Author’s response to reviews

Title: MOG antibody seropositivity in a patient with encephalitis: beyond the classical syndrome

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Author’s response to reviews:

Dear Editor,

We thank you and the reviewer for improving the manuscript with these precious comments. We addressed a point-by-point response to the comments and we highlighted all the changes suggested in the manuscript.

Thank you for your consideration of this revised version for possible publication in your journal.

Sincerely,

Sara Mariotto
Reviewer 1

1. “If available, I would like to know whether the concentration of the myelin basic protein (MBP) in the CSF was elevated or not, as the concentration of CSF MBP is reported to be elevated in several anti MOG antibody related demyelinating diseases. Please show the results only when the assay is already performed, as the assay is usually not routinely performed.”

We thank the reviewer for this useful comment. Unfortunately, we did not analyse the concentration of MBP in the CSF. Actually, an elevation of CSF MBP has been reported during exacerbations in patients with MOG-Ab and its reduction has been associated with clinical improvement (Ikeda et al 2014). However, in the previously reported cases of encephalitis associated with MOG-Abs an elevation of MBP was not found (Fujimori et al 2017 and Ogawa et al 2017) so that the pathogenetic role of MOG-Abs was questioned. In the case here proposed indirect immunohistochemical analysis performed with both serum and CSF seems to rule out other autoimmune disorders confirming the unique presence of MOG-Ab. We appreciate the suggestion to test MBP in the future in MOG-Abs positive patients in order to confirm the acute injury of myelin.

2. “If available, I would like to know the result of the diffusion weighted images (DWI, ADC) of the brain MRI, as the FLAIR images of the brain MRI described in the figure reminds us of the possibility of the vascular edema. Please describe the result by the sentence (not by the figure) in the manuscript, if possible.”

We are grateful to the reviewer for this comment that allows us to better explain neuroimaging findings. The description of DWI and ADC of the brain MRI has been now reported in the manuscript (pg. 4 lines 72-77).

3. “Could you describe the origin of the skin lesions? Did the lesions diminish after the immune therapy?”

We thank the reviewer for asking a comment on this point. The origin of the skin lesions remained undetermined. We considered them in the spectrum of signs and symptoms that sometimes precede MOG-Abs associated disorders (Jarius et al 2016). Actually, skin lesions spontaneously disappeared few days later, and this information has been now specified in the manuscript (pg. 3 lines 61-63).
4. “Could you rule out the possibility of the collagen diseases, vasculitis, Neuro-Bechet disease, Neuro-sweet disease, and Hashimoto encephalopathy?”

We appreciate the possibility to better discuss these data. An extensive autoimmune screening resulted negative and the criteria to demonstrate a concomitant autoimmune condition were not satisfied. This is now better explained in the manuscript (pg. 4 lines 82-86). In particular, in order to exclude Behçet disease, we ruled out mouth sores, genital sores arthritis or eye inflammation. As for Hashimoto’s encephalopathy, our patient did not satisfy the clinical and MRI criteria recently proposed (Graus et al 2016), thyroid function was normal, we did not detect serum thyroid antibodies and a prompt improvement after steroids was not observed. We did not perform a skin biopsy but lesions were not painful; their spontaneous disappearance in absence of steroids treatment and the lack of evidence of other organs involvement seem to argue against Neuro-sweet disease (Hisanaga et al 2005).

Reviewer 2

Major comment

“…I would appreciate a more deeply discussion explaining whether the present case fulfill or not the current ADEM criteria (Krupp LB, et al. Mult Scler 2013).”

We are very grateful to the reviewer for asking us a better explanation of these data. We added to the manuscript a more detailed discussion on this point mentioning also Krupp et al (pg. 5 lines 104-111). The case here reported satisfy both criteria of possible encephalitis of presumed infectious origin (Venkatesan et al 2013) and for possible autoimmune encephalitis (Graus et al 2016), data that underline the difficult differential diagnosis between these two conditions. In the case here proposed, some radiological features are in favour of a diagnosis of ADEM, as the multiple supratentorial lesions of the white matter, basal ganglia, brainstem and deep grey matter abnormalities in the thalamus and basal ganglia as well as the improvement of brain lesions in the follow-up and the good prognosis. Moreover, recently, Cobo-Calvo et al reported interesting results in a cohort of adult and pediatric patients tested for MOG-Ab and correlated bilateral thalamic affection with the encephalopathic onset observed in most MOG-Abs positive cases with ADEM. This suggestive radiological finding was noted in all pediatric cases and in 1 out of 2 adult patients with ADEM.

Actually, Graus and colleagues propose a diagnosis of definite ADEM in patients with “MRI signs of demyelination in absence of AQP4, NMDAR or MOG-Ab”. In our case, pleocytosis is higher than that is usually observed in patients with ADEM and the MRI findings are not completely compatible (Graus et al 2016; Baumann et al 2015; Ketelslegers et al 2010). Unfortunately, the criteria for ADEM have been proposed only for children (Krupp et al 2013) and the diagnosis in adults remains challenging. Our case could be part of the ones defined by
Graus et al as “MOG-Ab demyelinating disorders with encephalopathy” or a confirmatory case of an adult with MOG-Abs, encephalopathy and bilateral thalamic lesions. Since the role of MOG-Abs in adult patients with ADEM is still controversial, we prefer to define this case as “encephalitis with MOG-Abs”.

“…I would appreciate if authors may explain differences between both encephalitic processes: a pure cortical involvement as a part of MOG-Ab encephalitis (as Ogawa reported) or an ADEM with MOG antibodies”.

We thank the reviewer for asking a comment on this point. We better explained MRI findings in our case (pg. 4 lines 72-77) and the differences between the other encephalitic processes, as suggested (pg. 5-6 lines 119-125).

“…There is another report (Numa S et al. Inter Medicine 2016) describing a MOG positive patient with cortical and grey matter affection. In this case, authors defined the patient as an ADEM-like.”

We appreciate this suggestion. Actually, we did not mention the case of Numa et al. because, at the moment of MOG-Abs analysis, their patient had symptoms of optic neuritis, while we focused on adult subjects with MOG-Ab and encephalitis.

Minor concerns

We are grateful to the reviewer for these minor concerns, and we changed the manuscript accordingly:

• “Some authors (Hakohen Y et al. Neurology 2017) start using the term MOG-Ab-related disorders to describe clinical phenotypes related to this emerging entity. Thus, in the background I would suggest "the whole spectrum of clinical phenotypes associates with MOG-Ab-related disorders has still to be clearly defined""

Correction pg.3 lines 51-53.

• “I would revise whether confusion and altered consciousness are symptoms instead of signs”

Correction pg.3 line 58.

• “I would suggest authors to add the number of serum leucocytes, erythrocyte sedimentation and C reactive protein, also the kind of antibiotics used”

Correction pg. 3 lines 63-65.

• “I would change spinal cord was negative for spinal cord was normal”
Correction pg. 4 line 77.

• “Authors noted IgIV 0.5 g/kg for 5 day instead of 0.5g/kg/day for 5 days”

Correction pg. 4 line 92.

“Authors performed a myelin staining with serum of the patient suggesting MOG-Ab binds to MOG protein in brain sections of rat. However, whether MOG antibodies or other autoantibodies could be involved in patients with cortical affection in not completely known. Do the authors have access to CSF? In previous cortical encephalitis patients with MOG antibodies, MBP in CSF was negative suggesting that maybe other autoantibodies could be involved in the pathophysiology of the lesion.”

We appreciate the possibility to better discuss these data. Actually, we analysed both serum and CSF for MOG-Abs with immunohistochemistry as this point is now better mentioned in the manuscript (pg.4 line 90). The results reported in Fig.2 are obtained analysing CSF and this seems to rule out the presence of other autoimmune disorders confirming the unique role of MOG-Abs.