Pediatric acute disseminated encephalomyelitis associated with myelin oligodendrocyte glycoprotein antibodies

Приказ дечјег акутног дисеминованог енцефаломијелитиса удруженог са антителима према мијелин-олигодендроцитном гликопротеину

1University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
2Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia

Received: December 2, 2021
Revised: February 3, 2022
Accepted: February 4, 2022
Online First: February 14, 2022
DOI: https://doi.org/10.2298/SARH211202024R

*Accepted papers* are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author’s last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.

When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

*Correspondence to:
Tatjana REDŽEK-MUDRINIĆ
Hajduk Veljkova 10, Novi Sad, Serbia
E-mail: tatjana.redzek-mudrinic@mf.uns.ac.rs
Pediatric acute disseminated encephalomyelitis associated with myelin oligodendrocyte glycoprotein antibodies

SUMMARY
Introduction Myelin oligodendrocyte glycoprotein antibody associated disorders (MOGAD) are immune-mediated inflammatory conditions of the central nervous system (CNS) with a wide clinical phenotypic variability. In order to further understand the possible phenotype of MOGAD here we report a pediatric case of acute disseminated encephalomyelitis (ADEM) associated with MOG antibodies.

Case outline A previously healthy four-month-old infant presented due to a 1-day history of fever up to 39°C and vomiting. On admission, she was encephalopathic. Repetitive and frequent stereotyped dystonic movements were observed. Cerebrospinal fluid (CSF) examination showed pleocytosis (lymphocytes were predominant) and proteinorachy. CSF culture and virology results were negative. Serum MOG antibodies were positive. A prolonged electroencephalography (EEG) showed continuous high-amplitude slow rhythmic activity with captured stereotyped movement. Epileptic discharges were not seen. Although magnetic resonance imaging showed signs of acute demyelinating encephalomyelitis, our patient did not have seizures, despite neuroimaging findings of cortical lesions. Acute treatment with the corticosteroids led to excellent response with full recovery.

Conclusion This case emphasizes the inclusion of the MOG antibodies testing in the initial work-up in children presenting with acute encephalopathy associated with demyelinating or encephalitic abnormalities on brain and/or spinal magnetic resonance imaging even when the clinical phenotype is unusual. The prompt diagnosis of MOGAD is relevant for accurate disease monitoring and treatment strategies.

Keywords: MOG-antibody; ADEM; child; movement disorder

INTRODUCTION

Myelin oligodendrocyte glycoprotein antibody associated disorders (MOGAD) are immune-mediated inflammatory conditions of the central nervous system (CNS). MOGAD...
result from damage to myelin oligodendrocyte glycoprotein (MOG), expressed on surfaces of oligodendrocytes and myelin sheaths in CNS [1, 2].

Autoimmunity to MOG represents a real spectrum of acquired demyelinating disorders (ADS) with a wide clinical phenotypic variability. Typical MOGAD presentations consist of demyelinating syndromes including optic neuritis (ON) or transverse myelitis in adults and ON or acute disseminated encephalomyelitis (ADEM) in children [2, 3, 4]. Myelin oligodendrocyte glycoprotein antibodies (MOG-abs) are seen in up to fifty percent of children with ADS [5].

Brain magnetic resonance imaging (MRI) findings in pediatric ADEM with MOG-abs usually report diffuse signal changes in juxta cortical white matter, deep white matter and deep grey matter, seen on both T2 weighted and FLAIR images. More recently, the disease spectrum has been expanded due to reports of patients with MRI cortical signal changes [6].

The presence of MOG-abs is associated with a non-multiple sclerosis (non-MS) course [3]. Disease course can be either monophasic or relapsing, with subsequent relapses most commonly involving the optic nerve [7]. Because of its clinical course, it is frequently confounded with aquaporin-4 antibody (AQP4-ab) positive neuromyelitis optica spectrum disorders (NMOSD). Early and accurate diagnosis of these distinct conditions is very relevant as they have different therapeutic approaches and MOGAD is associated with a better outcome and a quicker response to the first line therapy [1].

In order to further understand the possible phenotype of MOGAD, here we report a case of pediatric ADEM associated with MOG-abs with a movement disorder, and without seizures, despite neuroimaging findings of cortical lesions.

**CASE REPORT**

A previously healthy four-month-old infant with normal antenatal profile presented due to a 1-day history of fever up to 39°C and vomiting, followed by acute onset of lethargy. Her
consciousness rapidly deteriorated, so they came to hospital. On admission, she was drowsy with eye opening to voice and response to pain. Her vital signs were within normal range. Neurological examination revealed four-limb weakness, hyperreflexia of deep tendon reflexes and bilateral extensor plantar response. Repetitive and frequent stereotyped dystonic movements were noted, characterized by symmetrical extension of the arms and flexion of the wrists which initially responded to intravenous midazolam. Phenobarbital maintenance dose was introduced.

Routine blood and metabolic tests were within normal range. The computerized tomography (CT) scan was unremarkable. Cerebrospinal fluid (CSF) examination showed pleocytosis of 256×10⁶/L (85% lymphocytes), high concentration of protein (0.67 g/L) with normal glucose, chloride and lactate levels. CSF culture, serological test for Borrelia burgdorferi and viral polymerase chain reaction (PCR) test for Herpes simplex virus (HSV) – 1/2 and varicella zoster virus were negative. The AQP4-ABS and N-methyl-D-aspartate receptor antibodies (NMDAR-Abs) in the serum and CSF were negative. Serum MOG-ABS were positive with a titer of 1:320 as well as serum and CSF oligoclonal bands, without additional bands in the CSF.

Brain MRI, on day 3 of admission, demonstrated cerebral oedema in the supratentorial white matter with the segmental nonhomogeneous T2/FLAIR hyperintense lesions of thalamus, and smaller lesions in the right lentiform nuclei and the posterior left internal capsule. The cortical disease was demonstrated in the right occipital cortex. The lesions with the similar MR characteristics were present infratentorial in the left middle cerebellar peduncle. There was a mild leptomeningeal enhancement. Spinal cord and optic nerve involvement were not shown (Figure 1). Three-Dimensional Time-of-Flight (3D TOF) magnetic resonance angiography was described as normal.
A prolonged 3-hour electroencephalography (EEG) showed continuous high-amplitude slow rhythmic activity 1-1.5 Hz with captured stereotyped movements. Epileptic discharges were not seen.

She was initially treated with double intravenous antimicrobials (ceftazidime and acyclovir) which were stopped after negative culture and virology results. She was given intravenous methylprednisolone (20mg/kg/24h) during 5 days followed by oral prednisolone (2mg/kg) weaning course over 8 weeks. During glucocorticoid therapy she made a gradual clinical improvement and at 2-month review she recovered almost completely, with normal mobility and no focal neurologic deficit other than using her left hand more. The control MOG-abs in serum were positive with a titer of 1:320.

We confirm that we have read the journal's position on issues involving ethical publication and affirm that this work is consistent with those guidelines.

All procedures performed in study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written consent to publish all shown material was obtained from the parents of the patient.

DISCUSSION

Myelin oligodendrocyte glycoprotein associated disease is a rare, antibody-mediated inflammatory demyelinating disorder of CNS with various phenotypes predominantly involving brain in the younger children. Even though the phenotype in younger children is similar to ADEM with alteration in mental status, most experts consider MOGAD as a distinct entity with different immune system pathology [8].

In our case, the poor marginated white matter changes in an encephalopathic child made us suspect an immune-mediated encephalopathy. Although the condition resembled the
diagnosis of ADEM, some of the features were not typical, in particular the cortical lesions and the movement disorder. The cortical lesions are more common in patients with encephalitis and MOG-abs presenting with increased frequency of seizures [9, 10].

The movement disorders are more frequently seen in NMDAR- abs encephalitis [11]. Brain MRI in NMDAR- abs encephalitis is usually normal. Despite basal ganglia involvement frequently described in children with MOGAD, the movement disorder is not a cardinal feature [4, 12]. There is a case report of pediatric MOG- abs positive ADEM associated with movement disorder and seizures [13]. Our patient had a prolonged video EEG that confirmed episodes of stereotyped movements which were not epileptic. These abnormal movements stopped immediately after intravenous methylprednisolone treatment. The maintenance dose of phenobarbital was discontinued as she did not have previous seizures despite cortical lesions.

Acute disseminated encephalomyelitis is the most frequent type of pediatric MOGAD, but there is only one study comparing pediatric ADEM patients with and without MOG- abs. The study pointed that it is not possible to distinguish ADEM patients with MOG- abs from those without it at the onset of disease, without testing for MOG- abs, based on a few clinical and radiological differences [14].

Serum MOG- abs were detected in our patient in the acute phase with a titer of 1:320. Based on the fact that the disappearance of the MOG- abs after the initial attack might have prognostic implication, we retested the serum MOG- abs in our patient after treatment with steroids. Serum MOG- abs were consistent with a titer of 1:320 at 2-month review. There is no recommendation for regular monitoring of MOG- abs titers for relapse prediction as the literature review showed that only sparse data are available on the usefulness of regular monitoring of antibody titers in individual patients known to be positive for MOG- abs. No long term data were provided for the most of reported monophasic MOG- abs positive ADEM children. Recent studies revealed a seroconversion in a few patients with relapsing disease as
well as falling the titers below cut-off temporarily following treatment with steroids and rising again at a later disease stage [15,16]. Acute treatment with corticosteroids is the current standard of care for MOGAD. Although initial event can be severe at presentation, acute treatment with intravenous methylprednisolone followed by slow oral prednisone taper showed excellent response with full recovery in most children. Intravenous immunoglobulins and plasmapheresis constitute second-line therapies in case of insufficient response to intravenous corticosteroids [17,18]. Our patient was treated with intravenous methylprednisolone (20mg/kg/24h) during 5 days followed by oral prednisolone (2mg/kg) weaning course over 8 weeks. During glucocorticoid therapy she made a gradual clinical improvement and at 2-month review she recovered almost completely.

In conclusion, our case emphasises the inclusion of the MOG-abs testing in the initial work-up in children presenting with acute encephalopathy associated with demyelinating or encephalitic abnormalities on brain and/or spinal MRI even when the clinical phenotype is unusual. The prompt diagnosis of MOGAD is relevant for accurate disease monitoring, treatment strategies and counselling of parents.

**Conflict of interest:** None declared.
REFERENCES

1. Lana-Peixoto MA, Talim N. Neuromyelitis Optica Spectrum Disorder and Anti-MOG Syndromes. Biomedicines 2019;7(2):42. PMID: 31212763. DOI: 10.3390/biomedicines7020042
2. Tenenbaum SN. Pediatric demyelinating disease and anti-MOG antibody. Clin Exp Immunol 2021;12:7-21. DOI: https://doi.org/10.1136/cexp.2019.01305
3. Ramanathan S, Mohammad S, Tantisis E, Nguyen TK, Merheb V, Fung VSC et al. Clinical, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. J Neurol Neurosurg Psychiatry 2018; 89(2):127–37. PMID: 29142145. DOI: 10.1136/jnnp-2017-316880
4. Hacohen Y, Wong YY, Lechner C, Jurynczyk M, Wright S, Konsukan B, et al. Disease Course and Treatment Responses in Children With Relapsing Myelin Oligodendrocyte Glycoprotein Antibody–Associated Disease. JAMA Neurol 2018;75(4):478–87. PMID: 29305608. DOI: 10.1001/jamaneurol.2017.4601
5. Reindl M, Jarius S, Rostasy K, Berger T. Myelin oligodendrocyte glycoprotein antibodies: How clinically useful are they? Curr Opin Neurol 2017; 30(3):295–301. PMID: 28248700. DOI: 10.1097/WCO.0000000000000446
6. Ogawa R, Nakashima I, Takahashi T, Kaneko K, Akaishi T, Takai Y, et al. MOG antibody-positive, benign, unilateral, cerebral cortical encephalitis with epilepsy. Neurol Neuroinflamm 2017;4(2):e322. PMID: 28105459. DOI: 10.1211/XNI.00000000000003322
7. Wynford-Thomas R, Jacob A, Tomassini V. Neurological Update: MOG Antibody Disease. J Neurol 2019;266(5):1280–86. PMID: 30569382. DOI: 10.1007/s00415-018-9122-2
8. Ambrosius W, Michalak S, Kozubski W, Kalinowska A. Myelin oligodendrocyte glycoprotein antibody-associated disease: current insights into the disease pathophysiology, diagnosis and management. Int J Mol Sci 2020;22(1):100. PMID: 3337417. DOI: 10.3390/ijms22010100
9. Krupp IB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders; revisions to the 2007 definitions. Mult Scler 2013;19(10):1261–7. PMID: 23572237. DOI: 10.1177/1352458513484547
10. Wegener-Panzer A, Cleavelend R, Wendel EM, Baumann M, Bertolini A, Hausler M, et al. Clinical and imaging features of children with autoimmune encephalitis and MOG antibodies. Neurol Neuroinflamm 2020;7(4):e731. PMID: 32358225. DOI: 10.1211/XNI.00000000000007371
11. Panzer J, Dalmau J. Movement disorders in paraneoplastic and autoimmune disease. Curr Opin Neurol 2011;24(4):346–53. PMID: 21577108. DOI: 10.1097/WCO.0b013e328347b307
12. Baumann M, Grantis A, Djurdjevic T, Wendel EA, Lechner C, Behring B, et al. MRI of the first event in pediatric acquired demyelinating syndromes with antibodies to myelin oligodendrocyte glycoprotein. J Neurol 2018;265:845-55. PMID: 29423614. DOI: 10.1007/s00415-018-8781-3
13. Sa M, Thornton R, Chong WK, Kaliakatsos M, Hacohen Y. Paediatric MOG antibody–associated ADEM with complex movement disorder: A case report. Mult Scler J 2019;25(1):125-30. PMID: 30379117. DOI: 10.1177/1352458518786074
14. Baumann M, Sahin K, Lechner C, Hennes EM, Schlanda K, Mader S, et al. Clinical and neuroradiological differences of paediatric acute disseminating encephalomyelitis with and without antibodies to the myelin oligodendrocyte glycoprotein. J Neurol Neurosurg Psychiatry 2015;86(3):265-72. PMID: 25121570. DOI: 10.1136/jnnp-2014-308346
15. Jarius S, Ruprecht K, Kleiter I, Borisow N, Asgari N, Pitarokoili K, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: Frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. J Neuroinflammation. 2016;13(1):279. PMID: 27788675. DOI: 10.1186/s12974-016-0717-1
16. Wang X, Zhao R, Yang H, Liu C, Wang W, Liu T, et al. Clinical analysis of myelin oligodendrocyte glycoprotein antibody-associated demyelination in children: A single-center cohort study in China. Mult Scler Relat Disord 2022;58:103526. PMID: 35063926. DOI: 10.1016/j.msard.2022.103526
17. Bruijstens AL, Wendel EA, Lechner C, Bartels F, Finke C, Breu M, et al. E.U. paediatric MOG consortium consensus: Part 5 – Treatment of paediatric myelin oligodendrocyte glycoprotein antibody-associated disorders. Eur J of Paediatr Neurol 2020;29:41-53. PMID: 33176999. DOI: 10.1016/j.ejpn.2020.10.005
18. Klein da Costa B, Banwell BL, Kazutoshi Sato D. Treatment of MOG-IgG associated disease in paediatric patients: A systematic review. Mult Scler Relat Disord 2021;56:103216. PMID: 34450460. DOI: 10.1016/j.msard.2021.103216

DOI: https://doi.org/10.2298/SARH211202024R Copyright © Serbian Medical Society
Figure 1. Brain magnetic resonance imaging demonstrating: A – cerebral oedema in supratentorial white matter (white arrow); B – segmental nonhomogeneous T2/FLAIR hyperintense lesions of thalamus (white arrowhead), right lentiform nuclei (black arrow) and posterior left internal capsule (long white arrow); the cortical disease is demonstrated in right occipital cortex (white circle); C – the lesions with similar magnetic resonance characteristics are presenting infratentorial in left middle cerebellar peduncle (black arrowhead); D – there is a mild leptomeningeal enhancement