Multiple sclerosis: more pieces of the immunological puzzle

During 2011 we have seen important progress in the understanding and treatment of multiple sclerosis (MS), particularly with regard to the role of the immune system. Inflammatory and neurodegenerative disease mechanisms are both implicated in MS, but whether these happen in sequence or are independent is still under investigation. The findings of a large genome-wide association study, in which 9772 patients with MS from across 15 countries were recruited, confirmed the 23 hitherto known susceptibility loci and suggested another 29 putative loci, all of immune origin. Therefore, growing evidence indicates that MS is based on dysregulation of the immune system, implicating both innate and adaptive immunity. However, what drives the immune deviation in MS?

For decades, immunologists and virologists have searched for an infectious agent in MS, and many viruses have been suspected to initiate the disease. Important work from Berer and colleagues2 has opened new horizons: commensal bacteria from the gut and myelin autoantigens might cooperate and trigger autoimmune demyelination. The researchers used transgenic mice to show that commensal gut flora—in the absence of pathogenic bacterial agents—is essential for triggering of immune processes that lead to a relapsing-remitting autoimmune disease driven by myelin-specific CD4+ T cells. Furthermore, recruitment and activation of autoantibody-producing B cells from the endogenous immune repertoire depended on availability of the target autoantigen, myelin oligodendrocyte glycoprotein, and commensal microbiota. These findings are still too limited for long-term antibiotic treatment or manipulation of the gut microenvironment of patients with MS to be attempted. However, the data provide evidence that implicates gut microbiota in the starting phase of human autoimmune diseases.

In addition to advances in understanding of the pathogenesis of MS, we have also seen renewed diagnostic criteria,3 based mainly on findings of the MRI in MS (MAGNIMS) studies.4 Since 2001, the requirements for dissemination in time have evolved, from the need for a second clinical event to acceptance of new lesions visible on follow-up MRI in the absence of a relapse. The updated criteria go even further: if old and new gadolinium-enhancing lesions are detected simultaneously on the first diagnostic MRI, the need for dissemination in time is fulfilled and only defined lesion sites are needed for a firm diagnosis to be made at the time of the first clinical event. Thus, in some circumstances, dissemination in space and time can be established with one scan. This change substantially modifies the idea of a clinically isolated syndrome, since diagnosis can be made at first presentation in 30–50% of patients, and much more care has to be taken in differential diagnosis at this early stage to exclude other potential CNS diseases. Many researchers from Europe, where CSF analysis has had a strong role in diagnosis of relapsing-remitting MS, regret the absence of CSF from the diagnostic algorithm, since these samples not only help in the exclusion of other diagnoses but also provide information directly from the inflamed tissue compartment. Only for primary progressive MS is CSF still part of diagnostic criteria.

We are approaching a period in which more effective and oral treatments for MS are likely to become available. Teriflunomide—the active metabolite of leflunomide, which has a long tradition of treatment of rheumatic diseases—has proven efficacious in patients with relapsing MS.5 This agent reversibly inhibits dihydroorotate dehydrogenase, which plays a part in DNA replication. At daily doses of both 7 mg and 14 mg, teriflunomide reduced the annualised relapse rate by 31% and MRI T2 lesion load by up to 67% compared with placebo. It seems to show robust safety, although its efficacy does not exceed that of current first-line disease-modifying drugs, and effective contraception is of utmost importance because this agent interferes directly
Headache: advances in understanding and treatment

Our understanding of the biological basis of headache has evolved over the past few centuries, from neurological, to vascular, to trigeminal vascular, to interlocking components of vascular, neurological, and biochemical substrates. With this evolution, our knowledge of potential treatment pathways, which might provide an understanding of the genomic components that themselves become targets for treatment, has also advanced.

One of the perplexing clinical issues in headache medicine has resulted from the use of MRI. With the advent of MRI came the discovery of white matter lesions (WMLs) in patients with migraine and other headaches. But what is the relevance of these lesions? Are they evidence of small vessel ischaemic disease? What is their cause and effect? Kurth and colleagues’ examined WMLs on MRI in various locations in the brains of patients with migraine and other headache disorders. They assessed the types of WML and investigated associations with patient demographics, risk factors, and type of headache and migraine to gain a better understanding of WMLs and their potential role in clinical features such as cognitive decline, with nucleic-acid metabolism, which is crucial during gestation.

Although natalizumab clearly has stronger therapeutic activity than teriflunomide, use of natalizumab comes at the expense of more than 181 cases worldwide of associated progressive multifocal leukoencephalopathy (PML).6 Although survival is much better in patients with MS than in individuals with HIV-associated PML, defence mechanisms in patients with MS are still poorly understood. Aly and colleagues’ showed the central importance for antiviral defence of the intrinsic JC-virus-specific CD4+ T-cell response, which also causes bystander damage of infected glia. Thus, a pivotal role for elimination of the virus at the expense of massive inflammation can be attributed to CD4+ T cells. Perhaps similar immunological approaches that cause less bystander damage can be used to combat primary viral infection.

Our knowledge of dysregulation of the immune system in MS is growing, as is the therapeutic potential of new drugs, including oral drugs, to treat relapsing MS. We hope that these findings will translate into availability of a wider range of drugs to treat MS in future years.

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