Author's reply

Dear Editor,

We want to thank the authors for the comments on our article. The authors explain that, at any moment, they have focused their concerns on the criteria to define metabolic syndrome, because if such definition does exist,[1] consensus criteria for diagnosis in adults do not exist,[2,3] neither do they in adolescents. In our article, our concern lay in demonstrating the presence of risk factors in a randomly selected sample and that these risk factors exist in such proportions that they can be grouped together, and, according to one of the several criteria suggested in the literature, based on pediatric reference values, they can give rise to the so-called metabolic syndrome. Therefore, we have not proposed an analysis of the associations between risk factors.

The authors believe that discussing criteria which have not reached consensus[2,3] leads to a shift in focus from the seriousness of the presence of isolated or associated risk factors at such an early life stage, and that a simple aggregate of such and such factor, in order to reach a diagnosis of metabolic syndrome, would mean admitting that the syndrome implies a higher risk than its components or that it is more severe than other risk factors for cardiovascular disease. For this reason, due to lack of scientific support, we do not concur with such conclusions. It is worth mentioning that some studies[4-6] have shown that risks attributed by the metabolic syndrome are not higher than the sum of its components, that is, the syndrome is not greater than the sum of its parts. Thus, all risk factors need to be fought individually, with no need for percentages of the syndrome for such and such criterion in order to enhance treatment, prescription and encouragement of healthy life habits.

Finally, the precursor of the idea of metabolic syndrome, Reaven,[7] in a recent review, has questioned the syndrome: "metabolic syndrome – rest in peace."

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Primary diffuse leptomeningeal gliomatosis: a rare disease in pediatric patients

Dear Editor,

The recent report about a rare pediatric brain tumor by Val Filho & Avelar[1] is interesting and deserves high consideration within the published literature about the topic, since it represents a very rare event. On behalf of its scientific accuracy, we must therefore make a major amendment about its diagnosis.

The authors made an adequate brief review about gliomatosis cerebri, a rare disease classified by the 2007 edition of the World Health Organization (WHO)[2] as a grade III lesion with poor prognosis. It was first described by Nevin in 1938[2] and is defined as "a diffuse glioma growth pattern consisting of exceptionally extensive infiltration of a large region of the central nervous system, with involvement of at least three cerebral lobes, usually with bilateral involvement of the cerebral hemispheres and/or deep gray matter, ..."[2] The main theory accepted to explain its origin is that it represents a subtype of otherwise ordinary diffuse glioma characterized by exceptional infiltrative capacity, classically without forming a tumor mass lesion.[2] It is a rare kind of lesion, with only few hundreds of cases described, less than 30% of them occurring in children. Although 17% of gliomatosis cerebri cases were reported as having additionally leptomeningeal involvement, this finding is not sufficient to make such diagnosis when isolated.[2] The WHO classification text further states that "gliomatosis cerebri should be distinguished from two other types of gliomatosis, i.e. leptomeningeal gliomatosis and gliomatosis peritonei. Leptomeningeal gliomatosis is the widespread infiltration of the subarachnoid space by a diffuse glioma, most commonly an intra-axial glioma that has invaded the leptomeninges (secondary leptomeningeal gliomatosis), or, rarely, leptomeningeal spread of a glioma originating in an ectopic leptomeningeal glial or glioneuronal rest (primary leptomeningeal gliomatosis)."[2]

These characteristics resemble the case reported by Val Filho & Avelar,[1] in which initially a diagnosis of obstructive hydrocephalus was made followed by the finding of "lesions scattering throughout the subarachnoid space, mainly in the posterior cranial fossa. These lesions diffusely covered a large part of the encephalon (...)."[1] Unfortunately, the image they pictured has no identification of the type of magnetic resonance imaging (MRI) sequence, but it is probably contrast-enhanced T1-weighted spin-echo. Although T2w/FLAIR images are the preferred studies for diagnosis of gliomatosis cerebri,[2] one can clearly see in their sequence of images that there is not an extensive involvement of the brain parenchyma.[1] Thus, their case report does not fulfill the criteria published by the WHO for the diagnosis of gliomatosis cerebri, but can be classified more properly as a very rare case of primary diffuse leptomeningeal gliomatosis (PDLG) in a young child with prolonged survival.

The first report of PDLG was published in 1954 by Moore. It is described more frequently along the spinal cord and associated with central nervous system (CNS) congenital dysraphism.[3] It must be distinguished from secondary meningeal gliomatosis, where there is leptomeningeal invasion by neoplastic diseases of the CNS parenchyma, especially oligodendroglioma,

medulloblastoma and gliomatosis cerebri. The diagnosis of true PDLG is exceptional and a report by Debono et al., in 2006, reviewed the literature so far and found 30 cases published, only nine of these cases in children aged 9-17 years old.[3] Since then, we have found additional 10 cases including Val Filho & Avelar's (Table 1), and seven more cases reported recently by Dörner et al.4 in their review that Debono et al.[3] did not cite. Of these, five were found in children aged 2-17 years old. This sums 47 cases reported in the literature, of which 14 in children. Definitive diagnosis of PDLG classically need postmortem detailed description,[3] and this fact would reduce the number of cases reported to 36.

Table 1 - New cases of PDLG published after the reviews of Debono et al.[3] and Dörner et al.[4]

Reference	Age (years), Sex	Meningeal site	Presentation	FU (months)	Diagnosis	Surgery	PO	Treatment	PM	Histology
1. Francischi E et al. J Neurooncol. 2005;73:261	40, Female	Diffuse	Ataxia, incontinence	17	Hydrocephalus	Yes	High grade	Temozolomide	No	Gliomatosis
2. Bohner, G et al. Acta Neuropathol. 2005;110:306	25, Male	Spinal, left temporal	Gait ataxia, Lhermitte´s sign, double vision, right abducens palsy	2	Benign IH	Yes	WHO grade I	CT w/ vincristine, carboplatin	Yes	Pilocytic astrocytoma*
3. Bourne, TD et al. J Neurosurg. 2006;105:465	2, Male	Diffuse	Malaise, anorexia, nausea, vomiting, macrocephaly	15	Leukodystrophy	Yes	Meningeal gliomatosis	HDC w/ vincristine, cisplatin, cyclophosphamide, etoposide + etoposide, cyclophosphamide, temozolomide, isotretinoin	No	Oligoden-droglioma†
4. Ozkul A et al. J Neurooncol. 2007;81:75	25, Female	Diffuse	Paraplegia, sensory loss	15	–	No	–	–	Yes	Oligoden-droglioma
5. Yomo S et al. J Neurooncol. 2007;81:209	52, Male	Diffuse	Coma, signs of IH	3	Meningitis	Yes	WHO grade III	RT, ranimustine, interferon	Yes	Anaplastic astrocytoma
6. Watanabe Y et al. J Neurooncol. 2008;86:207	48, Female	Left frontal, temporo-parietal, sylvian, cistern, spine	Headaches, right arm numbness, double vision	11	–	Yes	WHO grade IV	RT, ACNU, interferon	Yes	Gliosarcoma
7. Gonçalves AL et al. Arq Neuropsiquiatr. 2008;66:85	13, Male	Diffuse	Seizures	96	Encephalitis, hydrocephalus	Yes	WHO low grade	Temozolomide, cisplatin, etoposide, valproate	No	Low grade glioma
8. Ko MW et al. J Neurol Sci. 2009;278:127	24, Male	Inter-peduncular, cistern, spinal	Headache, back pain, vomiting, double vision, left facial weakness	6	Hydrocephalus	Yes	Chronic inflammation	Levetiracetam, steroids, cyclophosphamide	Yes	Anaplastic astrocytoma
9. Dörner L et al. Surg Neurol. [in press, epub]	2, Female	Diffuse	Somnolence, strabismus, vomiting	29	Meningeal inflammation	Yes	WHO grade I	CT w/ vincristine, carboplatin, etoposide (SIOP-LGG 2004)	No	Low grade astrocytoma

ACNU = nimustine; CT = chemotherapy; FU = follow-up; HDC = high-dose chemotherapy; IH = intracranial hypertension; PM = postmortem; PO = postoperative diagnosis; PTEN = phosphatase and tensin homolog; RT = radiotherapy; SIOP-LGG = International Society of Pediatric Oncology-Low Grade Glioma; TP53 = tumor protein 53.

* Sequencing of TP53 gene revealed a missense mutation in exon 5; PTEN expression was lacking.

† Karyotyping revealed 1p deletion. Patient was alive with stable disease and major sequelae at last evaluation.

Applying less strict criteria (including patients without necropsy and those reported alive) and pooling the data collected by Debono et al.[3] and Dörner et al.[4] with ours, we found that more common initial presentation included symptoms and signs of intracranial hypertension (IH), like vomiting and headache (37/47 cases, 79%), multiple cranial nerve palsies (especially neuro-ophthalmologic) (25/47 cases, 53%) and seizures (11/47 cases, 23%). There was slight male predominance (25/22 cases = 1.13 ratio). There were 14 WHO low-grade tumors (30%) and 23 high-grade tumors (49%). The problem of diagnosing histological grade in PDLG is that the disease is frequently misclassified,[2] making these numbers unreliable. Median survival calculated by the Kaplan-Meyer method using the reported survival rate of this group of patients is 5 months, and survival at 12 months is only 30%. This survival rate is biased by the fact that many of these reports were of postmortem diagnosis and, therefore, the patients did not receive treatment. Selecting only those patients that received specific treatment and reported survivals (19 cases), the Kaplan-Meyer median survival is 15 months, and the 1-year survival is 52%. Only four cases were reported to be alive at the time of their publication (1, 4, Table 1), all of them were children, and three of them were less than 3 years old. They received chemotherapy (CT) (three cases), or combined radiotherapy (RT) and CT (one case). All of the patients that survived 24 months or more in this pooled group are children (except for a 21 year old male), and all received CT or combined CT and RT. The more frequently used drug was cisplatin. Four cases reported using temozolomide (1, 5, Table 1), all of them had survival rates higher than the group median (range 15-96 months). Interestingly, the case reported by Gonçalves et al.[5] had a remarkable survival rate (only matched by another reported case, see references).[3,4] This child used valproate, a drug that has been recently reported to have antitumor effects that could enhance the effects of both RT and CT in brain tumor patients.[6] Val Filho & Avelar reported that their patient had seizures but did not disclose which anticonvulsants the child had used. Other authors equally have not reported on anticonvulsant usage, so we cannot say if any of the other cases used valproate either.

We conclude by stating that the report by Val Filho & Avelar can be reclassified as a very interesting case of PDLG in a young child, with one of the longest reported survival rates for this rare and grim disease. This exceptionally rare disease affects all ages, is uncommon in children in whom it seems to bear a better prognosis (only children were reported alive) and is responsive to cisplatin-based radiochemotherapy or temozolomide (that could be used as second choice). Even with multimodality treatment, it has a very poor prognosis with short reported median survival rate (15 months) comparing with other high-risk brain tumors such as glioblastoma multiforme and diffuse pontine glioma. One compelling report is that of a prolonged survival in a child who used CT and valproate, suggesting that epigenetic inhibition can have a role in its treatment in the future.

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Authors' reply

Dear Editor,

We would like to thank Dr. Francisco Helder Cavalcante Felix for his comments about our case report "Gliomatosis cerebri with favorable outcome in a child: a case report."[1] Dr. Felix has conducted an extensive research and a very elegant scientific discussion about the theme, which helped us to better understand this rare disease.

However, we would like to clarify some of Dr. Felix's comments.

As mentioned in his letter, the image showed was a magnetic resonance (MR) contrast-enhanced T1. According to our point of view (as a surgeon), this acquisition time shows better the findings in the subarachnoid space, as well in the parenchyma, in contrast to what was stated in the description.[2] Anyway, the child was exhaustively studied by MR imaging after the diagnosis, in all sequences, with and without contrast, and the images were analyzed by many radiologists, who agree with the diagnosis.

During some time, before the oncologic treatment, the patient seemed to have some involvement of the frontal and cerebelar lobes, as well the midbrain, what could explain the obstructive hydrocephalus (Figure 1). She also has, to this date, a cystic involvement of the spinal cord (syringomyelia), which resembles a regression of the tumor originally inside the organ (Figure 2).

Initially, she used phenobarbital and carbamazepine for the seizures. Currently, she is not using any drugs. She never used valproate.

Therefore, we conclude that this can be a mixed form, with characteristics of gliomatosis cerebri and primary diffuse leptomeningeal gliomatosis (PDLG), as perfectly pointed by Dr. Felix. In our daily clinical practice with patients, we observed that pure forms, as described in our reference sources, are less common than mixed presentations.

Again, we thank Dr. Felix for his contribution to the topic.

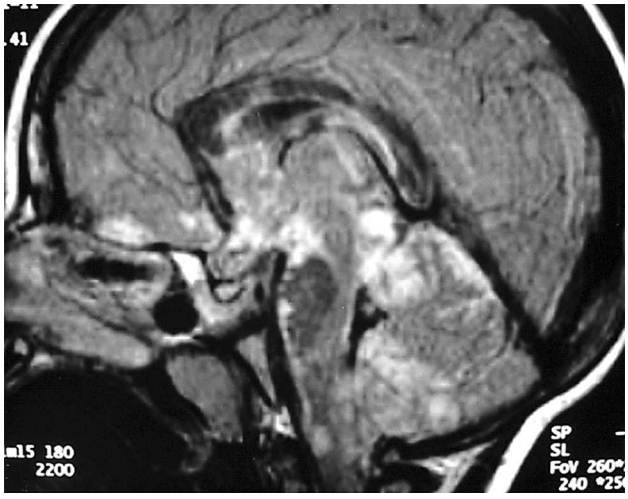

Figure 1 - Midbrain lesion leading to obstructive hydrocephalus

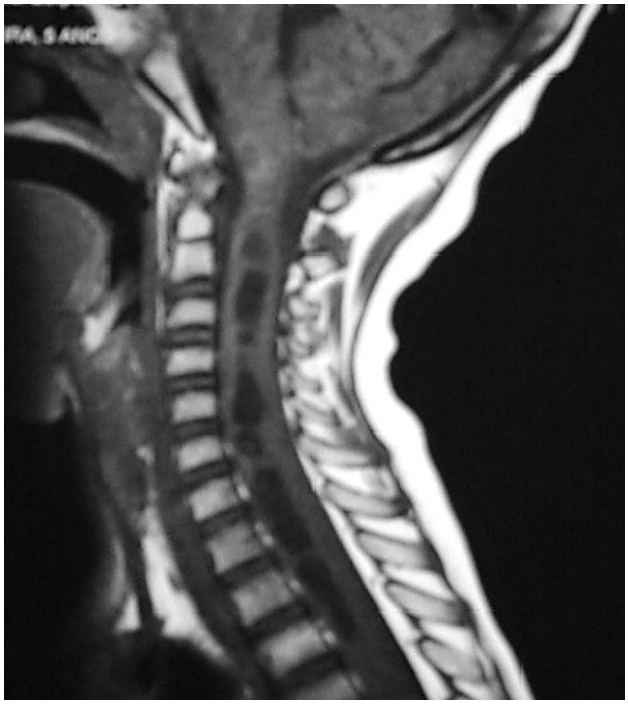

Figure 2 - Cystic involvement of the spinal cord (syringomyelia)

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