

Josep Dalmau, MD, PhD, Editor, *Neurology*[®]: *Neuroimmunology & Neuroinflammation*

Looks can be deceiving

A B-cell–mediated encephalopathy with normal MRI?

Neurol Neuroimmunol Neuroinflamm May 2018 vol. 5 no. 3 e461. doi:10.1212/NXI.0000000000000461

Advances in defining clinical criteria and immunologic biomarkers of autoimmune diseases such as MS or autoimmune encephalitides coupled with conventional MRI studies and diffusion tensor imaging (DTI) have revealed overlapping diseases characterized by autoantibodies against neuronal or glial surface proteins (NMDA receptor, aquaporin 4, or myelin oligodendrocyte glycoprotein)^{1,2} and may disclose in the future unclassified autoimmune disorders with yet unknown mechanisms. For those readers who are impatient, the future is now. In this issue of *Neurology*[®] *Neuroimmunology & Neuroinflammation*, Dr. Takewaki et al.³ describe 11 patients whose symptoms and clinical course mimicked MS, but without abnormalities on conventional MRI studies. None of the patients had oligoclonal bands in the CSF, and most had extensive white matter abnormalities identified by MRI DTI characterized by a decrease in fractional anisotropy values. Treatment with IV methylprednisolone and plasma exchange were often effective. These findings and the presence of frequent plasmablasts in the peripheral blood suggested that the underlying pathogenesis was likely mediated by B-cell mechanisms. The authors named this disorder “normal-appearing imaging-associated, neuroimmunologically justified, autoimmune encephalomyelitis.” In the accompanying editorial comment, Dr. Finke⁴ discusses the type of disease that these patients may have and indicates similar clinical-radiologic dissociations noted in other diseases. An example is anti-NMDA receptor encephalitis, where patients with severe symptoms often have normal conventional MRI studies, but DTI reveals extensive white matter abnormalities with decreased fractional anisotropy.⁵ Further studies are needed to characterize this category of MRI-negative autoimmune encephalitis, which perhaps in the future may be defined by yet unknown immunologic biomarkers.

In another study, Dr Rissanen et al.⁶ used PET to investigate the relationship of in vivo microglial activation to clinical and MRI parameters in MS. Microglia activation is associated with increased levels of the 18-kDa translocator protein, which the authors measured with the PET tracer [¹¹C] (R)-PK11195. Patients with secondary progressive and relapsing-remitting MS (RRMS) and age-matched healthy participants were included in the study. The authors found differences in the amount and distribution of the PET tracer in patients with secondary progressive as compared to RRMS and healthy participants. Higher binding of the tracer in normal-appearing white matter also associated with higher clinical disability and reduced white matter structural integrity. Among patients with MS, older age associated with higher microglial activation in normal-appearing white matter. The study suggests that increased microglial activity in the normal-appearing white matter correlates closely with impaired white matter structural integrity, providing a potential pathologic correlate to DTI parameters.

In another article, Dr. Radke et al. describe the composition, organization, and presence of different B-cell subpopulations in patients with dermatomyositis (DM) and the relationship of



MORE ONLINE

📄 **Editor Summary**
[NPub.org/N2/edsum](https://www.neurology.org/doi/10.1212/NXI.0000000000000461)

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at [Neurology.org/NN](https://www.neurology.org/NN).

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

these B-cell infiltrates to specific cytokines and chemokines involved in lymphoid neogenesis.⁷ Twenty-three patients were enrolled, including cases with anti-Mi2 autoantibodies and excluding those with antisynthetase antibodies or necrotizing myopathy and signal recognition particle antibodies. Based on the inflammatory infiltrates and B-cell distribution, 3 groups of adults with DM (aDM) were identified: (1) classic aDM, with inflammatory infiltrates diffusely distributed and mainly located in the perimysium and partly in the adjacent endomysium, and rare CD20⁺ B lymphocytes; (2) B-cell-rich aDM, with more inflammatory infiltrates and dense CD20⁺ B-cell aggregates; and (3) follicle-like aDM, showing follicle-like structures, resembling tertiary lymphoid organs with germinal centers and dark and light zone organization. A significant upregulation of numerous genes implicated in different aspects of the interferon signature was found in the B-cell-rich and follicle-like aDM. The authors suggest that assessment of B-cell architecture, including ultrastructure and function, together with interferon signature genes can be useful tools to stratify patients with DM and develop therapies targeting these disease subsets individually (e.g., B-cell immunity or type 1 interferon signaling).

In another article, Dr. Cohen Aubart et al.⁸ report a nationwide retrospective study of the clinical-pathologic presentations of muscular sarcoidosis. Forty-eight patients (28 women), median age at muscle symptom onset of 45 years (range 18–75 years), were enrolled. Forty patients had definite neurosarcoidosis confirmed by muscle biopsy, and 8 had probable neurosarcoidosis. Four clinical-pathologic patterns were identified, “myopathic,” defined by the presence of motor deficits; “nodular,” characterized by the presence of nodular lesions without motor deficit; “smoldering,” defined by the presence of constant myalgias and absence of nodular lesions, motor deficits and amyotrophy; and “combined myopathic and neurogenic,” characterized by the presence of a neurogenic pattern in electrophysiologic studies, in addition to muscle involvement. These 4 patterns differed according to symptom presentation (myalgia, nodules, and weakness), electrophysiologic and MRI findings, and response to treatment. After a median follow-up period of 6

years, patients with myopathic and neuromuscular patterns had the worse outcome.

In addition to these studies, the May issue of *Neurology: Neuroimmunology & Neuroinflammation* contains other interesting articles that I hope will catch your attention.

Study funding

No targeted funding reported.

Disclosure

J. Dalmau is the editor of *Neurology: Neuroimmunology & Neuroinflammation*; is on the editorial board of *Neurology UpToDate*; holds patents for and receives royalties from Ma2 autoantibody test, NMDA receptor autoantibody test, GABA (B) receptor autoantibody test, GABA(A) receptor autoantibody test, DPPX autoantibody test, and IgLON5 autoantibody test; and receives research support from NIH, Fundació CELLEX, and Instituto Carlos III (CIBERER and Fondo de Investigaciones Sanitarias). Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NN.

References

1. Titulaer MJ, Hofstberger R, Iizuka T, et al. Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. *Ann Neurol* 2014;75:411–428.
2. Hacohen Y, Absoud M, Hemingway C, et al. NMDA receptor antibodies associated with distinct white matter syndromes. *Neurol Neuroimmunol Neuroinflamm* 2014;1:e2. doi: 10.1212/NXI.0000000000000002.
3. Takewaki D, Lin Y, Sato W, et al. Normal brain imaging accompanies neuroimmunologically justified, autoimmune encephalomyelitis. *Neurol Neuroimmunol Neuroinflamm* 2018;5:e456. doi: 10.1212/NXI.0000000000000456.
4. Finke C. Diagnosing MRI-negative autoimmune diseases. *Neurol Neuroimmunol Neuroinflamm* 2018;5:e457. doi: 10.1212/NXI.0000000000000457.
5. Peer M, Pruss H, Ben-Dayan I, Paul F, Arzy S, Finke C. Functional connectivity of large-scale brain networks in patients with anti-NMDA receptor encephalitis: an observational study. *Lancet Psychiatry* 2017;4:768–774.
6. Rissanen E, Tuisku J, Vahlberg T, et al. Microglial activation, white matter tract damage and disability in multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm* 2018;5:e443. doi: 10.1212/NXI.0000000000000443.
7. Radke J, Koll R, Preusse C, et al. Architectural B-cell organization in skeletal muscle identifies subtypes of dermatomyositis. *Neurol Neuroimmunol Neuroinflamm* 2018;5:e451. doi: 10.1212/NXI.0000000000000451.
8. Cohen Aubart F, Abbara S, Maisonobe T, et al. Symptomatic muscular sarcoidosis: lessons from a nation-wide multicenter study. *Neurol Neuroimmunol Neuroinflamm* 2018;5:e452. doi: 10.1212/NXI.0000000000000452.

Neurology[®] Neuroimmunology & Neuroinflammation

Looks can be deceiving: A B-cell–mediated encephalopathy with normal MRI?

Josep Dalmau

Neurol Neuroimmunol Neuroinflamm 2018;5;

DOI 10.1212/NXI.0000000000000461

This information is current as of April 12, 2018

Updated Information & Services	including high resolution figures, can be found at: http://nn.neurology.org/content/5/3/e461.full.html
References	This article cites 8 articles, 0 of which you can access for free at: http://nn.neurology.org/content/5/3/e461.full.html##ref-list-1
Permissions & Licensing	Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at: http://nn.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://nn.neurology.org/misc/addir.xhtml#reprintsus

Neurol Neuroimmunol Neuroinflamm is an official journal of the American Academy of Neurology. Published since April 2014, it is an open-access, online-only, continuous publication journal. Copyright Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.. All rights reserved. Online ISSN: 2332-7812.

