DOI:10.1017/cjn.2024.339
This is a manuscript accepted for publication in *Canadian Journal of Neurological Sciences*. This version may be subject to change during the production process.

TITLE

Anti–Myelin Oligodendrocyte Glycoprotein Antibodies and Acute Haemorrhagic Encephalomyelitis

AUTHOR INFORMATION

Say Ying Tan
MBBS
Neurology Department, Queen Elizabeth Hospital, Kota Kinabalu, Malaysia
sayying0307@hotmail.com
Presaad Pillai
MBBS, MRCP
Neurology Department, Queen Elizabeth Hospital, Kota Kinabalu, Malaysia
presaad87@gmail.com
Jack Son Wee
MBBS, MRCP
Neurology Department, Queen Elizabeth Hospital, Kota Kinabalu, Malaysia
weejackson@gmail.com
Prabha Jaya Krishna
MD
Radiology Department, Queen Elizabeth Hospital, Kota Kinabalu, Malaysia
prabha.jkrishna@gmail.com
Yuen Kang Chia
MD, MRCP
Neurology Department, Queen Elizabeth Hospital, Kota Kinabalu, Malaysia
cyk1118@gmail.com
ORCID: 0000-0001-9395-3107
Joshua Chin Ern Ooi
MB BCh BAO, MSc
Neurology Department, Queen Elizabeth Hospital, Kota Kinabalu, Malaysia
joshuaooichinern@gmail.com
ORCID: 0000-0002-6235-3712
CORRESPONDENCE: Joshua Chin Ern Ooi, joshuaooichinern@gmail.com, +60164228810, Department of Neurology, Queen Elizabeth Hospital, 13A Jalan Penampang, 88000, Kota Kinabalu, Sabah, Malaysia

WORD COUNT FOR TEXT BODY

The text body contains 1349 words (after incorporation of suggestions by reviewers).

TEXT BODY

To the Editor,

The relationship between Acute haemorrhagic encephalomyelitis (AHEM) *also known as Acute Haemorrhagic Leukoencephalitis (AHLE)* and Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is garnering increasing attention.(1,2) AHEM, is a severe, rapidly progressive demyelinating disease affecting the white matter within the central nervous system (CNS) and is often considered a severe variant of acute disseminated encephalomyelitis (ADEM).(3) Unlike typical ADEM, AHEM predominantly affects adults and confers significantly poorer outcomes.(3) Its precise aetiology remains unclear but is presumed to be of autoimmune origin.(3)

Recent studies have detected anti-myelin oligodendrocyte glycoprotein auto-antibodies (MOG-Abs) in the serum of AHEM patients, sparking discussions about a potential link between MOGAD and AHEM.(1,2) MOGAD constitutes a syndrome of acquired CNS autoimmune demyelinating disorders purportedly driven by MOG-Abs, distinct from multiple sclerosis and aquaporin-4(AqP4)-seropositive neuromyelitis optica spectrum disorder (NMOSD).(4) Clinical manifestations of MOGAD are heterogeneous but are classically associated with ADEM (in children), optic neuritis, or transverse myelitis.(4) Patients may also experience brainstem, cerebellar or cortical encephalitis symptoms.(4) More recently, adult-onset AHEM has been suggested as an emerging MOGAD phenotype.(1,2)

Here we report a case of adult-onset AHEM in a patient with serum MOG-Ab positivity. Our findings add to the developing discussion between AHEM and MOGAD while also delving into the pathogenic relevance of MOG-Abs and the diagnostic complexities of MOGAD.

A previously healthy thirty-five-year-old man presented to a rural hospital with sudden-onset paraplegia, sensory loss up to T10, and urinary retention following an upper respiratory tract infection (URTI) one week prior. Within three days of admission, he developed bulbar symptoms, respiratory distress, and encephalopathy, necessitating intubation and ventilation.

Three days post-onset, cerebrospinal fluid (CSF) analysis revealed pleocytosis [270 WBC/μL (lymphocytes: 11%, neutrophils: 89%)] and elevated protein levels (2.5g/L). Investigations into infective causes including bacterial cultures, screening for tuberculosis, cryptococcus,

https://doi.org/10.1017/cjn.2024.339 Published online by Cambridge University Press

syphilis, PCR analysis for Japanese Encephalitis, Herpes Simplex viruses 1&2, Enteroviruses, Human Herpes virus 6, Varicella-zoster virus, and Human Parechovirus were negative. CSF oligoclonal bands and IgG index were not tested due to a temporary suspension of testing services by our national laboratory. His C-reactive protein level was initially mildly raised (33.9 mg/L) while his ANA, p-ANCA, and c-ANCA tests were negative. Other routine blood tests were unremarkable. He was empirically commenced on intravenous ceftriaxone and acyclovir.

Due to the lack of MRI services at the rural hospital where he was initially treated, our patient required transfer to our centre for further evaluation and care. However, logistical challenges and unstable haemodynamics resulting from nosocomial sepsis caused significant delays in his transfer.

Brain and whole spine MRIs, ultimately performed thirty days from symptom onset revealed T2W/FLAIR hyperintensities in the midbrain, pons, bilateral internal capsules, cerebellar peduncles, globus pallidi, and thalami. Additionally, a centrally located, longitudinally extensive transverse myelitis (LETM) was observed, involving the cervical and thoracic cord and conus medullaris. Grey matter involvement was also noted, creating the characteristic "H sign". [Figure 1 – Panel 1 (a-e), Panel 2 (a-c)] These lesions were not diffusion-restricted and non-enhancing. Multiple T1W hyperintensities suggestive of haemorrhages with concurrent SWI blooming artifacts indicative of microhaemorrhages were observed over the corpus callosum, both globus pallidi, thalami, pons, midbrain, left cerebellum, bilateral cerebellar peduncles and spinal cord. [Figure 1 – Panel 1 (f-l), Panel 2 (d,e)] Collectively, these clinico-radiological features characterise AHEM.

Serum MOG-IgG-Ab testing using a fixed-cell-based assay (fixed-CBA) (EUROIMMUN) performed thirty days post-onset yielded a low-positive result (cut-off 1:10), while serum anti-AqP4-IgG auto-antibodies were not detected. Despite concurrent treatment with intravenous methylprednisolone (1 g/day; 5 days) and plasma exchange (5 cycles over 10 days), the patient showed no improvement. A repeated lumbar puncture forty days post-onset demonstrated persistent pleocytosis and hyperproteinorachia albeit to a milder degree, but CSF testing for MOG-IgG-Ab was negative. Regrettably, his condition deteriorated, and he succumbed thirteen days after being transferred to our centre (forty-three days from symptom onset) due to an overwhelming nosocomial sepsis, prior to initiation of further

https://doi.org/10.1017/cjn.2024.339 Published online by Cambridge University Press

immunotherapies. A post-mortem brain biopsy was declined by his kin due to cultural considerations.

Two cases of adult-onset AHEM with positive MOG-Abs have been reported to date.(1,2) They are summarised in Table 1.

As per the 2023 consensus diagnostic criteria, our patient's clinical, laboratory, and radiological features are consistent with the diagnosis of MOGAD.(4) He experienced a core clinical demyelinating event, having presented with ADEM (in this case AHEM) and myelitis, while testing positive for serum MOG-IgG-Ab through a fixed-CBA at a low-titre. Additionally, he exhibited supporting features including LETM, conus involvement, the 'H sign', and the presence of multiple supra- and infratentorial lesions while also testing negative for anti-AqP4-IgG auto-antibodies. Interestingly, the low-titre MOG-Abs seropositivity raises several questions and affords us the unique position to discuss the potential pathogenicity of MOG-Abs in AHEM.

The timing of testing for MOG-Abs is crucial in MOGAD, as antibody titres significantly decline over time.(5) A study found that only 55% of patients tested within 30 days of symptoms had positive MOG-Abs result, with half of them becoming negative, and 28% becoming low positive 6–12 months later.(5) This temporal dynamic could explain the low-titre MOG-Ab positivity observed in our patient, as there was a significant delay in testing. Given the inherent complexity in diagnosing AHEM, it is plausible that some patients who would otherwise be MOG-Abs seropositive might fall outside the diagnostic window when tested, contributing to the relative rarity of reported MOG-Ab seropositivity in AHEM cases.

The possibility of a false positive MOG-Ab result warrants careful consideration, especially given our patient’s low-titre. While he met the consensus criteria for MOGAD and possessed classical features (LETM, conus involvement, and “H-sign”), his URTI and the moderately symmetrical brain MRI findings raise concerns for alternative diagnoses, such as viral, parainfectious, or autoimmune encephalitides. Although we addressed key differential diagnoses, resource limitations hindered a more thorough investigation of all possible causes.

In a similar vein, we emphasise that caution is essential when interpreting the potential pathogenicity of MOG-Abs in patients with neurological symptoms. Furthermore, MOG-Abs are also found in conditions like seropositive NMOSD,(6) glioblastoma,(7) and anti-NMDA-receptor antibody encephalitis,(8) where they are not deemed primary pathogenic drivers. This observation raises the question of whether the presence of MOG-Abs in AHEM may

https://doi.org/10.1017/cjn.2024.339 Published online by Cambridge University Press

merely represent an epiphenomenon, potentially complicating the understanding of their role in the disease process.

Histopathological disparities between MOGAD and AHEM further complicate their association. MOGAD is characterised by a primary immune attack on myelin, manifesting with perivenous and confluent demyelinating lesions.(9) Conversely, AHEM reveals a broader spectrum of pathology, including prominent haemorrhages, oedema, axonal injury, fibrinoid vessel necrosis, and complement deposition.(1,3) Early and extensive astrocyte injury is also reported, suggesting that demyelination in AHEM could be secondary to astrocyte damage, akin to observations in NMOSD.(1,3) This contrast prompts consideration of whether MOG-Abs actively participate in the primary pathogenic process of AHEM or or are instead secondary to extensive neuronal destruction. These differences may also explain why patients with MOGAD generally respond to immunosuppression, while AHEM does not.

However, treatment resistance does not entirely rule out MOGAD. Some patients with MOGAD respond poorly to steroids and plasma exchange but demonstrate dramatic improvement with third-line anti-IL-6R therapy.(10) Similarly, AHEM might represent a form of MOGAD that necessitates rapid escalation to third-line therapies. In the absence of a convincing alternative diagnosis, we proceeded with a MOGAD-directed treatment course. Unfortunately, our ability to initiate Tocilizumab was hindered by the patient's rapid decline and recurrent sepsis. Diagnostic delays, compounded by healthcare disparities in the rural setting, significantly reduced the window for intervention, and earlier diagnosis along with treatment escalation could have potentially changed the outcome.

Our unique case prompts more nuanced explorations of MOGAD's potential contribution to the pathogenesis of AHEM, highlighting that current data is still insufficient to establish a definitive aetiological link. The temporal dynamics of MOG-Abs titres, histopathological disparities, and variable treatment outcomes further underscores the necessity for cautious interpretation of MOG-Abs seropositivity in AHEM. Moving forward, prospective studies are needed to better understand the potential aetiological association between MOGAD and AHEM. Retrospective cohorts face challenges due to the dynamic decline of MOG-Abs titres over time. Increased clinician awareness and timely testing are crucial for early diagnosis and evaluation of second/third-line immunotherapy, potentially improving outcomes.

https://doi.org/10.1017/cjn.2024.339 Published online by Cambridge University Press

FIGURES AND TABLES

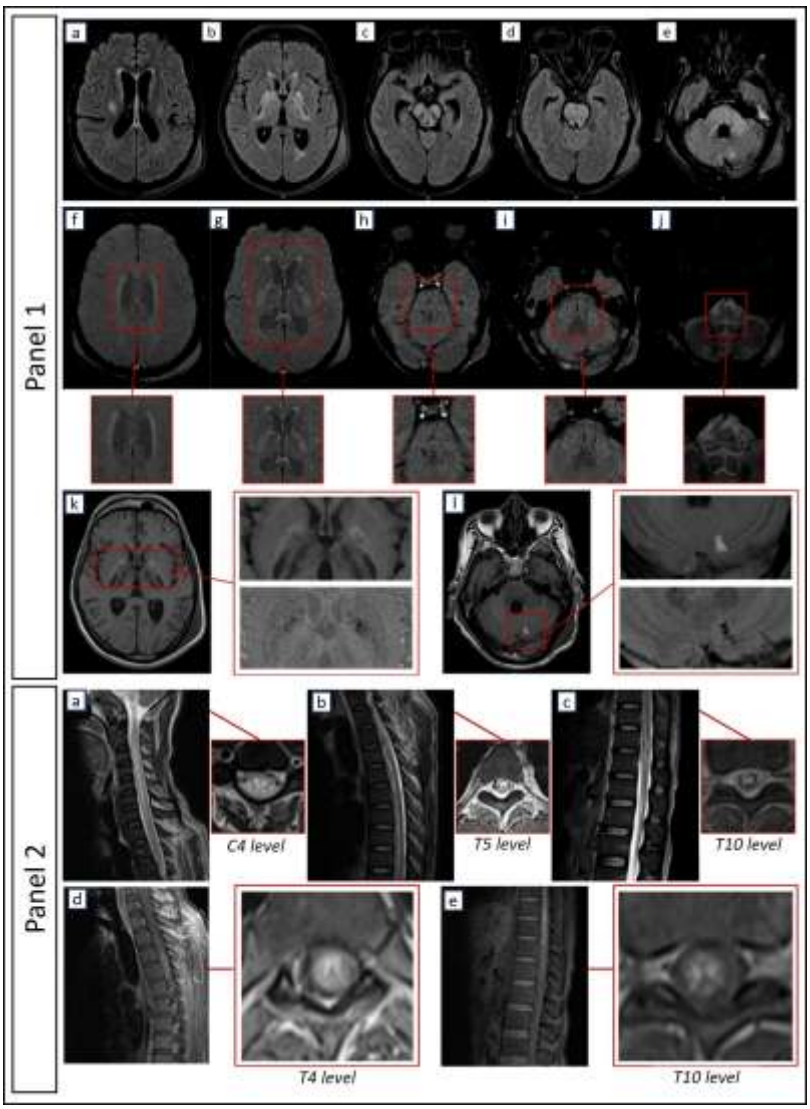

Figure 1: Brain and Spine MRI Performed 30 Days from Symptom Onset

n.b.: Panel 1: MR brain- (a-e): axial/T2-FLAIR brain images revealing (non-enhancing) hyperintensities in (a-b): bilateral internal capsules, (c): midbrain, (d): pons, (e): middle cerebellar peduncles. Note also the presence of ventriculomegaly along with symmetrical areas of perilesional hypointensities surrounding the bilateral (b): internal capsules and (c): medial lemniscus signifying extensive destructive processes. (f-j): axial/SWI brain images revealing multiple blooming artifacts suggestive of microhaemorrhages. (k-l): axial/T1W brain images revealing hyperintensities with concurrent blooming artifacts on SWI, signifying haemorrhages.

Panel 2: MR spine- (a-c): sagittal/T2-FLAIR spine images (and their corresponding axial views in red boxes) revealing a longitudinally extensive transverse myelitis involving the cervical (a), thoracic (b), and lower thoracic (c) spinal cord along with "H-sign" on the corresponding axial views. (d-e): sagittal/T1W spine images revealing hyperintensities suggestive of haemorrhages along with their corresponding axial views.

https://doi.org/10.1017/cjn.2024.339 Published online by Cambridge University Press

Table 1: Summary of Two Recent Cases of Adult-Onset Acute Haemorrhagic Encephalomyelitis with Anti-MOG Auto-Antibody Positivity

Article	Age/ Sex	Clinical Presentation	MRI findings	CSF analysis	MOGAD diagnosis	Brain biopsy	Treatment	Outcomes
Skarsta et al. April 2023 [1]	50s	SARS-CoV-2 vaccination 3 weeks prior ↓ Subacute visual impairment ↓ Fever and ataxia ↓ PAD10: Rapid neurological deterioration, intubated + ventilated, intensive care ↓ PAD32: Further deterioration, persistent loss of brainstem reflexes ↓ Death	Index scan (POD2): - Brain: Bilateral optic nerve enhancing T2/FLAIR hyperintensities. Small, non-enhancing T2/FLAIR hyperintensities in subcortical, periventricular, and pontine regions. - Spine: Unremarkable. 2nd scan (POD12): - Brain: New, size-progressive lesions with haemorrhagic and necrotic areas with an expansive effect in the brainstem.	1st LP: - Pleocytosis (77 cells/μL) - Elevated protein level (750 mg/L) - OCB: not detected 2nd LP: - Pleocytosis (887 cells/μL)	Serum MOG IgG auto-antibodies positive [1:320 (cut-off 1:10)] * Cell-based assay Serum anti-AQP4-IgG auto-antibodies negative	Not performed	1 g/day MTP (5 days) ↓ 2 g/day MTP and PLEX ↓ Cyclophosphamide (1 dose) ↓ Palliative care	Progressive deterioration then death

https://doi.org/10.1017/cjn.2024.339 Published online by Cambridge University Press

Bang et al. May 2023 [2]	54-year-old Female	Myalgia 3 weeks prior, Nausea, headache, and dizziness 2 weeks prior, Drowsiness 1 day prior ↓ Dysarthria, fever, left leg weakness, conjugate gaze palsy, tongue deviation to the left, and left central type facial palsy ↓ PAD1: Decreased verbal output, worsening left hemiparesis ↓ PAD2: Stuporous ↓ Post-MTP therapy: Rapid improvement in consciousness and other clinical symptoms	Index scan: - Brain: Multifocal, ill-defined, T2/FLAIR hyperintensities in the right basal ganglia, left temporal lobe, and left posterior pons. Hemorrhage on SWI in the right basal ganglia. Patchy enhancement over the right basal ganglia on contrast-enhanced T1W images.	LP: - Cell count: 6 cells/μL, - Elevated protein level (62 mg/dL) - OCB: not detected	Serum MOG IgG auto-antibodies positive * Live-cell fluorescence-activated cell-sorting assay Serum anti-AQP4-IgG auto-antibodies negative	Necrosis, diffuse neutrophilic, microglial and macrophage infiltrates with activated endothelial cells, and extravasated erythrocytes compatible with AHLE	1 g/day MTP (5 days) ↓ Mycophenolate mofetil (long-term)	Improved rapidly post-MTP therapy. Remained stable without recurrence during the 16-month follow-up period.

n.b.: SARS-CoV-2: Severe-Acute-Respiratory-Syndrome-Related Coronavirus-2; PAD: Post-onset day; POD: Post-onset day; MRI: Magnetic Resonance Imaging; T2/FLAIR: T2-weighted-Fluid-Attenuated Inversion Recovery; SWI: Susceptibility Weighted Imaging; T1W: T2-weighted imaging; LP: Lumbar puncture; OCB: Oligoclonal bands; MOG: Myelin Oligodendrocyte Glycoprotein; AqP4: Aquaporin 4; AHLE: Acute haemorrhagic leukoencephalitis; MTP: Methylprednisolone; PLEX: Plasma exchange.

https://doi.org/10.1017/cjn.2024.339 Published online by Cambridge University Press

REFERENCES

1. Skarsta L, Nicoletti T, Frick K, Kana V, De Vere-Tyndall A, Weller M, et al. Acute haemorrhagic leucoencephalitis as clinical manifestation of MOG antibody-associated disease. Vol. 94, Journal of Neurology, Neurosurgery and Psychiatry. BMJ Publishing Group; 2023. p. 583–5.

2. Bang SJ, Kim S, Seok HY. Acute hemorrhagic leukoencephalitis as a new phenotype of myelin oligodendrocyte glycoprotein antibody-associated disease. Vol. 44, Neurological Sciences. 2023.

3. Grzonka P, Scholz MC, De Marchis GM, Tisljar K, Rüegg S, Marsch S, et al. Acute Hemorrhagic Leukoencephalitis: A Case and Systematic Review of the Literature. Vol. 11, Frontiers in Neurology. Frontiers Media S.A.; 2020.

4. Banwell B, Bennett JL, Marignier R, Kim HJ, Brilot F, Flanagan EP, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. Vol. 22, The Lancet Neurology. 2023.

5. Forcadela M, Rocchi C, San Martin D, Gibbons EL, Wells D, Woodhall MR, et al. Timing of MOG-IgG Testing Is Key to 2023 MOGAD Diagnostic Criteria. Neurology(R) neuroimmunology & neuroinflammation. 2024 Jan 1;11(1).

6. Gou B, Yang P, Feng J, Li Y, Huang G, Shi J, et al. The case report of AQP4 and MOG IgG double positive NMOSD treated with subcutaneous Ofatumumab. J Neuroimmunol. 2023;376.

7. Amin M, Mays MA, Polston D, Flanagan EP, Prayson R, Kunchok A. Myelin oligodendrocyte glycoprotein (MOG) antibodies in a patient with glioblastoma: Red flags for false positivity. J Neuroimmunol. 2021;361.

8. Ding J, Li X, Tian Z. Clinical Features of Coexisting Anti-NMDAR and MOG Antibody-Associated Encephalitis: A Systematic Review and Meta-Analysis. Vol. 12, Frontiers in Neurology. Frontiers Media S.A.; 2021.

9. Takai Y, Misu T, Fujihara K, Aoki M. Pathology of myelin oligodendrocyte glycoprotein antibody-associated disease: a comparison with multiple sclerosis

https://doi.org/10.1017/cjn.2024.339 Published online by Cambridge University Press

and aquaporin 4 antibody-positive neuromyelitis optica spectrum disorders. Vol. 14, Frontiers in Neurology. Frontiers Media SA; 2023.

10. McLendon LA, Gambrah-Lyles C, Viaene A, Fainberg NA, Landzberg EI, Tucker AM, et al. Dramatic Response to Anti-IL-6 Receptor Therapy in Children With Life-Threatening Myelin Oligodendrocyte Glycoprotein-Associated Disease. Neurology(R) neuroimmunology & neuroinflammation. 2023 Nov 1;10(6).

https://doi.org/10.1017/cjn.2024.339 Published online by Cambridge University Press

CONFLICT OF INTEREST STATEMENT AND DECLARATION

All authors have no competing interests to declare.

ACKNOWLEDGEMENTS

This research was not funded by any agencies in the public or private sectors.

ETHICS STATEMENT

The patient's next of kin provided informed consent for the use of de-identified data for publication purposes

STATEMENT OF AUTHORSHIP

SYT is the main author of this manuscript. PP, JSW, PJK, YKC, and JCEO contributed equally to the management of the patient and drafting / editing of the manuscript.

https://doi.org/10.1017/cjn.2024.339 Published online by Cambridge University Press