

Precision in neuroimmunology

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In an era of precision medicine in which “omics” and deep sequencing provide an element of exactness to all medical specialties, the field of neuroimmunology benefits from the precision that autoantibodies (and their cognate antigens) provide in the characterization and diagnostic testing of several disorders, along with technological advances that help to observe clinically invisible brain alterations. An example is provided in this issue of *Neurology® Neuroimmunology & Neuroinflammation*, by the study of Oertel et al.¹ that shows microstructural visual system changes (e.g., reduced foveal thickness and fractional anisotropy reduction in the optic radiation) in patients with neuromyelitis optica spectrum disorder (NMOSD) without visual symptoms. In MS, the occurrence of progressive, insidious worsening is known to occur in some forms of the disease (e.g., primary progressive MS); a similar paradigm has been suggested for NMOSD in investigations that demonstrated spinal cord atrophy in patients without a history of myelitis² or clinical manifestations of optic neuritis or visual deficits.³ The authors of this study, accompanied by an editorial comment of Yamamura and Nakashima,⁴ discuss the importance of these findings in the context of diagnosis, assessment of the extent of disease, clinical follow-up, and as potential biomarkers of therapy response during novel drug development.

Dimethyl fumarate (DMF), an oral fumaric acid ester, has been shown to reduce clinical relapses and MRI evidence of inflammatory disease activity in relapsing-remitting MS. Although the exact mechanism of this drug is not well known, cytoprotective and immunomodulatory effects of DMF and its metabolite monomethyl fumarate have been suggested. Despite its cytoprotective potential, DMF is associated with lymphopenia (preferentially affecting CD8⁺ more than CD4⁺ T-cell counts) in up to 50% of patients,^{5,6} and with rare cases of progressive multifocal leukoencephalopathy (PML)⁷ that may be related to sustained lymphopenia. In their current report, Ghadiri et al.⁸ have used a combination of in vivo and in vitro studies to elucidate the reasons

for the preferential decrease of CD8⁺ vs CD4⁺ T cells in patients with MS. An important finding was that the propensity of DMF-induced apoptosis varied substantially across human T-cell subsets, with CD8⁺ T cells exhibiting greater susceptibility than CD4⁺ T cells, and with memory CD4⁺ and CD8⁺ T-cell subsets being disproportionately affected as compared to naive T-cell subsets. These data paralleled the findings in the patients treated with DMF and are consistent with previous publications.⁵ Additional investigations in the same manuscript are aimed to determine whether DMF might render circulating T cells more susceptible to apoptosis, if the differential T-cell apoptosis could be explained by a different degree of DMF exposure in different anatomic compartments, whether inhibition of proliferation could represent an alternate explanation for the differential lymphopenia, and the compensatory responses to DMF-induced lymphopenia. The authors propose that differential susceptibility of distinct T-cell subsets to DMF-induced apoptosis may contribute to both the efficacy and safety profiles of DMF. In line with the concept of precision in the field of neuroimmunology, this study raises the issue of whether future studies monitoring different T-cell subsets would be more useful than measuring total lymphocyte counts in assessing the potential adverse effects of DMF.

In another study, Maillart et al.⁹ describe the clinical and radiologic outcomes of 23 patients with relapsing-remitting MS who survived natalizumab-related PML and subsequently required continuation of treatment with disease-modifying treatments (DMTs). Post-PML DMT included one or more of the following, interferon beta, glatiramer acetate, DMF, or fingolimod. The mean follow-up was 24.1 months (SD, 10.8 months) with patients showing no clinical worsening of PML symptoms assessed by stability of Expanded Disability Status Scale (EDSS) at the last follow-up. No clinical relapses were observed while on fingolimod or DMF, whereas 3 patients who received glatiramer acetate as the first post-PML treatment, exhibited sustained MS radiologic activity after

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18 months. As far as natalizumab-related PML lesions are concerned, no radiologic worsening was observed at the end of the follow-up period. The authors acknowledge the limitation of the retrospective assessment of patients who were recruited at several different tertiary centers and indicate the need for prospective studies on post-PML treatment for MS using centralized quantitative assessment of the data.

Körtvelyessy et al.¹⁰ provide the clinical, radiologic, and pathologic findings of 2 patients who presented with symptoms of acute disseminated encephalomyelitis in association with antibodies to myelin oligodendrocyte glycoprotein (MOG), but with pathologic findings resembling the pattern II of MS, which in one patient was combined with features of pattern III. Both cases support previously known associations of MOG antibodies and underscore the complex pathologic manifestations associated with this autoimmunity.

Although there is circumstantial evidence that patients with ovarian teratoma (OT) do not harbor NMDA receptor (NMDAR) antibodies unless they develop anti-NMDAR encephalitis, the studies published to date consisted of small series of patients.¹¹ To further elucidate whether NMDAR antibodies may occur in patients with OT without neurologic symptoms, Gong et al.¹² used a commercially available cell-based assay to probe the sera of 96 patients with OT (80 with pathologically confirmed tumor) and 95 participants with benign ovarian cysts. None of the patients or case-control participants harbored NMDAR antibodies, suggesting that it is not necessary to perform antibody testing in patients with OT unless encephalitis is suspected.

In addition to these studies, the May issue of *Neurology: Neuroimmunology & Neuroinflammation* contains a study on dysregulation of MS risk genes and pathways at distinct stages of the disease, and a curious case of trigeminal autonomic headache and Horner syndrome as the first sign of granulomatous hypophysitis, among other interesting articles that I hope will catch your attention.

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REFERENCES

1. Oertel F, Kuchling J, Zimmermann H, et al. Microstructural visual system changes in AQP4-antibody-seropositive NMOSD. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e334. doi: 10.1212/NXI.0000000000000334.
2. Ventura RE, Kister I, Chung S, Babb JS, Shepherd TM. Cervical spinal cord atrophy in NMOSD without a history of myelitis or MRI-visible lesions. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e224. doi: 10.1212/NXI.0000000000000224.
3. Jeong IH, Kim HJ, Kim NH, Jeong KS, Park CY. Subclinical primary retinal pathology in neuromyelitis optica spectrum disorder. *J Neurol* 2016;263:1343–1348.
4. Yamamura T, Nakashima I. Foveal thinning in neuromyelitis optica: a sign of retinal astrocytopathy? *Neurol Neuroimmunol Neuroinflamm* 2017;4:e347. doi: 10.1212/NXI.0000000000000347.
5. Gross CC, Schulte-Mecklenbeck A, Klinsing S, Posevitz-Fejfar A, Wiendl H, Klotz L. Dimethyl fumarate treatment alters circulating T helper cell subsets in multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e183. doi: 10.1212/NXI.0000000000000183.
6. Spencer CM, Crabtree-Hartman EC, Lehmann-Horn K, Cree BA, Zamvil SS. Reduction of CD8(+) T lymphocytes in multiple sclerosis patients treated with dimethyl fumarate. *Neurol Neuroimmunol Neuroinflamm* 2015;2:e76. doi: 10.1212/NXI.0000000000000076.
7. Nieuwkamp DJ, Murk JL, van Oosten BW, et al. PML in a patient without severe lymphocytopenia receiving dimethyl fumarate. *N Engl J Med* 2015;372:1474–1476.
8. Ghadiri M, Rezk A, Li R, et al. Dimethyl fumarate-induced lymphopenia in MS due to differential T cell-subset apoptosis. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e340. doi: 10.1212/NXI.0000000000000340.
9. Maillart E, Vidal J-S, Brassat D, et al. Natalizumab-PML survivors with subsequent MS treatment: clinico-radiological outcome. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e346. doi: 10.1212/NXI.0000000000000346.
10. Kortvelyessy P, Breu M, Pawlitzki M, et al. ADEM-like presentation, anti-MOG antibodies and MS pathology: two case reports. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e335. doi: 10.1212/NXI.0000000000000335.
11. Tuzun E, Zhou L, Baehring JM, Bannykh S, Rosenfeld MR, Dalmau J. Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma. *Acta Neuropathol* 2009;118:737–743.
12. Gong S, Shi G, Guo J, et al. N-methyl-D-aspartate receptor (NMDAR) antibody in patients with ovarian teratoma lacking neurological symptoms. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e344. doi: 10.1212/NXI.0000000000000344.