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Short Communication

MOG antibody seropositive aseptic meningitis: A new clinical phenotype

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ABSTRACT

The spectrum of myelin oligodendrocyte glycoprotein antibody (MOG-Ab) associated demyelination is evolving. Our case report describes a unique clinical presentation of aseptic meningitis with demyelinating lesions of the brain resembling acute disseminated encephalomyelitis and MOG-Ab seropositivity. A 22-year-old lady presented with history of fever of one week duration followed by headache, vomiting and neck stiffness. She had bilateral papilledema and signs of meningeal irritation. Neuroimaging revealed T2 and FLAIR hyperintense lesions in the right caudate, temporal lobe and left insula with enhancement on gadolinium contrast along with leptomeningeal enhancement. An extensive search for infectious and inflammatory etiology was negative while serum was positive for MOG-Abs tested twice at an interval of 12 days. She showed remarkable clinical-radiological resolution with steroids and has remained symptom free on follow up.

1. Introduction

The clinical phenotype of myelin oligodendrocyte glycoprotein antibody (MOG-Ab) associated demyelinating syndrome is evolving and recent evidence suggests that it is distinct from other demyelinating disorders such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) (Ramanathan et al., 2018). This case illustrates an uncommon presentation of MOG-Ab associated demyelinating disorder, expanding the clinical spectrum of this disorder.

2. Case summary

A 22-year-old lady, with no pre-morbid illness, presented with complaints of acute onset fever of seven days duration followed by severe holocranial headache, neck pain and vomiting for 3 days prior to admission. On examination, she was conscious and well oriented with stable vital parameters. She had bilateral grade 2 papilloedema and visual acuity of 6/9 in both eyes which improved on pinhole examination. She had signs of meningeal irritation with neck stiffness and positive Kernig's sign, without any other focal neurological deficit.

Peripheral blood revealed leukopenia during the febrile episode followed by normal leukocyte counts a week later. Cerebrospinal fluid (CSF) examination showed 57 cells (43 lymphocytes, 7 polymorphs and 4 degenerated cells), protein was 121 mg/dL and glucose was 42 mg/dL. Magnetic resonance imaging at admission, on the 11th day of illness revealed altered signal intensity in the right mesial temporal region, right caudate, medial thalamus, left temporal lobe adjacent to the left temporal horn, the left temporal tip and the left insular region in the T2WI and FLAIR sequences(Fig. 1A-1C). The caudate lesion appeared hypointense on T1WI. On SWI, there was a focal hypointensity in the medial thalamus and subtle hypointensities in the right caudate (Fig. 1D-1E). None of the lesions showed diffusion restriction. Bilateral optic nerves and entire spinal cord were normal. On post contrast imaging, diffuse leptomeningeal enhancement was noted in the areas with altered signal intensity and even the parieto-occipital region. There was patchy parenchymal enhancement as well as tentorial enhancement (Fig. 2A-2F). Neither the optic nerves nor the spinal cord showed any abnormal enhancement.

In view of the clinical presentation with acute onset of fever, headache and signs of meningeal irritation, presence of leptomeningeal enhancement and CSF pleocytosis with elevated protein, possibility of acute meningitis was considered and patient was investigated extensively for etiology spanning infectious and inflammatory causes. The work up has been summarised in Table 1.

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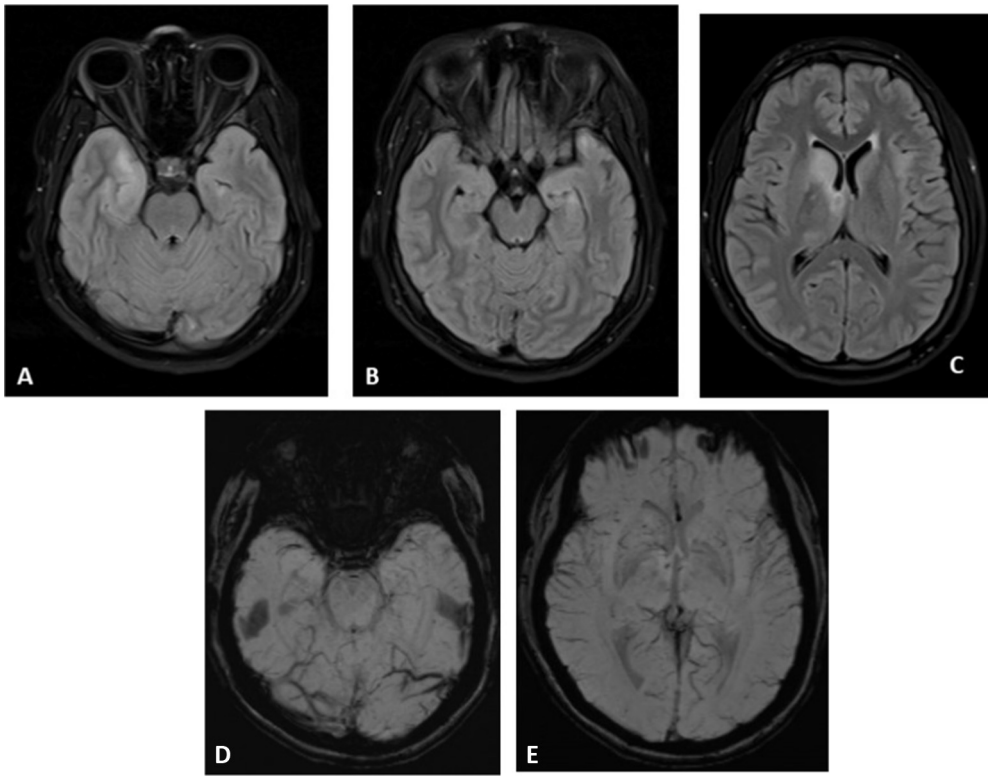

Fig. 1. 1A–1C: FLAIR axial: Bilateral optic nerves show normal signal intensity but altered increased signal is noted in right medial temporal region (A), adjacent to the left temporal horn and the left temporal tip (B), the right caudate, right medial thalamus and the left insular region (C).
1D-1E SWI axial image at the level of the midbrain does not show any abnormality (D) but the image at the ventricular level (E) shows a focal hypointensity in the right medial thalamus; subtle hemorrhagic foci are also noted in the right caudate.

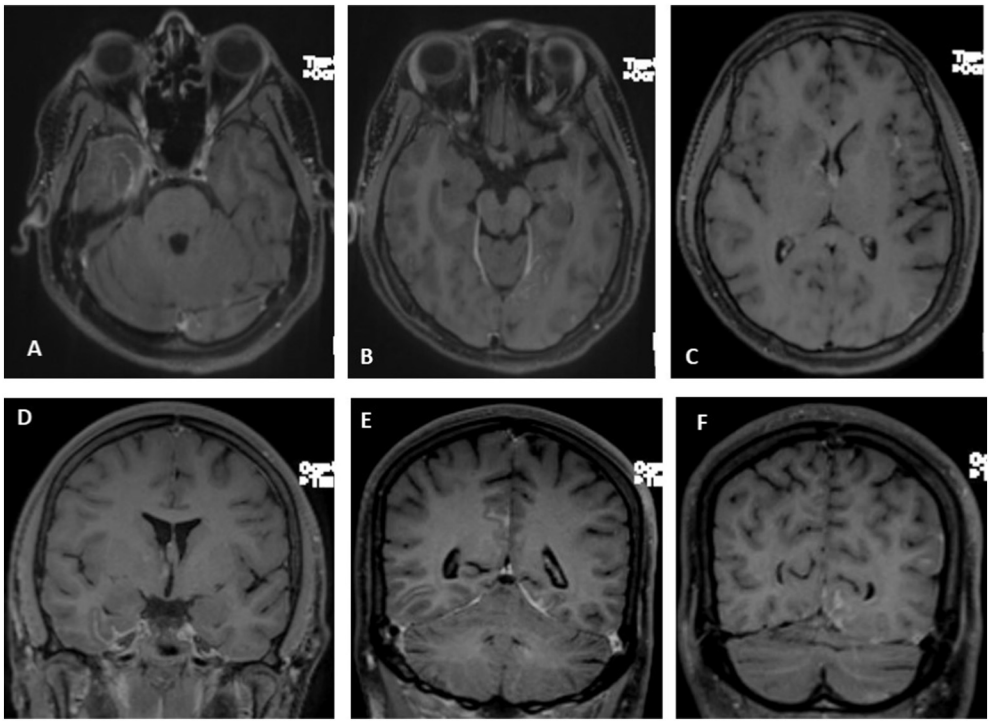

Fig. 2. 2A-2C: Post contrast T1 axial images: Note the leptomeningeal enhancement along the medial temporal region and along the anterior temporal pole. There is definite pachymeningeal enhancement along the tentorium (B). There is patchy enhancement in the right caudothalamic region and the left insular region – in the areas corresponding to the FLAIR hyperintensity in Fig. 1C.
2D-2F: Post contrast T1 coronal images show the right temporal leptomeningeal enhancement (D), tentorial enhancement along the left side and the sulcal enhancement in the right parieto-occipital region (E) and left occipital region (F).

Serum and CSF tested for antibodies associated with autoimmune encephalitis (NMDAR, AMPAR, CASPR-2, LGI-1 and GABA(B)R) by the indirect immunofluorescence assay on transfected cell lines were negative. Presence of associated demyelinating lesions of the temporal lobe, insula and caudate nucleus prompted us to look for primary or secondary demyelinating conditions. Serum and CSF anti-aquaporin-4 IgG antibody and CSF oligoclonal bands were negative. Serum was positive for MOG IgG antibody, tested by cell based immunoassay on transfected cells expressing the full-length MOG of human antibodies of immunoglobulin class IgG, on two occasions 12 days apart; whereas CSF was negative for the same. The method employed was indirect immunofluorescence on transfected cells at a titre of 1:10 dilution for in vitro determination of human IgG MOG antibodies using Euroimmun kits. Serum from the patient was shown to bind to transfected cells expressing the full-length MOG of human IgG using indirect immunofluorescence (Fig. 3).

Table 1
Investigations.

Category of tests done	Serum	CSF
Infectious etiology	• PCR for brucella, Dengue virus and Chikungunya virus - Negative	• Chikungunya IgM antibody – Negative • VDRL for treponema pallidum - Negative • PCR for Herpes simplex virus and Japanese • encephalitis virus – Negative • Indian ink for Cryptococcus – Negative • Ziehl Nielsen stain for acid fast bacilli – Nil • Gram stain and culture for bacteria, fungi and *Mycobacterium tuberculosis* – No growth
Immune etiology	• Antinuclear antibody - Negative • Antineutrophilic cytoplasmic antibodies - Negative • Antibodies associated with autoimmune encephalitis (NMDAR, AMPAR, LGI1,CASPR2, GABA(B)R) - Negative	• Antibodies associated with autoimmune encephalitis (NMDAR, AMPAR, LGI1,CASPR2, GABA(B)R) - Negative
Demyelinating disorders	• Anti-Aquaporin-4 IgG - Negative • MOG IgG antibody - Positive	• Anti-Aquaporin-4 IgG – Negative • Oligoclonal bands - Absent • MOG IgG antibody - Negative

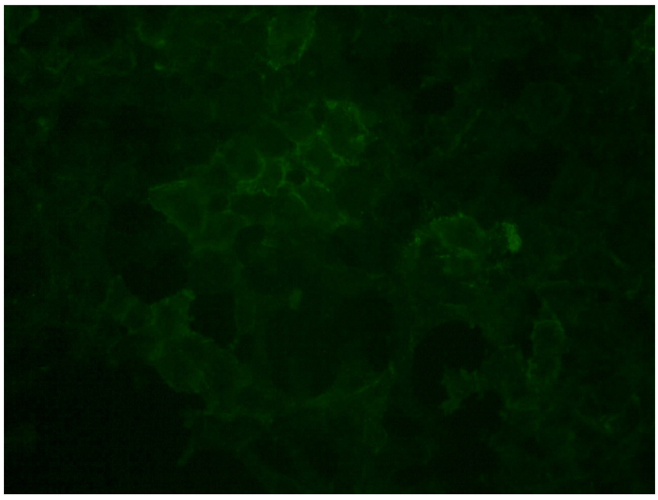

Fig. 3. Positive indirect immunofluorescence result of patient serum.
Indirect immunofluorescence shows granular membrane fluorescence in cell based assay using transfected cell line with full length MOG.

Visual evoked potentials performed to look for subclinical optic nerve involvement were normal. A diagnosis of MOG-Ab associated demyelinating syndrome was made. Pending investigation reports, she was started on intravenous acyclovir and ceftriaxone along with anti-oedema measures. On making the diagnosis of MOG-Ab associated demyelination, she received intravenous high dose methyl prednisolone for five days followed by oral steroids. Her headache decreased, papilloedema subsided and she became asymptomatic. She was discharged on oral steroid. CSF repeated after 3 weeks was normal, with 5 cells (all lymphocytes) and 27 mg/dL of protein. Repeat MRI brain showed resolution of the lesions in temporal lobe, putamen and thalamus with regression in the size of the lesion in right caudate nucleus. She has been symptom free for 3 months following the event. The serum MOG-Ab repeated during follow up has been negative.

3. Discussion

MOG-Ab associated syndrome is an autoimmune inflammatory central nervous system (CNS) demyelinating syndrome which presents as optic neuritis, myelitis, encephalitis and acute disseminated encephalomyelitis (ADEM) (Ramanathan et al., 2018; Jarius et al., 2016; Jurynczyk et al., 2017). Atypical presentations such as brainstem and cortical encephalitis have also been reported (Mariotto et al., 2017a; Ogawa et al., 2017). MOG is a glycoprotein which is a component of the CNS myelin sheath. It has a role in adhesion of myelin fibres and regulation of oligodendrocyte microtubule stability. It also modulates the interaction between myelin and the immune system via the complement pathway and its epitopes are highly immunogenic (Mayer and Minl, 2012; Weissert et al., 2002). MOG-Abs can activate the complement cascade and cause disorganisation of the oligodendrocyte cytoskeleton thus leading to inflammatory CNS demyelination. In a case series by Mariotto et al., 45% of the MOG-Ab positive cases had infectious and flu like prodromes (Mariotto et al., 2017b). A similar infectious prodrome was noted in our case. The infecting micro-organism possibly triggers an autoimmune reaction leading to the production of myelin oligodendrocyte glycoprotein specific T cells and B cells which participate in the immune attack against the central nervous system.

The presentation of MOG-Ab associated demyelinating syndrome as aseptic meningitis has been noted in only one case so far (Narayan et al., 2018). However, in the case reported by Narayan et al. the patient had optic neuritis preceding the aseptic meningitis presentation, whereas our patient had a monophasic presentation of aseptic meningitis along with only radiological evidence of demyelination. Since she presented with fever followed by headache and neck stiffness, a thorough search for possible infectious or inflammatory or auto-immune etiology was done. Her serum was positive for MOG-Abs though CSF was negative. MOG-Abs are generally detected in the serum more frequently than CSF as there is no intrathecal production of MOG-Abs. The absence of any other etiology and presence of MOG-Abs detected by cell based assay in the serum on two separate occasions 12 days apart favoured the possibility of MOG-Ab associated demyelination. Commercial tests can yield upto 20% false positive results (Waters et al., 2019). MOG IgG antibody was tested by cell based immunoassay using transfected cell lines in our Neuropathology Autoimmune laboratory. The method employed was indirect immunofluorescence on transfected cells expressing the full-length MOG of human antibodies of immunoglobulin class IgG. Cell based assay is the recommended test for detection of MOG IgG antibodies and is the current gold standard (Jarius et al., 2018). The repeat test for serum MOG-Ab was negative following treatment with steroids which is known to occur in MOG-Ab associated demyelination (Jurynczyk et al., 2017).

This case has the unique presentation of clinical features of aseptic meningitis coupled with demyelinating lesions in the brain resembling ADEM. Aseptic meningitis as an initial presentation of ADEM is known to occur and has been described earlier (Fujiki et al., 2008; Shintani et al., 2001). However, in the cases described so far, there were definite neurological symptoms of ADEM such as seizures, altered sensorium, paresis or other focal neurological symptoms which were absent in our patient. The symptoms of ADEM developed 5–19 days after the first symptoms of aseptic meningitis in the cases reported by Fujiki et al. Our patient was started on steroids within a week of onset of aseptic meningitis which may have altered the course of her illness and may be the

reason for the lack of clinical features of ADEM. MOG-Ab associated demyelinating disease is known to present as ADEM. Hence, our patient had both radiological and serological evidence of ADEM with clinical features of aseptic meningitis.

Another interesting finding in this case, was the leptomeningeal enhancement on contrast MR imaging of the brain. Leptomeningeal enhancement does not occur in demyelinating disorders such as multiple sclerosis, but has been described in few cases of NMOSD and couple of cases of MOG-Ab associated syndrome so far (Asgari et al., 2017; Numa et al., 2016). It can be speculated that the leptomeningeal enhancement is an indicator of the blood brain barrier disruption. In our case, we hypothesize that the preceding infection played a role in the alteration of the permeability or function of the blood brain barrier and thus permitted the access of the MOG-Abs to the central nervous system, similar to what has been described in NMOSD (Asgari et al., 2017).

4. Conclusion

Aseptic meningitis associated with radiological evidence of demyelination and leptomeningeal enhancement are the unique features in this case which have hitherto not been described and may be part of the expanding spectrum of MOG-Ab associated syndrome. This report serves to remind clinicians to test for serum MOG-Abs in cases of aseptic meningitis with ADEM like demyelinating lesions.

Declaration of conflict of interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

Asgari, N., Flanagan, E.P., Fujihara, K., Kim, H.J., Skejoe, H.P., Wuerfel, J., et al., 2017 Apr 21. Disruption of the leptomeningeal blood barrier in neuromyelitis optica spectrum disorder. Neurol. Neuroimmunol. Neuroinflamm. 4 (4), e343.

Fujiki, F., Tsuboi, Y., Hori, T., Yamada, T., 2008 Sep 15. Aseptic meningitis as initial presentation of acute disseminated encephalomyelitis. J. Neurol. Sci. 272 (1–2), 129–131.

Jarius, S., Kleiter, I., Ruprecht, K., Asgari, N., Pitarokoili, K., Borisow, N., et al., 2016. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 3: brainstem involvement - frequency, presentation and outcome. J. Neuroinflammation 13 (1), 281 Nov 1.

Jarius, S., Paul, F., Aktas, O., Asgari, N., Dale, R.C., 2018. de Seze J. MOG encephalomyelitis: international recommendations on diagnosis and antibody testing. J. Neuroinflammation 15 (1), 134 May 3.

Jurynczyk, M., Messina, S., Woodhall, M.R., Raza, N., Everett, R., Roca-Fernandez, A., et al., 2017 Dec 1. Clinical presentation and prognosis in MOG-antibody disease: a UK study. Brain. 140 (12), 3128–3138.

Mariotto, S., Monaco, S., Peschl, P., Coledan, I., Mazzi, R., Höftberger, R., et al., 2017 Oct 5a. MOG antibody seropositivity in a patient with encephalitis: beyond the classical syndrome. BMC Neurol. 17 (1), 190.

Mariotto, S., Ferrari, S., Monaco, S., Benedetti, M.D., Schanda, K., Alberti, D., et al., 2017 Decb. Clinical spectrum and IgG subclass analysis of anti-myelin oligodendrocyte glycoprotein antibody-associated syndromes: a multicenter study. J. Neurol. 264 (12), 2420–2430.

Mayer, M., Minl, E., 2012. Glycoproteins as targets of autoantibodies in CNS inflammation: MOG and more. Ther. Adv. Neurol. Disord. 5, 147–159.

Narayan, R.N., Wang, C., Sguigna, P., Husari, K., Greenberg, B., 2018. Atypical anti-MOG syndrome with aseptic meningoencephalitis and pseudotumor cerebri-like presentations. Mult. Scler. Relat. Disord. 27, 30–33 Oct 3.

Numa, S., Kasai, T., Kondo, T., Kushimura, Y., Kimura, A., Takahashi, H., et al., 2016. An adult case of anti-myelin oligodendrocyte glycoprotein (MOG) antibody-associated multiphasic acute disseminated encephalomyelitis at 33-year intervals. Intern. Med. 55 (6), 699–702.

Ogawa, R., Nakashima, I., Takahashi, T., Kaneko, K., Akaishi, T., Takai, Y., et al., 2017. MOG antibody-positive, benign, unilateral, cerebral cortical encephalitis with epilepsy. Neurol. Neuroimmunol. Neuroinflamm. 4 (2), e322 Jan 16.

Ramanathan, S., Mohammad, S., Tantsis, E., et al., 2018. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. J. Neurol. Neurosurg. Psychiatry 89, 127–137.

Shintani, S., Fumimura, Y., Shiigai, T., 2001. Acute disseminated encephalomyelitis following aseptic meningoencephalitis. Clin. Neurol. Neurosurg. 103 (3), 155–159 Oct.

Waters, P.J., Komorowski, L., Woodhall, M., Lederer, S., Majed, M., Fryer, J., 2019 Mar 12. A multicenter comparison of MOG-IgG cell-based assays. Neurology. 92 (11), e1250–e1255.

Weissert, R., Kuhle, J., de Graaf, K.L., Wienhold, W., Herrmann, M.M., Muller, C., et al., 2002. High immunogenicity of intracellular myelin oligodendrocyte glycoprotein epitopes. J. Immunol. 169, 548–556.