EDITORIAL OPEN ACCESS

It Is Time to See MOGAD From a Different Perspective Than Multiple Sclerosis

Rosa Cortese, Alessia Bianchi, and Nicola De Stefano

Neurol Open Access 2025;1:e000020. doi:10.1212/WN9.0000000000000020

Correspondence
Dr. Cortese
rosa.cortese@unisi.it

RELATED ARTICLE

Research Article
Investigating the Presence of Neurodegeneration Independent of Relapses in MOGAD Compared With Relapsing-Remitting Multiple Sclerosis
Page 000013

Disability accumulation independent of relapses is a hallmark of multiple sclerosis (MS) and is now formally recognized as progression independent of relapse activity (PIRA). This concept is a cornerstone of MS pathophysiology, shaping clinical trial endpoints and treatment paradigms.[1,2] However, whether this framework applies equally to antibody-mediated disorders such as myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) remains unclear. MOGAD has emerged as a distinct clinical and imaging entity.[3] Unlike MS, where diffuse and subclinical neurodegeneration contribute to gradual disability accumulation beyond clinical relapses, MOGAD has been perceived as more "relapse-dependent" disease. Yet, robust data confirming the absence of subclinical progression in MOGAD remain scarce, leaving key issues such as monitoring and long-term patient management unresolved.

In this issue of *Neurology®: Open Access*, Camera et al.[4] offer important insights into this debate. In a prospective longitudinal design, the authors recruited 20 patients with MOGAD, 32 patients with relapsing-remitting MS (RRMS), and 21 healthy controls, matched for age, sex, and baseline disability. Over a median follow-up of 17 months, participants underwent comprehensive clinical, cognitive, and neuroimaging assessments. The findings were clear: no patients with MOGAD showed clinical or cognitive PIRA, whereas approximately 6% of patients with RRMS exhibited progression. MRI analyses corroborated these clinical observations. Patients with RRMS experienced significant thalamic, hippocampal, and deep grey matter atrophy, while the MOGAD cohort showed no significant longitudinal brain volume loss or microstructural alterations.

These results are consistent with recent studies indicating that both PIRA and MRI activity are uncommon in MOGAD compared with MS, suggesting distinct mechanisms of disability accrual. From a clinical standpoint, this supports a management approach for MOGAD prevention focused on relapse. Furthermore, these findings challenge the direct application of the MS pathologic model to MOGAD and raise concerns regarding the reliability of MS neurodegeneration biomarkers, such as brain atrophy rates, for monitoring MOGAD. While some studies suggest that brain atrophy may occur in MOGAD, its clinical significance and underlying mechanisms remain unclear[5,6] Unlike MS, where progressive tissue damage and degeneration contribute significantly to brain volume loss, MOGAD is primarily driven by acute inflammatory demyelination, typically following a monophasic or relapsing course. Notably, significant volumetric differences have been observed between MOGAD patients with a relapsing course and those with a monophasic course, suggesting potential variations in their underlying pathophysiologic mechanisms.[7]

Some caveats must be noted here because they may limit the generalizability of these conclusions. As acknowledged by the authors, the study is limited by its small sample size, relatively short follow-up, and exploratory nature. The modest statistical power may reduce sensitivity to detect subtle or delayed neurodegenerative changes. In addition, differences in treatment exposure between cohorts (where most RRMS patients received disease-modifying therapies, while most of the patients with MOGAD did not) introduce a potential confounder, despite

Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy.

The Article Processing Charge was funded by the authors.

reflecting real-world practice. Finally, while the authors used advanced imaging modalities, the role of some metrics (e.g., cortical lesion analysis and NODDI parameters) in relation to PIRA remain unclear. The lack of uniform follow-up intervals and the omission of biomarkers such as serum neurofilament light chain or optical coherence tomography further highlights the need for complementary research.

To date, only few studies have rigorously evaluated PIRA in MOGAD.[8,9] A critical issue is that disability accumulation and neurodegeneration in antibody-mediated disorders like MOGAD are often assessed using conceptual definition developed for MS. However, applying the MS-derived concept of PIRA to MOGAD presents significant challenges. First, standard definitions of PIRA[2], typically requiring no relapses one month prior and 3 months following confirmed[2] disability worsening, may not capture the disease dynamics of MOGAD. Lesions in MOGAD often evolve over time, with clinical manifestations potentially emerging or resolving well beyond the time windows used in MS studies.[3] Disability interpreted as "progression" in MS may, in MOGAD, reflect incomplete recovery from a prior relapse. Furthermore, acute and chronic treatment strategies in MOGAD differ from those in MS, potentially influencing recovery trajectories.[3] In addition, the lack of consensus on optimal maintenance treatments for MOGAD introduces heterogeneity in patient outcomes, further complicating the assessment of disease progression and disability accumulation. Finally, the disability metrics embedded in MS-centric definitions of PIRA, such as the EDSS, may not fully capture MOGAD's unique clinical profile. In MOGAD, long-term disability often arises from visual impairment, sphincter dysfunction, and cognitive sequelae, which are poorly reflected in this scale. As a result, significant clinical changes in MOGAD could be missed when applying MS-oriented outcome measures.

Despite these limitations and the need of future larger, longitudinal studies, the absence of clinical or radiologic progression in MOGAD across multiple endpoints reinforces the prevailing notion of a primarily relapse-driven disease course. Clinically, this underscores the importance of focusing on relapse prevention in MOGAD, as opposed to targeting background progression as is done in MS.

Nevertheless, the implications of the study of Camera et al. extend beyond MOGAD alone. While MS has been extensively studied, research on MOGAD remains comparatively limited, with most insights into the antibody-associated disease being often extrapolated from the existing MS literature. This study urges the neurology community to critically reexamine how progression is conceptualized in antibody-mediated CNS diseases. Should MS-derived definitions such as PIRA still be applied to MOGAD or is it time to develop disease-specific definitions and monitoring strategies that reflect the distinctive pathophysiology of these disorders?

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/OA for full disclosures.

Publication History

Received by *Neurology® Open Access* March 27, 2025. Accepted in final form April 14, 2025.

References

1. Kappos L, Wolinsky JS, Giovannoni G, et al. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. *JAMA Neurol*. 2020;77(9):1132-1140. doi:10.1001/jamaneurol.2020.1568
2. Müller J, Sharmin S, Lorscheider J, et al. Standardized definition of progression independent of relapse activity (PIRA) in relapsing-remitting multiple sclerosis. *JAMA Neurol*. 2025:e250495. doi:10.1001/jamaneurol.2025.0495
3. Marignier R, Hacohen Y, Cobo-Calvo A. Myelin-oligodendrocyte glycoprotein antibody-associated disease. *Lancet Neurol*. 2021;20(9):762-772. doi: 10.1016/S1474-4422(21)00218-0
4. Camera V, Messina S, Tamanti A, et al. Investigating the presence of neurodegeneration independent of relapses in MOGAD compared to RRMS. *Neurol Open*. 2025.
5. Cortese R, Battaglini M, Parodi F, et al. Mild gray matter atrophy in patients with long-standing multiple sclerosis and favorable clinical course. *Mult Scler*. 2022;28(1):154-159. doi:10.1177/13524585211019650
6. Duan Y, Zhuo Z, Li H, et al. Brain structural alterations in MOG antibody diseases: a comparative study with AQP4 seropositive NMOSD and MS. *J Neurol Neurosurg Psychiatry*. 2021;92(7):709-716. doi:10.1136/jnnp-2020-324826
7. Rechtman A, Brill L, Zveik O, et al. Volumetric brain loss correlates with a relapsing MOGAD disease course. *Front Neurol*. 2022;13:867190. doi:10.3389/fneur.2022.867190
8. Akaishi T, Misu T, Takahashi T, et al. Progression pattern of neurological disability with respect to clinical attacks in anti-MOG antibody-associated disorders. *J Neuroimmunol*. 2021;351:577467. doi:10.1016/j.jneuroim.2020.577467
9. Molazadeh N, Akaishi T, Bose G, Nishiyama S, Chitnis T, Levy M. Progression independent of relapses in aquaporin4-IgG-seropositive neuromyelitis optica spectrum disorder, myelin oligodendrocyte glycoprotein antibody-associated disease, and multiple sclerosis. *Mult Scler Relat Disord*. 2023;80:105093. doi:10.1016/j.msard.2023.105093