Editor's Corner

Volume 5, Number 4, July 2018
Neurology.org/NN

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Body surface area and B-cell repopulation

Neurol Neuroimmunol Neuroinflamm 2018;5:e472. doi:10.1212/NXI.0000000000000472

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Editor Summary
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Many studies in neuroimmunology are focused on biomarkers of treatment response and disease outcome. These studies are clinically important considering the increasing armamentarium of drugs and paraclinical tests available and represent the main theme that unifies several of the articles included in the current issue of *Neurology® Neuroimmunology & Neuroinflammation (N2)*. Dr. Ellwardt et al.[1] investigated the factors that influence B-cell repopulation after B-cell depletion therapy in patients with neuromyelitis optica spectrum disorders and MS. The cohort consisted of 45 patients at their first treatment, 42 received rituximab and 3 ocrelizumab, and most were treated with body surface area (BSA)-adapted dosage of medication. B-cell repopulation was defined as the first detection of $CD19^+$ cells above 1% of total $CD45^+$ lymphocytes after treatment. Multiple factors were investigated including BSA, age, sex, CSF parameters, pre-treatment therapy, and absolute lymphocyte and leukocyte counts during treatment. The study shows that the only factor with significant influence on the $CD19^+$ B-cell recovery was the BSA. Patients with a larger BSA had a higher probability to reach 1% CD19 cells sooner than patients with a smaller BSA after B-cell depletion therapy. The authors suggest that this finding is due to a systematic underestimation of rituximab dosage when the Dubois equation is used for the BSA calculation, particularly in patients with large height and weight. Calculating the BSA with the Mosteller equation partially overcame this effect. In addition, the authors suggest that the use of the arbitrary dose of 375 mg/m^2 is not sufficient and should be increased, especially for patients with a high BSA. The authors acknowledge that some effects may have been overlooked because of the limited number of analyzed events, and that future investigations should consider including novel biomarkers (e.g., $CD27^+$ B cells among others), and the presence of gene polymorphisms (e.g., *FCGR3A*) that have been suggested to predict efficacy of B-cell targeted therapies.

There is currently no reliable prediction marker for early treatment response to any disease modifying treatment for relapsing remitting MS (RRMS). Therefore, to determine individual pharmacodynamic responses that can distinguish patients who will respond to dimethyl fumarate (DMF), Dr. Gafson et al.[2] examined the short-term changes in gene expression in peripheral blood mononuclear cells (PBMCs) of patients with RRMS treated with DMF. Blood samples were obtained from 24 patients at baseline, 6 weeks, and 15 months after initiating treatment. Using RNAseq, the authors identified a robust short-term transcriptomic response to DMF in PBMCs that was associated with activation of the Nrf2 and inhibition of the NFκB pathways in responders. In addition, these patients showed stabilization of gene expression between 6 weeks and 15 months. By contrast, no early transcriptional changes were identified in nonresponders, who also showed greater expression of proinflammatory pathway genes as compared with healthy controls. Findings from this study confirm previously reported modulating effects of DMF on genes related to antioxidant,[3] anti-inflammatory,[4] and NFκB pathways.[5] The authors acknowledge the small sample size and the use of only 3 time points in sample testing, indicating the need of further confirmatory work. Yet, these preliminary findings highlight the sensitivity of RNA-Seq whole transcriptomic

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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.

assays of PBMC, which although currently are expensive, have the potential to be streamlined and more accessible in the future.

Several studies have shown that neopterin, a pteridine produced in macrophages and dendritic cells, is an early marker of HIV-associated cellular immune activation and provides a sensitive measure of treatment efficacy and HIV disease course,[6,7] predicting HIV-related mortality.[8] The levels of neopterin are also associated with compromise of the blood-brain barrier, generalized brain atrophy, and HIV-associated cognitive impairment.[9,10] Based on these findings, Fleischman et al.[11] investigated in 66 HIV-infected, virally suppressed patients, the effects of the immune response and inflammatory cascade on MRI-derived regional brain volumes and cognition. Cross-sectional associations were examined between serum immune markers of activation (neopterin) and inflammation (interleukin [IL]-1β, IL-6, tumor necrosis factor alpha, and C-reactive protein) and several regional brain volumes and cognition. None of the inflammatory markers was associated with any regional brain volume, but higher neopterin levels were associated with lower presubiculum, cornu ammonis (CA)1, and CA4/dentate volumes, and deficits of cognition and semantic and working memory. Despite the limitations of the study noted by the authors (small number of patients with limited age range, no measurement of CSF neopterin, lack of adjustment to premorbid intelligence, and cross-sectional study), the findings suggest that serum neopterin levels and 3-T MRI neuroimaging (both clinically available and easy to obtain) may be useful in identifying HIV-infected adults at risk of developing further neuronal injury and cognitive impairment.

In addition to these studies, the July issue of N2 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 Euroimmun, NIH, Fundació CELLEX, 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.

Received May 8, 2018. Accepted in final form May 8, 2018.

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Neurol Neuroimmunol Neuroinflamm 2018;5;
DOI 10.1212/NXI.0000000000000472