CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Dramatic Response to Anti-IL-6 Receptor Therapy in Children With Life-Threatening Myelin Oligodendrocyte Glycoprotein-Associated Disease

Loren A. McLendon, MD, Claudia Gambrah-lyles, MD, Angela Viaene, MD, Nina A. Fainberg, MD, Elizabeth I. Landzberg, MD, Alexander M. Tucker, MD, Peter J. Madsen, MD, Jimmy Huh, MD, Maya R. Silver, MD, John D. Arena, MD, Martha F. Kienzle, MD, and Brenda Banwell, MD

Correspondence
Dr. Banwell
banwellb@email.chop.edu

Neurol Neuroimmunol Neuroinflamm 2023;10:e200150. doi:10.1212/NXI.0000000000200150

Abstract

Objectives

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an immune-mediated neuroinflammatory disorder leading to demyelination of the CNS. Interleukin (IL)-6 receptor blockade is under study in relapsing MOGAD as a preventative strategy, but little is known about the role of such treatment for acute MOGAD attacks.

Methods

We discuss the cases of a 7-year-old boy and a 15-year-old adolescent boy with severe acute CNS demyelination and malignant cerebral edema with early brain herniation associated with clearly positive serum titers of MOG-IgG, whose symptoms were incompletely responsive to standard acute therapies (high-dose steroids, IV immunoglobulins (IVIGs), and therapeutic plasma exchange).

Results

Both boys improved quickly with IL-6 receptor inhibition, administered as tocilizumab. Both patients have experienced remarkable neurologic recovery.

Discussion

We propose that IL-6 receptor therapies might also be considered in acute severe life-threatening presentations of MOGAD.

From the Division of Neurology (L.A.M., C.G., M.R.S., B.B.), Department of Pediatrics, Children's Hospital of Philadelphia; Department of Neurology, Perelman School of Medicine, University of Pennsylvania; Department of Pathology (A.V.), Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania; Division of Critical Care Medicine (N.A.F., E.I.L., J.H., M.F.K.), Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania; and Division of Neurosurgery (A.M.T., P.J.M., J.D.A.), Children's Hospital of Philadelphia; Department of Neurosurgery, Perelman School of Medicine, University of Pennsylvania.

Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

Introduction

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a monophasic or relapsing inflammatory demyelinating disorder, with international consensus criteria recently published.[1] The most common clinical presentations include acute disseminated encephalomyelitis (ADEM), optic neuritis, and transverse myelitis,[2] although cortical encephalitis with malignant cerebral edema has also been described.[2-5] Patients with severe ADEM (defined by encephalopathy and polyfocal neurologic deficits) may also have seizures and extensive cortical involvement that overlap with features seen in the cortical encephalitis phenotype. Attacks are typically responsive to corticosteroid therapy, IV immunoglobulin (IVIG), and/or therapeutic plasma exchange (PLEX).[1,6]

We present 2 patients with severe, acute manifestations of MOGAD, whose marked cerebral inflammation and edema stabilized with aggressive intracranial pressure monitoring, although with ongoing intermittent spikes in cerebral pressure.[5] Severe neurologic deficits failed to respond to acute therapies but did dramatically improve within 24 hours of administration of IL-6 receptor inhibition. Both patients have experienced remarkable neurologic recovery.

Case Presentation

Patient 1

A 7-year-old Hispanic boy presented with headache, vomiting, obtundation, and a generalized convulsive seizure. Lumbar puncture (LP) revealed markedly elevated opening pressure and CSF with lymphocytic predominant pleocytosis (WBC 68 cells/mm^3), as demonstrated in Figure 1.

Contrasted MRI demonstrated multifocal areas of restricted diffusion, cortical and subcortical T2/FLAIR hyperintensities, and mild leptomeningeal enhancement (Figure 2, A and B). He deteriorated over 48 hours to a Glasgow Coma Scale (GCS) of 8. Head CT revealed diffuse cerebral edema with impending herniation (Figure 2C). He was transferred to our tertiary pediatric intensive care unit (PICU).

An intraparenchymal intracranial pressure (ICP) monitoring catheter recorded pressures between 10 and 36 mm Hg, which improved, albeit with intermittent pressure spikes despite supportive strategies: hyperosmolar therapy, sedation and analgesia, pentobarbital coma, and hyperventilation (see also case report).[5] Serum MOG-IgG was clearly positive (titer 1:1,000, live cell-based assay, Mayo Clinic Laboratories).

Despite 4 days of methylprednisolone 1,000 mg IV daily (7 days total) and 3 sessions of PLEX (6 sessions total), ICP elevations continued. One tocilizumab 8 mg/kg/dose IV was given on day 13. Within 12 hours, his GCS improved to 12. His episodes of intracranial hypertension resolved. Over the next 72 hours, he became fully alert and followed simple commands. He received a second dose of tocilizumab on day 19 and was transferred from PICU on day 22. He received inpatient rehabilitation for 5 weeks.

Nine months after onset, neurologic examination normalized. However, he has ongoing impulsivity and mild behavioral issues. Brain MRI with and without contrast showed evolving FLAIR hyperintensities and developing encephalomalacia (Figure 2D). His course has been monophasic to date.

Patient 2

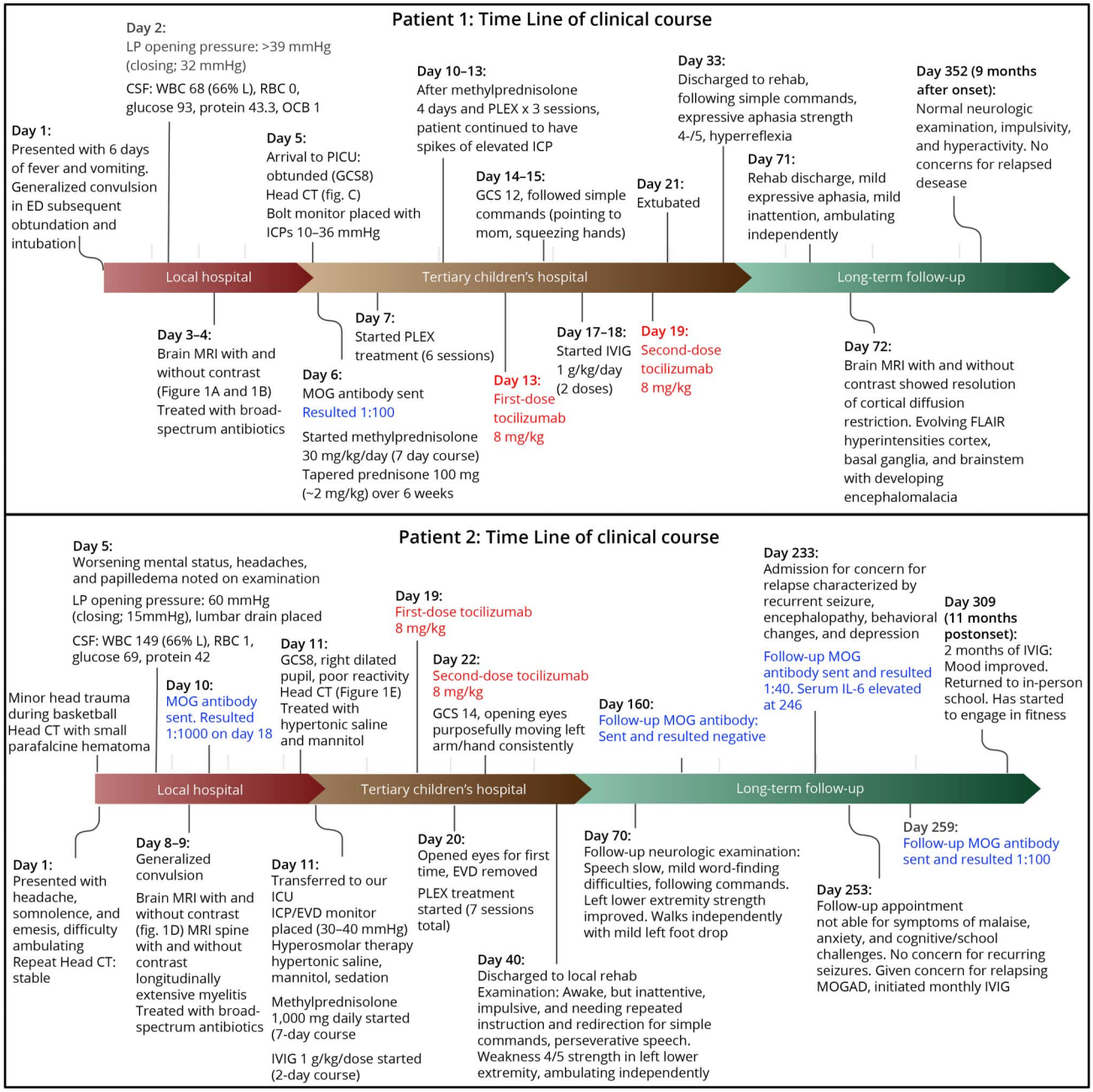
A 15-year-old White adolescent boy presented with headache, somnolence, and emesis. LP was performed and revealed an elevated opening pressure of 60 mm Hg. CSF analysis showed lymphocytic predominant pleocytosis (WBC 149 cells/mm^3), normal protein, and normal glucose level. He became progressively encephalopathic and was admitted to a local PICU.

On day 9, his mental status worsened and he seized. Contrasted brain MRI showed multifocal areas of T2/FLAIR hyperintensity with diffuse leptomeningeal enhancement (Figure 2E). On day 11, his right pupil was dilated and poorly reactive. CT demonstrated diffuse cerebral edema with impending tonsillar herniation (Figure 2F). After ICP monitor placement, hyperosmolar therapy with hypertonic saline and IV mannitol was administered. He was transferred to our PICU; there his GCS was 8, with minimal withdrawal to noxious stimulation, brisk reflexes, and a right-sided extensor response. He had multiple episodes of ICP crisis (range: 30–40 mm Hg) despite supportive strategies (Figure 1). He received methylprednisolone 1,000 mg IV daily for 7 days and IVIG 2 g/kg divided over 2 days. An external ventricular drain and meningeal and brain parenchymal biopsy were performed. Pathology demonstrated neutrophilic predominant inflammation with microglia activation and scattered CD3$^+$ lymphocytic inflammation (Figure 3). Serum MOG-IgG was clearly positive (titer 1:1,000, live cell-based assay, Mayo Laboratories).

Owing to ongoing, severe cerebral edema despite symptomatic therapies, tocilizumab 8 mg/kg/dose IV was given for 2 doses 3 days apart (days 19 and 22). Within 24 hours of the first dose of tocilizumab, ICPs normalized. By 48 hours, he was awake (GCS of 14) and identified family members. After completion of 7 sessions of PLEX (started on day 20), he received 2g/kg of IVIG divided over 3 days. He was transferred to a local rehabilitation unit on day 40. Five months after onset, he had a normal neurologic examination and mild memory/cognitive impairment. MRI showed improvement in T2/FLAIR hyperintensity (Figure 2G), and serum MOG-IgG was negative.

Seven months after onset, he presented with recurrent seizures, positive serum MOG-IgG (1:40), and elevated serum IL 6 (246 pg/mL). Given concern for MOGAD relapse, monthly IVIG was started. He returned to school with no further relapses or seizures.

Figure 1 Clinical Course for Each Patient

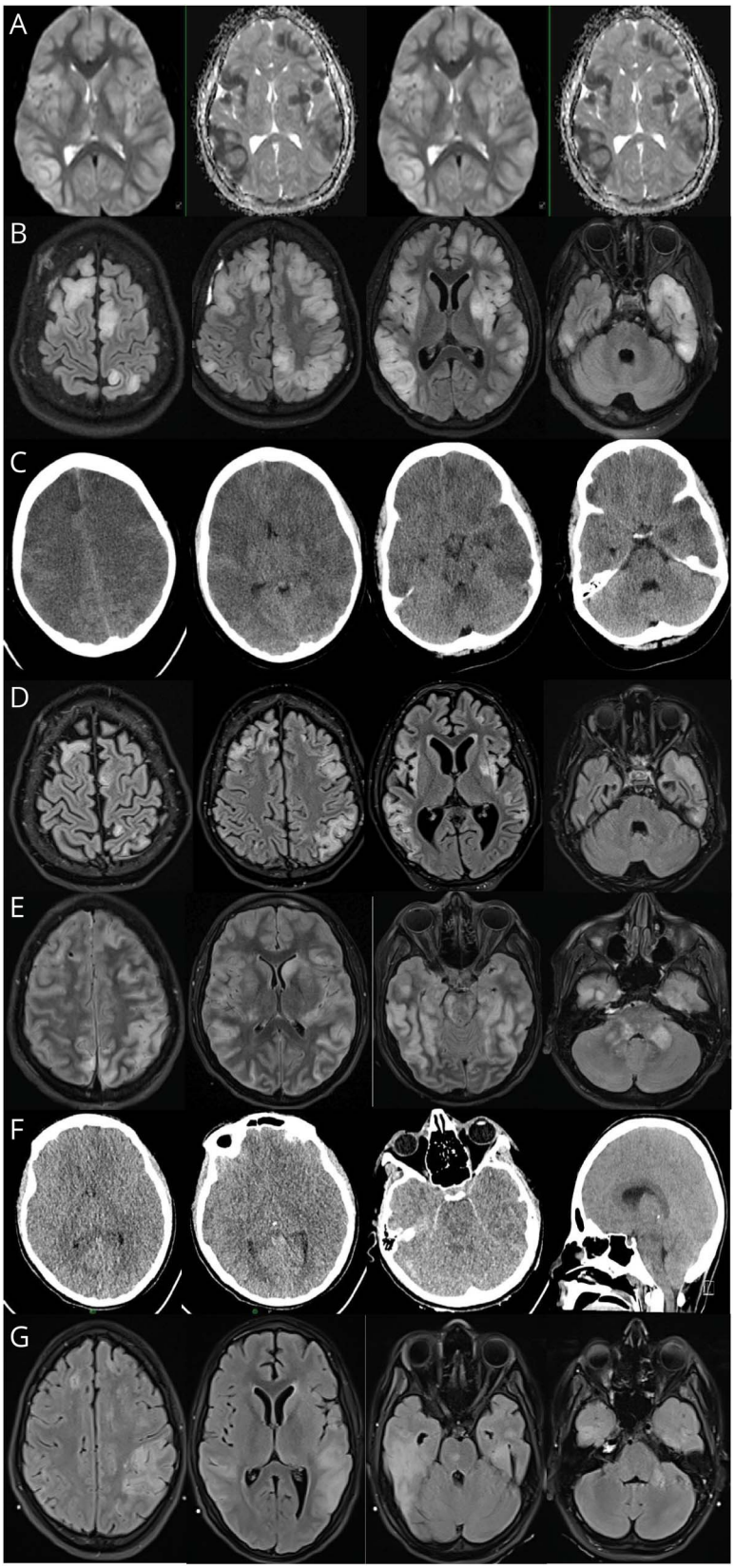


Discussion

Malignant cerebral edema secondary to MOGAD is life-threatening and may not respond quickly to corticosteroids, PLEX, or IVIG. We report 2 children who experienced rapid resolution of raised ICP and cerebral edema after treatment with the IL6 receptor blocker, tocilizumab.

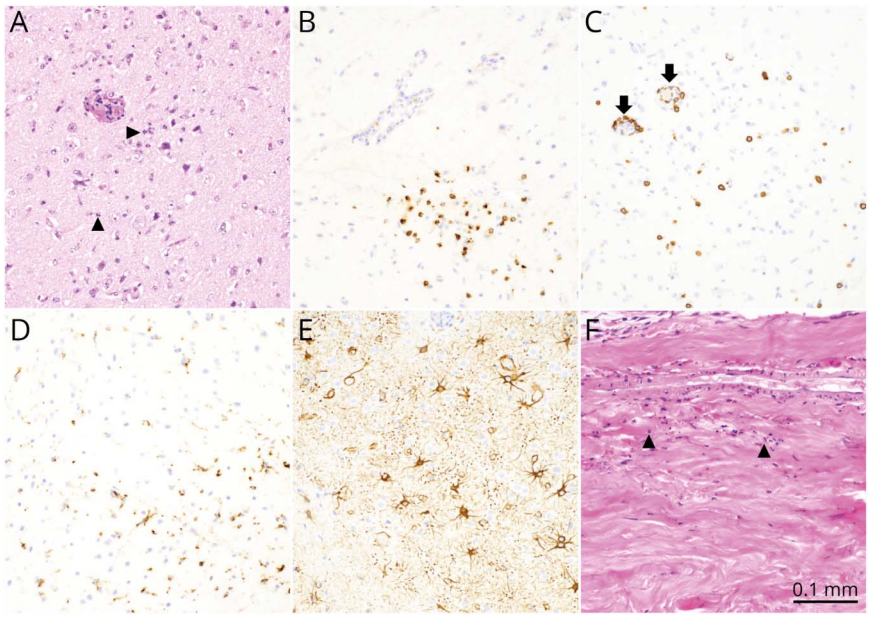
Our decision to administer IL-6 receptor blockade was based on studies demonstrating elevated cytokine concentrations, particularly IL-6, in MOGAD.[7] In a study of CSF and serum obtained from 29 untreated patients (15 children) with MOGAD, CSF IL-6 concentrations were elevated compared with patients with multiple sclerosis (n = 20) and were comparable with levels measured in patients with AQP4 antibody–positive neuromyelitis optica spectrum disorder (NMOSD) (n = 20).[7] Phase III studies of anti-IL-6 receptor therapies in NMOSD clearly demonstrated suppression of relapses, and these therapies are approved for this condition.[8,9] Case reports describe tocilizumab treatment in relapsing patients with MOGAD who have failed treatment with other therapies with prolonged periods of disease suppression.[10-12] Clinical trials of IL-6 receptor blockade for relapsing patients with MOGAD are now enrolling.[8]

Figure 2 Neuroimaging Features of Malignant MOGAD



Patient 1: (A) MRI performed on day 2 (at outside hospital) demonstrating multifocal areas of restricted diffusion weighted imaging on the left with apparent diffusion coefficient correlate on the right. (B) MRI multifocal areas of T2/FLAIR hyperintensity in cortical and subcortical matter, basal ganglia, and brainstem and mild leptomeningeal enhancement (not pictured). (C) Head computed tomography performed on day 5 showing diffuse cerebral edema with effacement of sulci. (D) MRI on day 39: interval evolution of the multiple extensive cortical and subcortical lesions of both cerebral hemispheres and in the brainstem as detailed. This includes developing encephalomalacia in many of the previously involved regions. The cerebrum has overall, mildly decreased in volume. Patient 2: (E) Brain MRI with T2/FLAIR hyperintensity in the frontotemporal and occipital lobes and bilateral cerebellar peduncles with diffuse leptomeningeal enhancement (not pictured). (F) Head CT obtained on day 11 on arrival to CHOP showing diffuse cerebral edema in supratentorial and infratentorial parenchyma with effacement of sulci, fissures, basal cistern, and cerebellar tonsillar descent. (G) Brain MRI showing partial improvement in T2/FLAIR hyperintensity of lesions involving both cerebral hemispheres, diencephalon, and brainstem. MOGAD = myelin oligodendrocyte glycoprotein antibody-associated disease.

Figure 3 Patient 2 Pathology



(A) A biopsy of the superficial cortex shows scattered neutrophilic inflammation (arrowheads, hematoxylin, and eosin stain, ×200 magnification). (B) Neutrophils within the brain parenchyma are highlighted with myeloperoxidase (myeloperoxidase immunostain, ×200 magnification). (C) Scattered T lymphocytes are present around vessels (arrows) and within the brain parenchyma (CD3 immunostain, ×200 magnification). (D) Reactive microglia are present, often in regions of neutrophilic inflammation; collections of macrophages are not seen (CD68 immunostain, ×200 magnification). (E) Reactive astrocytes within the cortex are highlighted with GFAP (GFAP immunostain, ×200 magnification). (F) A biopsy of the dura shows focal neutrophilic inflammation (arrowheads, hematoxylin, and eosin stain, ×200 magnification). Scale bar in F applies to all images.

IL-6 is known to promote $CD4^+$ T-cell differentiation into a Th17 phenotype and is capable of activating plasmablasts and B cells (potentially promoting MOG-IgG production).[13] Murine models of experimental autoimmune encephalitis (EAE), which are induced by MOG immunization, require both MOG antibody production and MOG-reactive T cells for clinical disease.[14] IL-6 in the brain increases permeability of the blood-brain barrier (BBB),[14,15] leading to increased ingress of activated MOG-reactive cells and circulating MOG-IgG antibodies.[15]

BBB disruption is an important consideration for the use of anti-IL-6 receptor therapies, which bind the soluble and fixed IL-6 receptor leading to increased levels of circulating IL-6.[13] Tocilizumab is not believed to cross the BBB,[16] would not be able to mitigate IL-6 binding in the CNS, and, conceptually, could worsen cerebral symptoms in MOGAD. As an analogous example, patients with chimeric antigen receptor T-cell toxicity have increased circulating IL-6 levels in both peripheral cytokine release syndrome (CRS) and in CNS immune effector cell–associated neurotoxicity syndrome (ICANS).[16] Tocilizumab is effective only in CRS and is not advised in ICANS because of concerns of further elevation of IL-6 without the ability of tocilizumab to effectively cross the BBB to mitigate this effect.[16] In AQP4-NMOSD and MOGAD, however, AQP4- or MOG antibodies increase BBB permeability through reduced expression of endothelial tight junction proteins.[9] This BBB disruption leads not only to entry of plasmablasts and T cells but also to entry of therapeutic antibodies. In cell-based modeling, satralizumab was shown to cross through BBB endothelia in the presence of serum-containing AQP4-IgG,[9] potentially explaining why IL-6 receptor blockade with tocilizumab or satralizumab might be both efficacious and safe in NMOSD and possibly MOGAD, as in our patients.[13] Siltuximab, a direct IL-6 inhibitor, which reduces IL-6 concentrations, would be an interesting consideration for future trials.

We propose that IL-6 receptor therapies might also be considered in acute severe life-threatening presentations of MOGAD.

Acknowledgment

The authors thank the patients and the parents of their patients who provided verbal and written consent to include their children in the medical literature.

Study Funding

The authors report no targeted funding.

Disclosure

J.W. Huh was funded by NIH R01NS110898 and R01NS113945 (but no relevance to this report). B. Banwell serves as a consultant to Novartis, Roche, UCB, GlaxoSmith Kline, Teva Neuroscience, Sanofi-Genzyme, University of Texas Southwestern, and JRD pharmaceuticals. The other authors have no relevant disclosures. Go to Neurology.org/NN for full disclosures.

Publication History

Received by *Neurology: Neuroimmunology & Neuroinflammation* February 20, 2023. Accepted in final form June 8, 2023. Submitted and externally peer reviewed. The handling editor was Editor Josep O. Dalmau, MD, PhD, FAAN.

Appendix Authors

Name	Location	Contribution
Loren A. McLendon, MD	Division of Neurology, Department of Pediatrics, Children's Hospital of Philadelphia; Department of Neurology, Perelman School of Medicine, University of Pennsylvania	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design
Claudia Gambrah-lyles, MD	Division of Neurology, Department of Pediatrics, Children's Hospital of Philadelphia; Department of Neurology, Perelman School of Medicine, University of Pennsylvania	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Angela Viaene, MD	Department of Pathology, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Nina A. Fainberg, MD	Division of Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia	Drafting/revision of the manuscript for content, including medical writing for content
Elizabeth I. Landzberg, MD	Division of Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia	Drafting/revision of the manuscript for content, including medical writing for content
Alexander M. Tucker, MD	Division of Neurosurgery, Children's Hospital of Philadelphia; Department of Neurosurgery, Perelman School of Medicine, University of Pennsylvania	Drafting/revision of the manuscript for content, including medical writing for content
Peter J. Madsen, MD	Division of Neurosurgery, Children's Hospital of Philadelphia; Department of Neurosurgery, Perelman School of Medicine, University of Pennsylvania	Drafting/revision of the manuscript for content, including medical writing for content
Jimmy Huh, MD	Division of Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia	Drafting/revision of the manuscript for content, including medical writing for content
Maya R. Silver, MD	Division of Neurology, Department of Pediatrics, Children's Hospital of Philadelphia; Department of Neurology, Perelman School of Medicine, University of Pennsylvania	Drafting/revision of the manuscript for content, including medical writing for content
John D. Arena, MD	Division of Neurosurgery, Children's Hospital of Philadelphia; Department of Neurosurgery, Perelman School of Medicine, University of Pennsylvania	Drafting/revision of the manuscript for content, including medical writing for content
Martha F. Kienzle, MD	Division of Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia	Drafting/revision of the manuscript for content, including medical writing for content
Brenda Banwell, MD	Division of Neurology, Department of Pediatrics, Children's Hospital of Philadelphia; Department of Neurology, Perelman School of Medicine, University of Pennsylvania	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

References

1. Banwell B, Bennett JL, Marignier R, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: international MOGAD panel proposed criteria. *Lancet Neurol.* 2023;22(3):268-282. doi:10.1016/s1474-4422(22)00431-8
2. de Mol CL, Wong Y, van Pelt ED, et al. The clinical spectrum and incidence of anti-MOG-associated acquired demyelinating syndromes in children and adults. *Mult Scler.* 2020;26(7):806-814. doi:10.1177/1352458519845112
3. Fadda G, Armangue T, Hacohen Y, Chitnis T, Banwell B. Paediatric multiple sclerosis and antibody-associated demyelination: clinical, imaging, and biological considerations for diagnosis and care. *Lancet Neurol.* 2021;20(2):136-149. doi:10.1016/s1474-4422(20)30432-4
4. Ogawa R, Nakashima I, Takahashi T, et al. MOG antibody-positive, benign, unilateral, cerebral cortical encephalitis with epilepsy. *Neurol Neuroimmunol Neuroinflamm.* 2017;4(2):e322. doi:10.1212/nxi.0000000000000322
5. Fainberg N, Silver M, Arena J, et al. 547: cerebral edema in MOG antibody disease treated with invasive multimodal. *Crit Care Med.* 2023;51(1):261. doi:10.1097/01.ccm.0000907916.29570.f1
6. Hacohen Y, Banwell B. Treatment approaches for MOG-Ab-associated demyelination in children. *Curr Treat Options Neurol.* 2019;21(1):2. doi:10.1007/s11940-019-0541-x
7. Kaneko K, Sato DK, Nakashima I, et al. CSF cytokine profile in MOG-IgG+ neurological disease is similar to AQP4-IgG+ NMOSD but distinct from MS: a cross-sectional study and potential therapeutic implications. *J Neurol Neurosurg Psychiatry.* 2018;89(9):927-936. doi:10.1136/jnnp-2018-317969
8. Roche H-L. *A Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Satralizumab in Patients with Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (Meteoroid) [online].* Accessed October 16, 2023. clinicaltrials.gov/ct2/show/NCT05271409?recrs=ab&cond=MOG&age=0&draw=2&rank=2.
9. Takeshita Y, Fujikawa S, Serizawa K, et al. New BBB model reveals that IL-6 blockade suppressed the BBB disorder, preventing onset of NMOSD. *Neurol Neuroimmunol Neuroinflamm.* 2021;8(6):e1076. doi:10.1212/nxi.0000000000001076
10. Elsbernd PM, Hoffman WR, Carter JL, Wingerchuk DM. Interleukin-6 inhibition with tocilizumab for relapsing MOG-IgG associated disorder (MOGAD): a case-series and review. *Mult Scler Relat Disord.* 2021;48:102696. doi:10.1016/j.msard.2020.102696
11. Novi G, Gastaldi M, Franciotta D, Pesce G, Benedetti L, Uccelli A. Tocilizumab in MOG-antibody spectrum disorder: a case report. *Mult Scler Relat Disord.* 2019;27:312-314. doi:10.1016/j.msard.2018.11.012
12. Ringelstein M, Ayzenberg I, Lindenblatt G, et al. Interleukin-6 receptor blockade in treatment-refractory MOG-IgG-associated disease and neuromyelitis optica spectrum disorders. *Neurol Neuroimmunol Neuroinflamm.* 2022;9(1):e1100. doi:10.1212/nxi.0000000000001100
13. Fujihara K, Bennett JL, de Seze J, et al. Interleukin-6 in neuromyelitis optica spectrum disorder pathophysiology. *Neurol Neuroimmunol Neuroinflamm.* 2020;7(5):e841. doi:10.1212/nxi.0000000000000841
14. Lassmann H, Brunner C, Bradl M, Linington C. Experimental allergic encephalomyelitis: the balance between encephalitogenic T lymphocytes and demyelinating antibodies determines size and structure of demyelinated lesions. *Acta Neuropathol.* 1988;75(6):566-576. doi:10.1007/bf00686201
15. Takeshita Y, Obermeier B, Cotleur AC, et al. Effects of neuromyelitis optica-IgG at the blood-brain barrier in vitro. *Neurol Neuroimmunol Neuroinflamm.* 2017;4(1):e311. doi:10.1212/nxi.0000000000000311
16. Freyer CW, Porter DL. Cytokine release syndrome and neurotoxicity following CAR T-cell therapy for hematologic malignancies. *J Allergy Clin Immunol.* 2020;146(5):940-948. doi:10.1016/j.jaci.2020.07.025