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A surprise with MuSK antibodies

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This issue of *Neurology*[®] *Neuroimmunology* & *Neuroinflammation* (N2) contains several studies that reveal surprising or unexpected findings such as the mechanisms underlying muscle-specific kinase (MuSK) antibody pathogenicity, presence of inflammatory cells in normal muscle, and the isolated CNS manifestation of a systemic disease. Here is a brief overview of these and other studies.

Approximately 5% of patients with myasthenia gravis harbor IgG4 autoantibodies against MuSK.¹ IgG4 antibodies are unable to bind complement or many Fc receptors of immune cells; moreover, they exchange Fab arms with other IgG4 molecules (becoming functionally bispecific and monovalent), which renders them unable to crosslink and internalize the target antigen.² To better understand how MuSK IgG4 antibodies alter the clustering of acetylcholine receptor (AChR), Huijbers et al.³ investigated how the functional property of Fab-arm exchange contributes to pathogenesis. In a remarkable set of experiments using patient-derived MuSK monoclonal antibodies (or recombinant MuSK [rMuSK] antibodies), the authors compared the effects of monovalent rMuSK antibodies (functionally bispecific; each arm of the antibody different, as occur in the human disease) with bivalent rMuSK antibodies (monospecific; both arms of the antibody identical). Whereas the monovalent rMuSK antibodies abolished agrin-induced MuSK phosphorylation and AChR clustering, as expected, the unanticipated finding was that the bivalent monospecific rMuSK antibodies had the opposed effect, that is, they activated MuSK phosphorylation and partially induced AChR clustering, independently of agrin. The authors conclude that in addition to antibody titers and target epitopes, the pathogenicity of MuSK antibodies depends on valency/autoantibody subclass, providing a novel mechanism whereby Fab-arm exchange of IgG4 renders antibodies monovalent and pathogenic.

As effective treatments of relapsing-remitting multiple sclerosis (MS) become available, quantitative biomarkers of disease activity and predictive and prognostic biomarkers will play an increasing role in determining treatment strategies. In a pilot study, Akgün et al.⁴ studied 15 patients with relapsing-remitting MS and a highly active disease course treated with alemtuzumab to determine whether serial serum neurofilament (sNfL) levels could serve as predictors of treatment response and identify patients at risk of relapse. All 15 patients responded to alemtuzumab treatment with decreased clinical and MRI activity. This was accompanied by a decrease in sNfL within the first 6 months after treatment. For those patients defined as no evidence of disease activity-3 (NEDA-3) (absence of relapses, disability worsening, and MRI activity), the decrease of sNfL persisted over time. Increases of sNfL of >20 fold were associated with clinical or MRI disease activity; even patient-reported relapse-suspicious symptoms were accompanied by an increase in sNfL. For patients who developed relapses, sNfL started to increase as early as 5 months before the clinical/MRI relapse, then peaked at the clinical onset of the relapse, and subsequently decreased within 4–5 months. Patients who required alemtuzumab retreatment had higher sNfL levels at baseline compared with those who did not need retreatment. Overall, the results suggest that peak levels of sNfL are directly linked with clinical onset or relapses and acute changes in MRI activity, and that a rising of sNfL levels anticipates clinical relapses. This study follows a number of reports investigating sNfL in MS, and although a larger number of

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patients need to be studied, these data support serial sNfL measurement as a predictive and prognostic biomarker of response to immune reconstitution treatment.

Although there are precise clinical and histologic criteria for the diagnosis of polymyositis, dermatomyositis, and inclusion body myositis, sometimes muscle biopsies of patients who do not fulfill any of these criteria show inflammatory cells. Of interest, the normal limits for the presence of lymphocytes and macrophages in muscle have not been defined. Therefore, Johannssen et al.⁵ aimed at determining the number of T cells and macrophages in normal muscle and the frequency of myositis in patients with isolated muscle pain or increased levels of serum creatine kinase (sCK). For this, the authors examined muscle biopsies of 71 patients using immunohistochemistry with a variety of antibodies against subsets of lymphocytes, macrophages, and expression of major histocompatibility complex (MHC) Class I, perforin, and myeloid-related protein 8 (MRP8), which is a marker of activated macrophages. Four groups of patients were established according to the presence of (1) myalgia without further clinical or laboratory findings, (2) increased sCK without symptoms, (3) myalgia and abnormal EMG findings, and (4) healthy participants with susceptibility to malignant hyperthermia. Muscle biopsies of healthy participants showed a considerable number of macrophages and T cells comparable to those of groups 1 and 2. Only biopsies from group 3 had significantly increased mean numbers of perimysial macrophages and CD8⁺ T cells and were also positive for MRP8 expression. The authors conclude that the mere presence of immune cells in muscle biopsy should not be overinterpreted. Moreover, in patients with myalgia, elevated sCK, or both, the muscle biopsy is unlikely to show a specific pathology unless the EMG shows signs of myopathy. Future studies should assess whether the latter group of patients may benefit from immunotherapy.

There are a substantial number of patients with clinical and laboratory evidence of a brain inflammatory process, but a definitive diagnosis remains elusive. Thus, it was very interesting to read the article by Benson et al.⁶ in which they provide a definitive diagnosis for 3 children with treatment refractory neuroinflammation of unclear etiology. Initially, after extensive evaluations, these children were diagnosed with neuroinflammatory disorders such as chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), multiphasic acute disseminated encephalomyelitis, or small vessel CNS vasculitis. Responses to treatment were disappointing. Genetic testing eventually revealed that all 3 children had gene mutations associated with familial hemophagocytic lymphohistiocytosis (HLH). Patients with this rare hyperinflammatory disease manifest with cytokine storm and multiorgan dysfunction and commonly have CNS manifestations. Hematopoietic stem cell transplantation (HCT) can provide a definitive cure. The

report includes a 4th case, the asymptomatic sibling of one of the patients who was found to have a relevant gene mutation while being evaluated as a donor for her sisters' HCT. Her MRI was consistent with multifocal inflammation. All 4 patients had HCT with neurologic stabilization or improvement while the 4th patient remained asymptomatic. Of interest, patient 2 relapsed, leading to the discovery that her sibling donor had a monoallelic gene mutation. The patient responded to a second HCT from an unrelated donor. The authors suggest that the differential diagnosis of pediatric patients with treatment refractory or recurrent CNS inflammation of uncertain etiology should include CNS-isolated forms of HLH, and if confirmed, screening of siblings is important.

In addition to these studies, the May issue of N2 contains an interesting case discussion in the section "Diagnostic and Treatment Challenges" of a patient who developed a cerebellar syndrome after treatment with natalizumab, as well as other interesting articles that I hope will catch your attention.

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Disclosure

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References

1. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. *Nat Med* 2001;7:365–368.
2. van der Neut Kolfschoten M, Schuurman J, Losen M, et al. Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. *Science* 2007;317:1554–1557.
3. Huijbers MG, Vergoossen D, Fillié-Grijpma Y, et al. MuSK myasthenia gravis monoclonal antibodies: valency dictates pathogenicity. *Neurol Neuroimmunol Neuroinflamm* 2019;6:e547. doi: 10.1212/NXI.0000000000000547.
4. Akgün K, Kretschmann N, Haase R, et al. Profiling individual clinical responses by high-frequency serum neurofilament assessment in MS. *Neurol Neuroimmunol Neuroinflamm* 2019;6:e555. doi: 10.1212/NXI.0000000000000555.
5. Johannssen K, Schwab N, Wessig C, Reiners K, Wiendl H, Sommer C. Myalgia with the presence of pathological EMG correlates with perimysial inflammatory infiltrates. *Neurol Neuroimmunol Neuroinflamm* 2019;6:e549. doi: 10.1212/NXI.0000000000000549.
6. Benson LA, Li H, Henderson LA, et al. Pediatric CNS-isolated hemophagocytic lymphohistiocytosis. *Neurol Neuroimmunol Neuroinflamm* 2019;6:e560. doi: 10.1212/NXI.0000000000000560.

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