Acute haemorrhagic leucoencephalitis as clinical manifestation of MOG antibody-associated disease

Dear Editor,

We read with interest the recently published article 'MOG antibody-associated encephalitis in adult: clinical phenotypes and outcomes' by Lee *et al*.[1] The authors illustrate three core disease phenotypes consisting of cortical encephalitis, limbic encephalitis and acute disseminated encephalomyelitis (ADEM), showing good response to immunosuppressive treatment and positive long-term outcomes. However, we would like to raise attention towards an emerging MOG antibody-associated clinical presentation characterised by a highly aggressive disease course with unfavourable prognosis suggestive for acute haemorrhagic leucoencephalitis (AHLE).

MOG antibody-associated disease (MOGAD) is a recently described autoimmune disease of the central nervous system. Accumulating evidence suggests that MOGAD has a remarkably heterogeneous spectrum. Besides cases of cerebellitis and autoimmune encephalitis, also a syndrome of encephalitis with steroid-responsive seizures, so-called FLAMES (FLAIR-hyperintense lesions in anti-MOG-associated encephalitis with seizures), is now recognised to be a specific feature of MOGAD. Interestingly, MOGAD can present with a monophasic clinical course in 50% of cases, which sets it clearly apart from multiple sclerosis and neuromyelitis optica spectrum diseases (NMOSD).

CASE PRESENTATION

Here, we report a case of a previously healthy patient in their 50s with subacute gradual visual impairment. The patient suffered from arterial hypertension and received a SARS-CoV-2 vaccination 3 weeks before hospital admission. The patient's medical history was otherwise unremarkable. On neurological examination, the patient showed bilateral optic disc swelling without any other focal deficits. Blood tests showed mild C-reactive protein (CRP) elevation and mild leucocytosis. Cerebrospinal fluid (CSF) analysis revealed pleocytosis (77 cells/µL) and elevated protein (750 mg/L, normal values <500 mg/L). Oligoclonal bands were not detectable. Brain MRI (figure 1A–F) revealed bilateral T2/FLAIR (fluid attenuated inversion recovery) hyperintense signal alterations of both optic nerves with contrast enhancement and small subcortical, periventricular, and pontine T2/FLAIR hyperintense lesions without contrast enhancement. Spinal MRI was unremarkable. Despite intravenous steroid treatment (1 g/day methylprednisolone over 5 days), the patient developed gait ataxia and fever. Escalation therapy with methylprednisolone 2 g/day and plasma exchange was initiated. A second lumbar puncture revealed a massive increase in

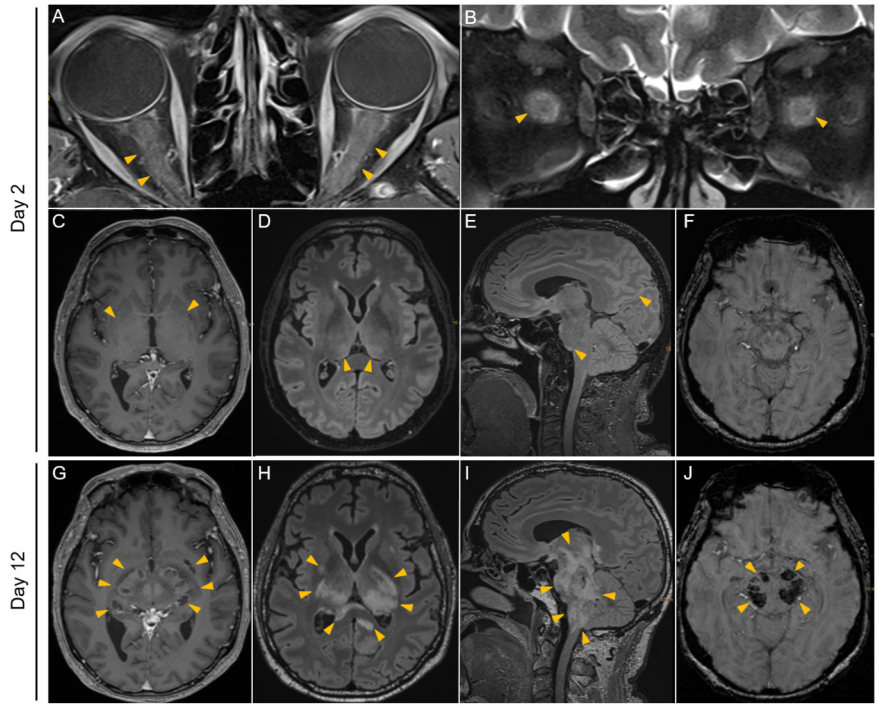

Figure 1 Comparison of patient's brain MRI 2 days and 12 days after the onset of symptoms (Most important findings are indicated by arrow heads) /A–F: initial brain MRI. (A) Axial fat-saturated T1ce showing bilateral hyperintensities of the optic nerve with extensive postcontrast enhancement. (B) Coronal T2 depicting hyperintense optic nerves with oedematous perineuritis. (C) Axial T1ce showing spotty contrast enhancement of mild dilated perivascular spaces in the basal nuclei. (D) Axial FLAIR revealing subtle bilateral thalamic hyperintensities. (E) Sagittal FLAIRce depicting focal subpial lesions in the pons and pial contrast enhancement especially of the left parietal lobe. (F) Axial SWI documenting no evidence of paramagnetic lesions. (G–J) Follow-up brain MRI 12 days after symptoms onset. (G) Axial T1ce showing bilateral ovoid basal ganglia lesions with circular contrast enhancement and hypointense core. (H) Axial FLAIR depicting diffuse hyperintense signal alterations of deep grey nuclei, posterior limb of internal capsules and splenium. (I) Sagittal FLAIR revealing massive tumefactive brainstem lesions. (J) Axial SWI revealing extensive deposition of paramagnetic material, suggestive for haemorrhagic transformation. Ce, contrast enhancing; FLAIR, fluid attenuated inversion recovery; SWI, susceptibility weighted imaging.

cell count (887 cells/µL). Bacterial, viral and fungal multiplex-PCR were negative. Extensive evaluation of collagen vascular disease and autoimmune encephalitis was negative. Considering Behçet's syndrome, HLA-B*51 was tested and turned out to be negative. Testing for serum AQP4-IgG and MOG-IgG in a cell-based assay revealed a marked titre positivity for MOG antibodies of 1:320 (cut-off 1:10), which has been confirmed in a reference laboratory (1:640, cut-off 1:160, University of Innsbruck, Austria). Ten days after symptoms onset, the patient's neurological status rapidly deteriorated with requirement of mechanical ventilation and intensive medical care. A new MRI scan revealed new and size-progressive lesions with haemorrhagic and necrotic areas as well as an expansive effect in the brainstem and medulla oblongata (figure 1G–J), indicating a progression to AHLE. One dose of cyclophosphamide as a rescue therapy was administered. Despite this early and aggressive treatment, the patient's condition deteriorated to persistent loss of brain stem reflexes. Thirty-two days after hospital admission, therapy was converted to a palliative concept. The patient died shortly after extubation.

DISCUSSION

Although MOGAD is a relatively new defined autoimmune disorder, an increasing number of reports have documented its heterogeneous spectrum of clinical manifestations. Here, we report a case of initial MOGAD diagnosis that progressed to AHLE with fatal outcome despite aggressive treatment. Notably, our patient initially presented with bilateral optic neuritis without signs of encephalopathy. The disturbance of consciousness due to deep brain structure damage abruptly developed only in the course of the disease. Furthermore, absence of tumefactive haemorrhagic lesions at the initial brain MRI and the mild improvement of visual acuity during the steroid treatment were suggestive of classical MOGAD. Such a MOGAD variant has not been reported yet.

AHLE, also known as Weston-Hurst disease, is now considered a variant of ADEM. Both typically present with acute encephalopathy and multifocal neurological deficits due to multiple inflammatory demyelinating lesions in cerebral hemispheres, brainstem and spinal cord. AHLE differs from ADEM in the fulminant and often fatal clinical course.[2] Being a rare disease with a complex diagnostic workup, AHLE is likely to be under-reported. The role of MOG-Ab in the development of AHLE is not known. In children with ADEM, seropositivity for MOG-Ab is found in up to 57% of cases[3] and is associated with an increased risk for relapse. Nevertheless, persistent relapse activity in ADEM has also recurred in cases without MOG-Ab. In our case, a false-positive test result seems very unlikely, as the MOG-Ab titre was high. The findings on sequential MRI scans and CSF analysis make it also unlikely that the initial presentation was already a manifestation of AHLE, but support the initial manifestation of a typical MOGAD disease instead. Moreover, haemorrhages have been increasingly described in MOGAD over the last few years, but have not received much attention yet.[4] However, systematic MOG-Ab testing in a larger AHLE population is needed in the future to study the potential link between MOG-Ab and AHLE.

MOGAD and ADEM respond well to corticosteroids and plasma exchange or intravenous immune globulin therapy (IVIGs) and typically have a good clinical outcome.[3] In contrast, the treatment of AHLE remains challenging and the mortality rate is high. Several therapeutic approaches have been tried, including intravenous high-dose steroids, IVIGs, plasmapheresis, in some cases followed by cyclophosphamide, rituximab or even decompressive craniectomy, yet with very limited success.[2] Neuropathological studies of AHLE lesions show not only demyelination and perivascular inflammation but also fibrinoid vessel necrosis with deposition of complement, prominent haemorrhages, oedema and axonal injury.[5] Moreover, early extensive astrocyte injury in AHLE has been reported,[5] suggesting

that demyelination might be secondary to astrocyte damage as observed in NMOSD and possibly in tumefactive demyelinating lesions. Given that such an inflammatory necrosis-associated environment typically involves a strong complement activation, a therapy focusing on complement inhibition in fulminant MOGAD cases might be worthwhile.

Overall, the presented case expands our knowledge about the heterogeneous manifestation of MOGAD and suggests a putative role of MOG-Ab in the pathophysiology of AHLE. Further investigation of the association between MOG-Ab and AHLE is warranted in future studies.

Laura Skarsta,[1] Tommaso Nicoletti,[1] Katja Frick,[2] Veronika Kana,[1] Anthony De Vere-Tyndall,[3] Michael Weller,[1,4] Patrick Roth,[1,4] Marina Herwerth [1,5]

[1]Department of Neurology, University Hospital Zurich, Zurich, Switzerland
[2]Institute of Intensive Care Medicine, University Hospital Zurich, Zurich, Switzerland
[3]Department of Neuroradiology, University of Zurich, Zurich, Switzerland
[4]Department of Neurology, University of Zurich, Zurich, Switzerland
[5]Institute of Pharmacology and Toxicology, University of Zurich, Zurich, Switzerland

Correspondence to Dr Marina Herwerth, Department of Neurology, University Hospital Zurich, Zurich, 8091, Switzerland; marina.herwerth@uzh.ch

Acknowledgements We thank Markus Reindl (University of Innsbruck, Austria) for measuring MOG-Ab as reference laboratory. We thank Matthias Wyss for comments on the manuscript.

Contributors LS, TN, KF, VK and MH are responsible for the concept, drafting and manuscript design. TN, VK and ADV-T drafted the figure with input from all the authors. MW and PR were involved in interpretation and revision of data for the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained from next of kin.

Ethics approval This manuscript was approved by the institutional board (USZ Data Governance Board) with the ID: DUP-1026. Participants gave informed consent to participate in this study.

Provenance and peer review Not commissioned; internally peer reviewed.

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2023-331350).

LS and TN contributed equally.

To cite Skarsta L, Nicoletti T, Frick K, *et al*. *J Neurol Neurosurg Psychiatry* 2023;**94**:583–585.

Received 28 February 2023
Accepted 1 March 2023
Published Online First 7 April 2023

J Neurol Neurosurg Psychiatry 2023;**94**:583–585.
doi:10.1136/jnnp-2023-331350

ORCID iD
Marina Herwerth http://orcid.org/0000-0001-5125-4594

REFERENCES

1 Lee W-J, Kwon YN, Kim B, *et al*. MOG antibody-associated encephalitis in adult: clinical phenotypes and outcomes. *J Neurol Neurosurg Psychiatry* 2023;94:102–12.
2 Grzonka P, Scholz MC, De Marchis GM, *et al*. Acute hemorrhagic leukoencephalitis: a case and systematic review of the literature. *Front Neurol* 2020;11:899.
3 Otallah S. Acute disseminated encephalomyelitis in children and adults: a focused review emphasizing new developments. *Mult Scler* 2021;27:1153–60.
4 Hochmeister S, Gattringer T, Asslaber M, *et al*. A fulminant case of demyelinating encephalitis with extensive cortical involvement associated with anti-MOG antibodies. *Front Neurol* 2020;11:31.
5 Robinson CA, Adiele RC, Tham M, *et al*. Early and widespread injury of astrocytes in the absence of demyelination in acute haemorrhagic leukoencephalitis. *Acta Neuropathol Commun* 2014;2:52.