Commentary

Anti-Viral T-Cell Immunity + Anti-CNS Autoantibody = A Model for Human Acute Disseminated Encephalomyelitis or Multiple Sclerosis Relapse?

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In this issue of *The American Journal of Pathology*, Burrer et al.¹ report exacerbation and increased mortality in three mouse models of otherwise relatively benign viral encephalitis by the genetic introduction or passive transfer of myelin oligodendrocyte glycoprotein (MOG)-specific antibody. In mouse hepatitis virus (MHV) encephalomyelitis, enhanced central nervous system (CNS) inflammation and demyelination are attributed to anti-MOG antibody-mediated mechanisms rather than to the anti-viral T-cell response. The authors demonstrate that exacerbation of clinical disease is associated with increases in neutrophil and NK cell infiltration of the central nervous system and greater tissue damage.

This report highlights the important question as to how closely the widely used mouse models of CNS demyelinating diseases replicate their human counterparts and specifically, to which human disease, ie, multiple sclerosis (MS) or acute disseminated (perivenous) encephalomyelitis (ADEM), they may be most relevant. By definition, relapses of MS occur in patients who have experienced prior clinical neurological dysfunction, whereas patients with ADEM are characteristically clinically intact before the disease onset. Moreover, relapses in MS patients have as their pathological substrate CNS tissues that have been previously compromised, ie, plaques with an impaired blood-brain barrier.² Although there currently is no consensus as to the relationship of ADEM to MS or whether they should be considered distinct entities, the absence of prior CNS injury in the mice and the histopathological similarities between their CNS lesions and those in human ADEM (Figure 1) argue that the models in this report more closely resemble ADEM than MS.

ADEM refers to a group of inflammatory/demyelinating disorders with distinct clinical and pathological features

and presumed pathogenetic mechanisms. Patients present with an abrupt onset of a neurological syndrome; in the majority of cases, there is a history of a preceding febrile illness or a vaccination, most commonly for smallpox or rabies, within 2 to 14 days before the onset.^{2,3} ADEM is more commonly seen in children and has been reported following a large number of viral, bacterial, and other infections and vaccinations. The first episode of MS may not be clinically distinguishable from ADEM but unlike MS, ADEM usually has a monophasic course with good recovery.⁴

ADEM lesions from a representative autopsied case are shown in Figure 1. Numerous inflammatory lesions were found almost exclusively in the pons, medulla, cerebellar peduncles, and white matter of the upper cervical spinal cord. The lesions varied in their appearances and extent of tissue injury. Some foci consisted of small mononuclear cells in perivascular spaces with preservation of the surrounding myelin and axons (Figure 1, A and B); others were associated with more edema and myelin destruction (Figure 1, C and D). In these areas, lymphocytes and macrophages extended into the parenchyma and the latter contained Luxol fast blue-positive myelin fragments. Additional areas had prominent dense neutrophil aggregates (Figure 1, E and F). Despite the intensity of the inflammation in these foci, neuron cell bodies were often preserved, suggesting specific immune targeting of non-neuronal tissue components. Other areas showed marked vascular damage indicated by fibrin leakage, more widely dispersed neutrophils, and more extensive demyelination (Figure 1G). Consistent with a recent study,⁵ axonal transection and loss were also

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Figure 1. Representative fields demonstrate the spectrum of lesion pathology in the CNS of a previously neurologically intact 70-year-old man who developed ADEM 1 week following an influenza vaccination and who died 6 weeks later following aspiration pneumonia and sepsis. **A:** Typical perivascular mononuclear cell inflammatory cuff in cerebellar white matter with relative preservation of surrounding parenchyma. Most of the cells are small lymphocytes, but some are foamy macrophages, suggesting adjacent myelin breakdown and phagocytosis. **B:** Serial section to **A** with mostly intact myelin (blue) and axons (black). **C:** Cerebellar white matter inflammatory/demyelinating focus with prominent perivascular vacuolation (edema). **D:** Serial section to **C** demonstrating inflammation, perivascular edema, and demyelination. **E:** Upper cervical spinal cord lesion with marked neutrophil infiltrates and relative preservation of anterior horn cell somata (**arrows**). **F:** Serial section to **E** highlighting both neutrophil (lower portion of figure) and mononuclear cell infiltration of parenchyma and demyelination. One preserved neuron cell body is seen (**arrow**). Myelin is relatively preserved in the upper portion of the field. **G:** Completely demyelinated upper cervical cord lesion with vessel wall breakdown and diffuse fibrin exudation. There are numerous parenchymal neutrophils in the peripheral portions of the field. **H:** Upper cervical spinal cord lesion with axon retraction bulbs (**arrows**) indicating transection. **A, C, E,** hematoxylin and eosin; **B, H,** Luxol fast blue-Bielschowsky preparation; **D, F, G,** Klüber-Barrera stain. Original magnifications: **A, B,** $\times 160$; **C-G,** $\times 80$; **H,** $\times 200$.

present in the more severe lesions (Figure 1H). Although areas of demyelination coalesced in one portion of the cerebellar white matter to form a larger lesion, there were no typical MS plaques. No CNS infection was documented either during the patient's life or at autopsy. Extensive subpial demyelinating lesions similar to those in the mice may also be prominent in human ADEM cases.²

The ADEM case demonstrates complex injury patterns, ie, encephalitis associated with variable but generally focal demyelination and an apparently superimposed process with dense neutrophil infiltrates, prominent vascular damage, and larger areas of tissue injury.^{2,6} Very similar pathological findings are illustrated in the mice with enhanced disease in the study of Burrer et al.¹ Therefore, the combination of antimicrobial and autoimmune mechanisms in the mouse models might be recapitulated in ADEM.

Earlier studies of experimental autoimmune encephalomyelitis (EAE) in which anti-MOG monoclonal antibody was passively transferred into animals with mild disease demonstrated enhanced clinical disease scores and CNS lesions with prominent perivascular edema, neutrophil infiltrates, and demyelination.⁷⁻⁹ In these models,

breach of the blood-brain barrier secondary to the initiating autoimmune T-cell inflammatory response allows circulating anti-MOG antibodies to enter CNS tissue. The major processes leading to greater tissue damage and clinical disease manifestations are therefore attributable to increased autoantibody access and targeting of CNS myelin superimposed on an initial, less pathogenic autoimmune T-cell inflammatory response. Recently, two groups have also demonstrated that the combined cooperation of B- and T-cell anti-MOG immunity in transgenic mice leads to their development of a spontaneous disease with similarities, eg, CNS lesion localization, to human Devic's disease, which has been regarded as a variant of MS.¹⁰⁻¹² Taken together, the EAE models indicate that spontaneous CNS demyelinating diseases that mimic those occurring in humans can be initiated in the absence of an active CNS infection and may therefore more closely resemble postvaccinal ADEM. Based on the temporal association in the illustrated case of ADEM, influenza vaccination but not CNS infection seems to have been the critical initiating event.

The target autoantigens in human demyelinating diseases, particularly MS, have long been considered to be

myelin components, ie, myelin basic protein, myelin proteolipid protein, and MOG. This paradigm is, however, undergoing reconsideration and expansion, because there is a growing number of potential CNS autoantigens of both myelin- and non-myelin-producing cells, eg, astrocytes¹³ and axons,¹⁴ that may be T- and B-cell autoimmune targets in MS and related diseases.

A number of CNS viral infection models elucidate various aspects of T- and B-cell immunity in the pathogenesis of infection-associated CNS demyelinating diseases.^{15–19} In these models, the tissue injury induced by the infection, the immune response to the virus, or a combination thereof results in pathogenic targeting of autoantigen(s). Cross-recognition by the immune system of self and foreign antigens, ie, molecular mimicry, is thought to be the major mechanism responsible for the enhanced CNS autoimmune T- and B-cell responses.^{1,20} Because systemic but not active CNS infections are associated with relapses in chronic MS patients,²¹ similar combinations of systemic antipathogen immunity and anti-CNS autoimmunity may contribute to those relapses.¹ In the illustrated ADEM case, it is also possible that concurrent sepsis could have accentuated the CNS inflammation.

In summary, models using laboratory virus strains and transgenic mice as in the study by Burrer et al¹ permit characterization of autoimmune target antigens and exquisitely precise dissection of cellular and molecular mechanisms in complex CNS diseases. In humans, these mechanisms tend to be more often inferred and are not subject to comparable analyses or experimental manipulation. The relevance and ultimate usefulness of the animal disease models depend, however, on their critical assessment in the context of the appropriate human conditions, particularly by rigorous correlations of clinical and pathological features.

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