Author’s response to reviews

Title: Sequential occurrence of eclampsia-associated posterior reversible encephalopathy syndrome and reversible splenial lesion syndrome (a case report): proposal of a novel pathogenesis for reversible splenial lesion syndrome

Authors:

YANG Qing (56469225@qq.com)

CHANG Can-can (18502407175@163.com)

Meng-xiao Liu (18221880692@163.com)

Yong-Qiang YU (yongqiang_yu@sohu.com)

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Author’s response to reviews:

Dear Editor and Reviewers:

Thank you for your letter and the reviewers’ comments concerning our manuscript entitled "Sequential occurrence of eclampsia-associated posterior reversible encephalopathy syndrome and reversible splenial lesion syndrome: proposal of a novel pathogenesis for reversible splenial lesion syndrome" (Manuscript ID MIM-D-18-00278). Those comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in the paper by using the track changes mode in MS Word (the line Numbers as: Restart as each page mode). The main corrections in the paper and the responds to the editor and reviewer’s comments are as flowing:

Responds to the Reviewer 1 (Alexander McKinney)’s comments:

Alexander McKinney (Reviewer 1): Summary: Interesting article. There are several names for this syndrome, but as the authors state, this generally seems to be potentially reversible, and the etiologies may overlap with PRES and ATL (Acute Toxic Leukoencephalopathy); please see suggested references below. While the authors may have correctly suggested that it is related to mannitol, which may be true. However, it also likely involves a component of endothelial injury
and perhaps toxic demyelination (see Ref 1-2 below), which has been suggested as both a cause of PRES and ATL, based on histopathology. Indeed, early reports of PRES and ATL have been described, and have overlapping etiologies (Ref 3-4 below). Hence, if RSL/MERS is considered a variant of ATL, then these overlaps in etiologies would make sense, and endothelial injury would be a common pathway. As Mannitol can reduce brain edema it may have ameliorated the injury, although in higher amounts it has been described to induce endothelial injury as well.

Suggestions:

1) address discussion above in manuscript regarding PRES, ATL, and that MERS may be a subtype of ATL and that endothelial injury may be a reason for the concomitant PRES-MERS here.

Response:

We cited relevant literatures (suggested by Dr. Alexander) to discuss the correlation of PRES, ATL and RESLES. We mentioned the theory that RESLES might be a subtype of ATL or a variant of ATL in this revised version as: “PRES and ATL have been described by Alexander et al., and have overlapping etiologies. The etiologies of RESLES may overlap with PRES and ATL, it also likely involves a component of endothelial injury and perhaps toxic demyelination, which has been suggested as both a cause of PRES and ATL, based on histopathology. They also envisioned that RESLES is a variant of ATL (or a subtype), and endothelial injury may be a reason for the concomitant PRES-RESLES(MRES). As Mannitol can reduce brain edema, it may have ameliorated the injury, although in higher amounts it has been described to induce endothelial injury as well. However, we feel it is still imperfection in using the mechanism of endothelial injury alone to explain the case.” (page 5, line13 to 20).

2) please add suggested Refs for that discussion, which may add to the understanding of why this phenomenon occurs.

Response:

We cited relevant literatures (suggested by Dr. Alexander) in this revised version as:
“PRES and ATL have been described by Alexander et al., and have overlapping etiologies [5,7]. The etiologies of RESLES may overlap with PRES and ATL, it also likely involves a component of endothelial injury and perhaps toxic demyelination[8,9], which has been suggested as both a cause of PRES and ATL, based on histopathology. They also envisioned that RESLES is a variant of ATL (or a subtype), and endothelial injury may be a reason for the concomitant PRES-RESLES(MRES). As Mannitol can reduce brain edema, it may have ameliorated the injury, although in higher amounts it has been described to induce endothelial injury as well. However, we feel it is still imperfection in using the mechanism of endothelial injury alone to explain the case. " (page 5, line13 to 20).

Discussion: the idea that severe HTN exceeds autoregulatory limits is not new, and has been around for 20 years. This has been disproved in a number of PRES cases and studies that have shown that HTN is not present in up to nearly 1/2 of PRES patients, although certainly can occur in a subpopulation. Hence, the reason that endothelial injury is now considered a more common pathway of injury for most or all PRES patients (Ref 1)

Response:
In this revision, we have modified the corresponding paragraph to: “Early hypothesis suggests that severe hypertension exceeds the autoregulatory limits of the cerebral vasculature and leads to breakthrough of the blood–brain barrier, fluid leakage, and vasogenic edema. Endothelial injury is now considered a more common pathway of injury for most PRES patients [8].(page6, line 12 to 15)

3) Please remove "this is the first case..". It could be the first called MERS/PRES, although if it is considered a subtype of ATL it is not. Perhaps a better way to state this is "There are scant, if any, cases described of concomitant PRES-MERS, although preliminary cases of toxic leukoencephalopathy (ATL) have been described with PRES" (Ref. 3). Or something like that.

Suggested Refs:


Response:

According to the reviewer's suggestion, We have modified the words to: “There are scant, if any, cases described of concomitant PRES- RESLES(MERS), although preliminary cases of acute toxic leukoencephalopathy (ATL) have been described with PRES[5].”(page 3, line 21 to page 4, line 1). In order to introduce the proper noun "MERS", we added the words as: “The syndrome was once named: Clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS).” (page 3, line 15 to 16)

Responds to the Reviewer 2(Christian Roth)’s comments:

Christian Roth (Reviewer 2): The authors present a typical case of posterior reversible encephalopathy syndrome in a young pregnant woman with eclampsia. Clinical signs and symptoms as well as the MRI imagines were characteristically for PRES. However, control MRI showed a new lesion in the corpus callosum which was interpreted as reversible splenial lesion syndrome (RESLES).

This is an interesting case report. The combination of these two neuroradiological syndromes has never been published before. However, there are some queries:

- The authors discuss a novel PRES pathophysiology. They present their own hypothesis of mannitol-induced RESLES. However, they do not present any pathophysiological findings. It is
only a theory. I think the main aspect of the paper is the question why PRES and RESLES occur sequently. RESLES might be a part of PRES as cytotoxic edema may be observed in PRES patient too.

Response:

We cited relevant literatures to discuss the correlation of PRES, ATL and RESLES. We mentioned the theory that RESLES might be a subtype of ATL or a variant of ATL in this revised version as:“ PRES and ATL have been described by Alexander et al., and have overlapping etiologies. The etiologies of RESLES may overlap with PRES and ATL, it also likely involves a component of endothelial injury and perhaps toxic demyelination, which has been suggested as both a cause of PRES and ATL, based on histopathology. They also envisioned that RESLES is a variant of ATL (or a subtype), and endothelial injury may be a reason for the concomitant PRES- RESLES(MRES). As mannitol can reduce brain edema, it may have ameliorated the injury, although in higher amounts it has been described to induce endothelial injury as well. However, we feel it is still imperfection in using the mechanism of endothelial injury alone to explain the case.” (page 5, line13 to 20).

However, we also highlight our point of view in the discussion section: “that is a dual role for AQP4 in the edema process: deleterious during cytotoxic edema formation and beneficial during the angiogenic edema resolution phase”. We think this two-way adjustment has the potential to cause PRES and RESLES to occur sequentially. In fact, the exact pathological mechanism of RESLES is still unclear so far. we hope that the hypothesis of the possible mechanism of RESLES we proposed can provide another meaningful way for future research.

- There is another interesting aspect which should be discussed. Why did the RESLES lesion resolve completely? MRI showed restricted diffusion on DWI and MRI imagines due to cytotoxic edema. Normally, these lesions can be seen permanently on T2 weighted imagines and are responsible for poor outcome of PRES patients.

Response:

First of all, I would like to thank the viewer for the important comments and help in revising this article.
In most cases, the clinical and imaging abnormalities of RESLES (or MERS) are reversible. However, in some cases (such as in patients with severe hypoglycemia), if it is not treated in time, marked central nervous system damage may occur (can be seen permanently on T2 weighted imagines); therefore, Starkey et al. suggested that the syndrome be named “Cytotoxic Lesions of the Corpus Callosum (CLOCCs),” to highlight the partial irreversibility of the disease.

Our results of a quantitative ADC study on RESLES (this article have been accepted and will be published in no more than two or three month in MRMS) show that: The genu of the corpus callosum shows a slight diffusion restriction in the acute stage of type I MERS (RESLES), but that this recovers after treatment, as it does in the splenium of the callosum. That means the lesions in type I MERS (RESLES) may be more widespread than previously thought. We further speculate that the reason for varying ADC values (cytotoxic edema) in the SCC (splenium of the corpus callosum) and GCC (genu of the corpus callosum) of MERS patients is that the corpus callosum may have a special receptor or protein gradient from the posterior to the anterior. The receptor or protein most likely to be involved is aquaporin 4 (AQP4). To the best of our knowledge, no existing experiments are exactly on the gradient difference of AQP4 receptor/protein in corpus callosum. However, It is still some relevant evidence to support this speculation: Aquaporins (AQPs) are an evolutionarily conserved family of membrane transporter proteins that regulate the flow of water and in some cases, glycerol and other small molecules across cellular membranes. AQP4-knockout mice show a decrease in cytotoxic brain edema after water intoxication and focal cerebral ischemia, and AQP4-overexpressing mice show accelerated progression of cytotoxic brain edema. These findings suggest that AQP4 contributes to the development of cytotoxic brain edema. A high concentration of AQP4 is found on astrocyte end-feet in contact with all blood vessels and astrocyte. The AQP4 distribution differs significantly within brain structures such as the hippocampus, the brainstem and particularly the corpus callosum. Badaut et al. reported that at high magnification, AQP4 staining in the corpus callosum reveals that AQP4 has “patchy” distribution, following the direction of the neuronal processes. This higher density leads to a tendency for development of cytotoxic edema in the corpus callosum to develop when cytokinopathy occurs. Lu et al. investigated the correlations among DWI, histopathology and AQP4 expression in rat brain that was re-perfused after acute ischemia. They found a close correlation between AQP4 expression and the cerebral intracellular edema, and that AQP4 mRNA expression was negatively correlated with regional ADC values. This correlation has also been reported elsewhere. That altered ADC values may indirectly reflect the level of AQP4 expression. Various of conditions such as infection, sudden discontinuation of anti-epileptic drugs, endocrine abnormalities, and drug toxic effects, etc. which have been reported to trigger MERS, can also affect the AQP4 protein expression, leading to increased expression levels through a complex cell-cytokine or an intracranial microenvironment osmotic mechanism. AQP4 channel activation will result in an influx of water into astrocytes, resulting in intra-cellular edema and reduced diffusion (cytotoxic edema).
The link between AQP4 and MERS could be indirectly tested or explained by a series of experiments and studies1-12.

Based on our hypothesis about the mechanism of RESLES, the upregulation of AQP4 is temporary and slight in most cases, so the clinical and imaging manifestations of most patients are reversible after the etiology is controlled or proper treated.

Therefore, we have added the following paragraph in this revised version:

“In most cases, the clinical and imaging abnormalities of RESLES are reversible. However, in some cases (such as in patients with severe hypoglycemia), if it is not treated in time, marked central nervous system damage may occur (can be seen permanently on T2 weighted images). Based on our hypothesis about the mechanism of RESLES, the upregulation of AQP4 is temporary and slight in most cases, so the clinical and imaging manifestations of most patients are reversible after the etiology is controlled or proper treated.” (page 7, line 3 to line 8)


- Why did they treat with mannitol? This is not a common therapy in PRES patients.

Response:

The treatment of seizure in eclamptic women is the main step of the treatment, where magnesium sulfate is the drug of choice although there are other antiedema medications that can be considered (such as mannitol and dexamethasone). [1]

Mannitol can be used as antiedema agent and can open the blood–brain barrier. Mannitol cannot cross the blood–brain barrier, but can lower intracranial pressure by decreasing the overall water content and cerebrospinal fluid volume [2]. Mannitol can also increase intravascular tonicity.
which causes its osmotic action [3]. Demir et al[4]. also compared the effectiveness of mannitol and magnesium sulfate in ameliorating vasogenic edema, when used concomitantly with antihypertensive therapy in PRES patients.

We have reviewed some literatures and consulted the relevant clinicians. We concluded that it is feasible to use mannitol properly in patients with PRES. However, the clinical use of mannitol for a long time and relatively large doses may bring some unexpected effects. We think that the case we provided here may be caused by a relatively large doses of mannitol and a longer period of use. (the continuous mannitol used time and dosage of mannitol have been described in detail in the paper.)


