded that the resonance is more sensitive than the tomography in the detection of lesions and their extension, suggesting that the MRI should be the first imaging examination in the evaluation of GC. Other authors have emphasized the use of MRI, or even better of PET, in GC, always correlating them with the pathological study, by stereotaxic biopsy or autopsy. Nevertheless the studies with resonance still underestimate the extension of the tumor, when compared to the post mortem findings.

A recent review of GC, done by Jennings et al., showed that, in 151 cases, the most frequently affected areas the of CNS, mostly by post mortem examination, were: oval center and cerebral hemispheres (76%), mesencephalon (52%), pons (52%), thalamus (43%), basal ganglia (34%),
cerebellum (29%), corpus callosum and fornix (25%), leptomeninges (17%), bulb (13%), hypothalamus (9%), optical nerve and chiasm (9%) and spinal cord (9%). In 13% of the autopsies there were evidences of uncus and/or cerebellar amygdalas herniation.

The nature of the cells involved in GC is uncertain, for the glial cells recall spongioblasts, astrocytes or oligodendrocytes. The consensus in the literature in the last 50 years is to consider GC rather a glial neoplastic proliferation with several degrees of anaplasia than an anomaly of development or a hamartoma.

Histologically it includes astrocytic elements with varied degrees of polymorphism and small round cells of glial origin. The concentration of small glial cells in the molecular layer of the cortex and their elongated form with "spongioblastic" aspect have been strongly emphasized. Nevertheless, these quoted aspects could be sufficient to distinguish this kind of growth from that seen in the astrocytomas group. According to a review, different degrees of glial neoplasia may coexist in GC, such as astrocytoma, anaplastic astrocytoma, atypical or anaplastic oligodendroglioma, multiform glioblastoma and small undifferentiated cells. Glial polimorphism, "transitional" glia and secondary structures of Scherer - satelitis, pial diffusion and para-ependymal diffusion - were also described. GC may be a neoplastic proliferation almost exclusively of oligodendrocytes. Artigas et al., in their report of 10 cases, mentioned the finding of typical areas of oligodendrogioma in two cases.

The ultra-structural aspects were also described. According to Cérvos-Navarro et al., GC could be a neoplastic process of small undifferentiated elements, transitional forms from astroglia to oligodendroglia, and anaplastic forms of astrocytic origin in all stages of development.

The immunohistochemical findings in GC are consistent with these subcellular results. The GFAP was positive in most cells in 7 out 10 cases of Artigas et al. Galatioto et al. reported in their case that most proliferated cells were positive to GFAP and/or S-100 protein, but there were variable amounts of unstained fusiform cells, whose nature was not established. Other authors found positive GFAP cells inconstant, accounting for about 20% of cells in the hypercellular areas. Ng reported a case with astrocytic tumoral cells and microglia. Wilson et al. documented in their case, tumoral cells with weak or moderate reaction to GFAP, in contrast to reactive astrocytes strongly positive, and weak reactions to vimentine.

Several studies evaluated the proliferative potential of neoplastic cells in GC, concluding that in this entity there is an invasive feature in the central nervous system (CNS), which frequently shows a tendency to malignancy, but has proliferative potential significantly smaller than the low-grade gliomas. As to prognosis, radiotherapy has a questionable value, chemotherapy is of little value and steroids may be useful in short term. In long term any therapy was effective, and the prognosis remains poor.

It has to be mentioned that there are very rare cases which developed GC after previous treatment of other malignancy.

Zülch defined GC as a diffuse blastomatous growing of glial cells in one or both brain hemispheres, with variable degrees of differentiation. The neoplastic cells could resemble spongioblasts, astrocytes or oligodendrocytes and might contain circumscribed focuses of multiform glioblastoma. He recommended that this entity should be differentiated from other similar diseases such as diffuse gliomas and multicomponent gliomas. As to age in incidence, he stated that GC seems to be more frequent in the middle age. As to topography, it may affect the deep white matter of brain hemispheres and cerebellum, the midbrain, the spinal cord, or all these structures. He emphasized that despite the diffuse enlargment of the affected structures, there was a rough preservation of the original form of the affected brain structure. Small focuses of necrosis and bleeding may occur, associated with anaplastic transformation.

According to the 1993 edition of World Health Organization, GC is a "diffuse infiltration of neoplastic glial cells in the brain, affecting several brain lobes and, in some occasions, infratentorial
structures and the spinal cord". The neoplastic cells vary in shape from oval to elongated and also as to atypia and mitotic activity. They seem to migrate between the myelinated paths without destruction of the brain parenchyma. The lack of reactivity to GFAP is very common, perhaps reflecting the loss of differentiation, and a focal transformation into glioblastoma may occur. It corresponds histologically to the degrees III or IV.

According to the 1993 edition of Armed Forces Institute of Pathology, GC is an "extraordinary diffusely infiltrative glioma that may affect the supratentorial compartment, the posterior fossa or even the intra-spinal parenchyma, sometimes in continuity". It is controversial whether it is a disease or represents a group of histogenetically different tumors with a tendency to diffuse infiltration. The term GC is in general restricted to lesions where the infiltrative capability is beyond the degree of anaplasia and the tendency to form cellular masses. In the past the diagnosis was made by autopsy, but currently it is established by sensitive neuroradiologic techniques such as MRI, which shows a diffuse increase in T2. The disease affects all ages. Macroscopically it may be well defined or not; in some cases there is a mass effect; the process may be diffuse and affect all levels of the CNS; the midbrain and the spinal cord are affected only in unusual cases. Microscopically there is a broad variation in the cytologic and histologic aspects, and the cellularity is quite variable. The proliferated cells look like astrocytic elements and their aspect ranges from benign to frankly malignant, with formation of secondary structures but with mild destruction of the pre-existent parenchyma. Mitosis are not common and vascular proliferation and necrosis are absent. Nevertheless, in some cases one can observe focal anaplastic changes. There are occasional lesions of GC reported with oligodendrocytic elements. In some elongated cells the immunohistochemistry shows positivity to GFAP, which is apparent in the star cells with astrocytic phenotype seen in the secondary structures. As to the biologic behaviour, GC is not cured by surgical resection because of its infiltrative feature, and its clinical course is quite variable. Nevertheless, it is expected that the cases with cytologic malignancy and high mitotic index be more aggressive than the cases with quiet nucleus and without mitosis.

These findings fulfill the criteria for the diagnosis of GC. However, one must consider the hypothesis of diffuse glioblastosis, glioma in multiple focuses and solitary diffusely infiltrative glioma, because the differential diagnosis of these entities is highly controversial and discussed in the literature.

Russell and Rubinstein point out the diffusion of the process, for there are cases where, besides the cerebral affection, there is extension to the cerebellum, midbrain and even to the spinal cord. They argue that the secondary structures observed in GC originate from several areas. Therefore they consider not reasonable the interpretation that the diffusion of the process should be a result of the diffuse infiltration from one solitary focus.

In our case, countless areas of neoplastic proliferation were seen in the cerebral hemispheres, cerebellum and midbrain, with dissemination through secondary structures in the surrounding areas. These structures were more apparent at the level of the molecular layer of the cerebellar cortex. The rarity of cerebral and cerebellar tissue not affected is outstanding.

Another aspect observed in our case was the focuses of malignant transformation, with micronecrosis, endothelial proliferation and pleomorphism with bizarre giant or multinucleated cells, many of them GFAP-positive, with frankly glioblastomatous aspect. Nevin identified, in his second case, an area of anaplasia, with morphology of glioblastoma. It is referred in the literature the presence of focal areas of anaplastic transformation in some cases, in several cases, and even the finding of circumscribed focuses of glioblastoma. Russell and Rubinstein even justified that, for this reason, they had included GC in the diffuse cerebral astrocytomas.

As to the superficial cortical layer and subependymal neoplastic dissemination observed in our case, others have also seen it in large extension of the neuraxis, without the development of
a definite tumor mass, and in four cases found meningeal and ventricular secondary gliomatosis. Another interesting feature in this case is the spinal fluid examination, normal in two occasions, also reported by others\textsuperscript{7,8,9,10}.

Currently\textsuperscript{11} GC is considered an uncommon form of glioma, representing a distinct clinic and pathologic entity. It has therefore macroscopic and/or radiologic features that demonstrate the diffuse affection of the CNS and microscopic features quite different from those observed in the diffuse glioma. Certainly it has not been fully reported, for the infiltrative nature of the lesion may not be apparent during the lifetime.

Finally, it is important to point out that the definitive diagnosis can only be made by autopsy, as shown in most of the reported cases including the latest ones\textsuperscript{9,25,29} and the present case.

REFERENCES


