Peer Review File

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Review comments

Reviewer A

Comment 1: The following would help improve the quality of this manuscript. In the abstract several terms (ADEM-OCE) are not spelled out prior to introduction.

Reply 1: *Thank you for your comment. The following terms have been spelled out in the abstract prior to the introduction: Pediatric-onset multiple sclerosis (POMS, line 8), acquired demyelinating syndromes (ADS, line 10), oligoclonal bands (OCB, line 17), magnetic resonance imaging (MRI, line 17), acute disseminated encephalomyelitis (ADEM, line 18), methylprednisolone (line 19).*

Comment 2: Case presentation: Explain the severity of the score of EDSS (with reference) and what is considered an abnormal score.

Reply 2: *Thank you for your comment. In the case presentation, we added explanation for EDSS score including an explanation of an abnormal score with references in lines 63-67.*

Changes in the text: *"Due to suspicion of ADS, patient was evaluated according to the Expanded Disability Status Scale (EDSS), which measures current level of disability in patients with MS. EDSS ranges from 0 to 10 taking into account ambulation and neurologic impairment of eight functional systems in central nervous system. An EDSS score of 0 indicates normal neurological status, meanwhile a score of 10 indicates death due to MS. The patient received a score of 3.5 and was admitted for further investigations."*

Comment 3: Line 81-82 this sentence is disjointed and does not explain which IQ test was used. It would also be warranted in the discussion to explain how this score might be related to POEMS or whether it may be the result of other factors as this is currently unclear.

Reply 3: *Thank you for your comment. Additional information in regards to the IQ test used and scoring was added in lines 94-97. In the discussion, additional information was added with regards to other factors that might influence cognitive scores, lines 137-141.*

Changes in the text case report and discussion:

"Cognitive testing with Wechsler Intelligence Scale for Children revealed an overall intelligence quotient (IQ) of 55 (0.1 percentile) at 8 years old with lowest scores achieved in processing speed and visual-spatial processing. No previous testing was conducted before the onset of POMS prior to first hospitalisation, despite suspicions of learning difficulties due to incompliance."

"Additionally, it has been reported that lower IQ scores are associated with younger age at MS onset. Our patient had learning difficulties prior to his first hospitalization but additional testing, including cognitive assessment was never done. It cannot be

excluded that cognitive deficit was the presenting symptom of POMS in our patient. However, learning difficulties have also been identified in the patient's brother therefore causative or contributing genetic and social factors cannot be excluded and are more likely in this case."

Comment 4: Discussion: More specifically indicating whether other similar cases have been reported with similar outcome would be useful. How novel is this type of case report?

Reply 4: *Thank you for your comment. Similarities of our cases have been analyzed in discussion, additionally stressed features regarding the uniqueness of our case report – overlapping clinical, radiological and laboratory features, as well as atypical demographic characteristics, furthermore, accompanied with difficulties to determine encephalopathy in children with learning disabilities. Regarding outcome, POMS has a more inflammatory course with more frequent clinical relapses than adult MS, however patients tend to have better recovery from relapses. In our patient, EDSS between attacks is 3.0 due to cognitive impairment, the contributing factors of which we describe in detail in the discussion lines 137-141.*

Changes in the text: "*Previous cases of POMS in prepubertal children as young as 2 and 4 years old have been reported, both of which had negative OCB and were diagnosed with ADEM. Neither patient presented with encephalopathy – one of the main reasons why ADEM was suspected in our patient in the first episodes."*

"This case is unique due to presence of several atypical demographic and overlapping clinical, radiological and laboratory features of ADS."

Comment 5: Tables and figure. Much more extensive legends are needed explaining how symptoms and encephalopathy were determined. More detailed description of the MRI needs to be incorporated. As Well as how these related to DZ pathology

Reply 5: *Thank you for your comment. Symptoms were determined by neurological examination, as well as EDSS by a certified pediatric neurologists. As described in the discussion, encephalopathy can be difficult to assess in children with learning difficulties or psychiatric comorbidities (line 130-137). In the table, more detailed descriptions of the symptoms were omitted because they are mentioned both in the abstract and case description. Information about the MRI findings have been added to the images in Table 1. Additionally, one of the FLAIR axial images was replaced by a sagittal image as we felt it contributed more to the article.*

Reviewer B

I would like to thank the authors for this good work. Nevertheless, some points deserve to be reviewed before the article is considered for publication.

Comment 1: In Abstract-Background, the authors need to clearly clarify why the case report is unique and what it contributes to the existing literature. For the authors' reference, specify like "Here we report a case of … This case is unique in terms of…".

Reply 1: *Thank you for your suggestion. Features regarding the uniqueness of our case report – overlapping clinical, radiological and laboratory features, as well as atypical demographic characteristics, furthermore, accompanied with difficulties to determine encephalopathy in children with learning disabilities has been described in the background as well as in discussion.*

Comment 2: Abstract-Case Description should incorporate the patient's main symptoms (e.g., a 5-day history of nausea, vomiting, gait instability, strabismus in the left eye, and head tilting to the left), interventions, outcomes, and follow-ups. In other words, the authors should present relevant events in the patient's history in chronological order that could help readers follow along with the progression of the patient's condition.

Reply 2: *Thank you for your suggestion. Several changes (including the incorporation of the main symptoms, interventions, follow-ups and outcomes) have been made to the abstract-case description to fulfil structure requirements, which can be seen in lines 15-26. We hope this will bring more clarity to the reader in following the events that lead to diagnosis and start of treatment.*

Changes to text: *The following has been added to the abstract-case description: A 7-year-old boy initially presented with a 5-day history of nausea, vomiting, gait instability, strabismus in the left eye, head tilting to the lift and signs of encephalopathy with positive oligoclonal bands (OCB) and multiple demyelinating lesions in the brain on magnetic resonance imaging (MRI), leading to a diagnosis of acute disseminated encephalomyelitis (ADEM). The patient was treated with methylprednisolone pulse therapy (MP) and symptoms resolved. He experienced a second episode with 1-day complaints of vertigo and diplopia with suspected encephalopathy, however OCB were negative, resulting in a diagnosis of multiphasic ADEM. Finally, after a third demyelinating event that occurred without encephalopathy, the patient was diagnosed with POMS. Disease-modifying therapy was initiated with glatiramer acetate, which was discontinued due to frequent relapses and switched to rituximab. Patient had an anaphylactic reaction to rituximab but has now been relapse free for over two years on natalizumab.*

Comment 3: I found the current manuscript was inconsistent the structure template for the case report in the authors' instruction (https://cdn.amegroups.cn/static/public/Case-Reports-Structure-template.docx?v=1731481383876). The authors should provide a structured informative introduction, namely three subsections "Background", "Rationale and Knowledge Gap", and "Objective", to improve clarity.

Reply 3: *Thank you for your comment. The introduction has been restructured to meet the structure template of the journal to improve clarity.*

Comment 4: Whilst interesting, the case report does not maximize the opportunity for introduction. The introduction is brief with important details missing.

(1) Firstly, the authors mentioned "Several criteria have been proposed to differentiate POMS from other acquired demyelinating syndromes (ADS), particularly acute

disseminated encephalomyelitis (ADEM) and neuromyelitis optica spectrum disorders". A detailed background description about "other acquired demyelinating syndromes" should be provided.
(2) Then, the authors also should introduce the "several criteria".
(3) Meanwhile, in Introduction-Rationale and Knowledge Gap, the authors could clearly report what is not done and how this manuscript differentiates from existing case reports.
(4) In addition, consider including a description about the published similar cases in Introduction-Rationale and Knowledge Gap. The text might benefit in further clarifying the unique point based on comparing similar published studies.
(5) Finally, please also highlight the unique point of this case report when stating the aim of the manuscript in Introduction-Objective.
Reply 4: *Thank you for your comment. The introduction has been restructured and rewritten with additional information about ADS diagnostics, similar cases reported as well as aim of this manuscript.*
Changes in text:
Rationale and Knowledge Gap: Timely diagnosis of POMS remains crucial for initiating appropriate disease-modifying treatments and reducing long-term disability[12]. However, diagnosing acquired demyelinating syndromes (ADS) in pediatric patients can be difficult, especially after the first demyelinating attack. Several criteria have been proposed to differentiate POMS from other acquired demyelinating syndromes (ADS), such as acute disseminated encephalomyelitis (ADEM), neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody spectrum diseases (MOGAD)[10,11]. These include age at onset, presence of clinical symptoms (such as encephalopathy), specific antibodies or oligoclonal bands and MRI findings. In this clinical case, we describe the challenges encountered in diagnosing POMS in a 7 year-old prepubertal male patient with numerous atypical features, including gender, age at onset, encephalopathy, inconclusive OCB and MRI findings. Still, specific biomarkers for diagnosis of POMS are lacking, therefore the patient received a final diagnosis only after his third episode of central nervous system (CNS) demyelination.
Objective: To highlight the challenges encountered by physicians when managing the complexities of diagnosing childhood ADS.

Comment 5: Table 1 uses pictures instead of text descriptions, which rely on subjective interpretation. Consider describing the key and detailed image features instead of only providing MRI pictures in the main text and Table 1.
Reply 5: *Thank you for your comment. More detailed descriptions of the MRI findings have been added Table 1. Additionally, one of the FLAIR axial images was replaced by a sagittal image as we felt it contributed more to the findings.*

Comment 6: Are there cognitive data at the baseline?

Reply 6: *Thank you for your question. No previous cognitive testing was conducted prior to first hospitalisation despite suspicions of learning difficulties due to incompliance.*

Comment 7: "Magnetic resonance imaging (MRI) of the brain revealed multiple lesions in the cortex, subcortex, periventricular areas of all lobes, corpus callosum, brainstem, medulla, and cerebellar peduncles", consider specifically explaining the key discriminatory features. For the authors' reference, is the boundary of the lesion clear? Is there a Dawson's finger sign? Black hole (T1 low signal)? What is the morphology of the infratentorial/spinal cord lesion?
Reply 7: *Thank you for your questions and suggestions. In our patient there were multiple, diffuse, bilateral, well marginated, bright plaques on Flair and T2, with no contrast enhancement, no restricted DWI, located in periventricular white matter and juxta cortical, involving also corpus callosum. Dawson fingers were described. There were no chronic black holes in T1. Infratentorial hyperintense plaques located in pons, both middle cerebellar peduncle and cerebellum were present. Whole spinal cord was involved, with multiple T2 and Stir bright, non-enhancing plaques. Additional information incorporating this information has been added to the discussion in lines 142-151.*

Comment 8: Supplement the reasons for not undergoing spinal cord MRI during the first episode.
Reply 8: *Thank you for your comment. The reasoning was included in the case presentation in lines 71-72. In retrospect, spinal MRI would have been done in the first demyelinating episode, especially after the findings of OCB.*
Changes in text: *Spinal MRI was not done as the child did not demonstrate extremity weakness, sensory changes or symptoms of bowel or bladder dysfunction.*

Comment 9: "treated with intravenous methylprednisolone (IVMP) for 5 days", "The patient was diagnosed with relapsing-remitting pediatric-onset multiple sclerosis (POMS) and received acute treatment with intravenous methylprednisolone (IVMP) for 5 days followed by oral prednisolone taper over 11 weeks", please also report the recommended dosage and frequency of the treatment.
Reply 9: *Thank you for your comment. Dosages and frequency of the treatment was included in the case presentation in lines 73-74, 84-85 and discussion in lines 170-174*
Changes in text: *The following information was added to the case description:*
The patient was diagnosed with ADEM and treated with intravenous methylprednisolone (IVMP) 27 mg/kg/day for 5 days according to guidelines[16–18].
Given the mild encephalopathy, absence of previously positive OCBs, and the patient's age, he was diagnosed with multiphasic ADEM and treated with IVMP for 5 days followed by an oral prednisolone taper 1 mg/kg/day (maximal dose 60 mg) over 11 weeks.
The following information was added to the discussion:

Regarding treatment, in case of ADS acute attack, first-line therapy is IVMP 20-30 mg/kg/day (maximum of 1 g) for 3-5 days, however, approaches to subsequent tapering with oral steroids may vary. Some experts support the use of tapering in patients with ADEM and NMOSD started at 1 mg/kg/day (up to a maximum of 60 mg/day) and tapered over 3-6 weeks in case of ADEM and even up to 2-6 months until long-term immunosuppression is established, if indicated. In our case, oral steroid tapering was initiated after the second and third attack, followed by MS diagnosis and disease modifying treatment (DMT).

Comment 10: Please explain the reason for not reexamining the OCB for the third time.
Reply 10: *Thank you for your comment. Reasoning was included in the case presentation in lines 91-93.*

Comment 11: "Long-term treatment with glatiramer acetate", "treatment was escalated to rituximab", "The treatment was then switched to natalizumab", report the recommended dosage, frequency, and duration of treatment.
Reply 11: *Thank you for your comment. The discussion was modified to include information about POMS treatment with DMTs, however we felt that since the main idea of this article was to highlight diagnostic challenges, including information about treatment dosage, frequency and duration of the different DMTs was beyond the scope of this case report. See lines 175-184.*
Changes in text: *The following was added to the discussion:*
In case of POMS compared to adult-onset MS, there is a significant disparity in the availability of DMT and DMT for children remains mostly off-label. DMT choice is based on limited data from available randomized controlled clinical trials (RCTs), nonetheless there are data available derived from adult RCTs and pediatric observational studies. Our patient initially received DMT with glatiramer acetate with insufficient treatment response, followed by rituximab with unfortunate anaphylactic reaction and currently is on natalizumab treatment. After initiation of natalizumab, our patient did not experience clinical attacks and no new contrast enhancing and non-enhancing lesions in the brain or spinal cord have been identified.

Comment 12: "Unfortunately, the patient experienced an anaphylactic reaction", more details about the "anaphylactic reaction" should be provided.
Reply 12: *Thank you for your comment. Additional information regarding the anaphylactic reaction was added to the case presentation in lines 100-101.*
Changes in text: *The following was added to the case presentation:*
Unfortunately, the patient experienced an anaphylactic reaction with progressive whole body urticaria, pruritus, mild eyelid edema, dry cough, which resolved after stopping the infusion.

Comment 13: Consider providing the corresponding evidence supporting each therapy, such as case reports, guideline recommendations, or reviews.

Reply 13: *Thank you for your comment. While the authors have considered providing evidence supporting each therapy with guidelines and recommendations, due to the aim of this article, which is to highlight diagnostic challenges of acquired demyelinating syndromes, as well as case report structure limitations, it was decided that this information would be too extensive to include in the manuscript.*

Comment 14: In Table 1, the authors also need to add the information about treatment, outcome and follow-up.
Reply 14: *Thank you for your comment. Several additions have been made to Table 1, including acute treatment. Outcome is reflected by EDSS score. Follow-up is described in the case presentation text.*

Comment 15: Discussion should be structured in five parts: a) Key Findings, b) Strengths and limitations, c) Comparison with similar researches, d) Explanations of findings, e) Implications and actions needed.
Reply 15: *Thank you for your comment. The discussion has been restructured to meet the structure requirements of the journal.*

Comment 16: Summarize the case in the first paragraph, noting how it differs from previously described cases. Please elaborate on this in your discussion based on comparison with other similar case reports.
Reply 16: *Thank you for your comment. The case has been shortly summarized in the first paragraph of the discussion and comparisons with similar case reports have been added in lines 107-113.*
Changes in text: *We present a diagnostically challenging case of a 7-year-old boy with a final diagnosis of pediatric-onset multiple sclerosis (POMS), though only after the third demyelinating event. Our patient had multiple atypical features, which hindered diagnosis, including age of onset, gender, suspicions of encephalopathy, uncertain MRI and OCB findings. Previous cases of POMS in prepubertal children as young as 2 and 4 years old have been reported, both of which had negative OCB and were diagnosed with ADEM. Neither patient presented with encephalopathy – one of the main reasons why ADEM was suspected in our patient in the first episodes.*

Comment 17: Consider expanding the discussion about the symptoms and treatments for POMS, which would strengthen the educational value of the report.
Reply 17: *Thank you for your comment. The discussion was modified to include information about POMS symptoms and treatment with DMTs, however we felt that since the main idea of this article was to highlight diagnostic challenges, including information about treatment dosage, frequency and duration of the different DMTs was beyond the scope of this case report. See line 128-129 and lines 170-184.*
Changes in text: *The following was added to the discussion.*
Most common presenting symptoms of POMS include optic neuritis, sensory or motor symptoms and brainstem symptoms.

Regarding treatment, in case of ADS acute attack, first-line therapy is IVMP 20-30 mg/kg/day (maximum of 1 g) for 3-5 days, however, approaches to subsequent tapering with oral steroids may vary. Some experts support the use of tapering in patients with ADEM and NMOSD started at 1 mg/kg/day (up to a maximum of 60 mg/day) and tapered over 3-6 weeks in case of ADEM and even up to 2-6 months until long-term immunosuppression is established, if indicated. In our case, oral steroid tapering was initiated after the second and third attack, followed by MS diagnosis and disease modifying treatment (DMT). In case of POMS compared to adult-onset MS, there is a significant disparity in the availability of DMT and DMT for children remains mostly off-label. DMT choice is based on limited data from available randomized controlled clinical trials (RCTs), nonetheless there are data available derived from adult RCTs and pediatric observational studies. Our patient initially received DMT with glatiramer acetate with insufficient treatment response, followed by rituximab with unfortunate anaphylactic reaction and currently is on natalizumab treatment. After initiation of natalizumab, our patient did not experience clinical attacks and no new contrast enhancing and non-enhancing lesions in the brain or spinal cord have been identified. Currently, although our patient's physical status is stable, cognitive impairment is the primary reason for his current baseline EDSS of 3.

Comment 18: All findings described in the current Discussion seem to be found in published literature. Although the reported case is challenging, the authors need to prove something new for the clinical practice.

Reply 18: *Thank you for your comment. All findings might be described separately as atypical findings in POMS, however when these features are present or overlap, it challenges the clinician to make the right diagnosis. As a result, in many cases initiation of treatment is delayed until further attacks, which increases long-term disability. This article brings attention to the necessity of making further strides in this field, for example, by discovering new biomarkers for early POMS recognition.*

Comment 19: In addition, consider discussing the implications of this case for future practice.

Reply 19: *Thank you for your comment. Information regarding implications and actions needed were added to the discussion, see lines 185-192.*

Changes in text: *Implications and actions needed: This clinical case illustrates the disease course and diagnostic challenges of early-onset POMS. Diagnostic delay is still a major problem for POMS patients, particularly for those in pre-pubertal age due to clinical, radiological and laboratory feature overlap with other ADS as well as the rarity of MS in this age group. To improve diagnostic accuracy there is a need for increased awareness about MS in children. Although over the years the diagnostic criteria have changed several times and include clinical, radiographic, and laboratory criteria, it still might not be enough to avoid misdiagnosis and diagnostic delay, if atypical features are present. There is still need for further diagnostic accuracy improvements, particularly for patients in pre-pubertal age.*

Comment 20: Finally, I would recommend that the authors further explicitly discuss the limitations, except for the inherent limitations of a case report - a single case. For the authors' reference, was the assessment timely? Is there anything that could be further improved about the assessment and interventions?

Reply 20: *Thank you for your comment. Additional information was added in the strengths and limitations section of the discussion. See lines 114-121.*

Changes in text: *Strengths and limitations: Strengths of our clinical case are highlighting the numerous challenges in navigating differential diagnosis of ADS in young children. Limitations of our clinical case include inability to generalize our findings as alternative diagnosis, such as ADEM and MOGAD are known to be more likely in children under the age of ten. In hindsight, spinal MRI in the first episode would have been done. OCB in CSF generally have high sensitivity for MS depending on methods used, they can be present in cases of other inflammatory CNS diseases. In addition, it is important to remember that negative OCB does not exclude a POMS diagnosis especially early on in the disease or in children. Potential future directions for POMS research could be biomarkers with higher sensitivity and specificity for POMS.*