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Neuroinflammation of the central and peripheral nervous system: an update

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Summary

Inflammatory disorders of the peripheral nervous system (PNS) and central nervous system (CNS) are common, and contribute substantially to physical and emotional disability of affected individuals. Often, the afflicted are young and in their active years. In the past, physicians and scientists often had very little to offer in terms of diagnostic precision and therapeutic effectiveness. During the past two decades, both of these relative shortcomings have clearly improved. Some of the recent developments in clinical neuroimmunology are illustrated in this special edition of *Clinical and Experimental Immunology*.

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Inflammatory disorders of the peripheral nervous system (PNS) and central nervous system (CNS) are common, and contribute substantially to the physical and emotional disability of affected individuals. Often, the afflicted are young and in their active years. In the past, physicians and scientists usually had very little to offer in terms of diagnostic precision and therapeutic effectiveness. During the past two decades, both of these relative shortcomings have clearly improved. Some of the recent developments in clinical neuroimmunology are illustrated in this special edition of *Clinical and Experimental Immunology*.

Clinical medicine has always relied heavily, and sometimes exclusively, upon clinical phenotypes. In the absence of disease-specific biomarkers, phenotypes are often heterogeneous and ill-defined. Sequencing of the human genome, advancement in imaging, large-scale genomics and proteomics have attempted to provide a clearer definition of human disease entities. Some of these attempts are now materializing.

The human nervous system is designed functionally from top to bottom, or head to toe: the CNS consists of the brain and spinal cord, where information is received and generated, and finally relayed via motor outputs to the periphery. The PNS is constituted of neurones and their cellular process which, in turn, provide sensory information from the periphery to the CNS. In addition, there are efferent and afferent autonomic pathways between these two compartments. In the periphery, innervation of muscle via spinal cord motor neurones and the neuromuscular junction enable voluntary motor activities.

The most common inflammatory disorder of the CNS is multiple sclerosis (MS). MS is widely considered an autoimmune disorder, although putative autoantigens have not yet been identified. Nevertheless, the vast majority of patients with MS respond to immunomodulatory or immunosuppressive therapies, and during the past two decades tremendous progress has been made in developing more effective therapeutic interventions. One group of therapies that is considered second- and third-generation is that of monoclonal antibodies (mAbs). The first member of this group to be approved in MS was natalizumab, a humanized recombinant mAb against α4-integrin. Many other molecular and cellular targets are now being assessed therapeutically by mAb, and a review by Rommer *et al.* provides information about approved agents and those that are currently in development [1]. Specifically, the authors outline the biological rationale for each agent, and the stage of their current development. As stated above, the development of new therapies for MS has been very dynamic over the past decades. Currently, there are nine approved agents, and the general neurologist is often overwhelmed with choices. Melzer and Meuth review the pros and cons of individual drugs, their specific indications and potential side effects [2]. While no treatment algorithms are provided, this review will help the practitioner to identify therapeutics that may meet certain criteria.

An important aspect of treatment decisions is the safety of a therapeutic intervention. All currently approved agents are approved for the relapsing–remitting form of MS, which is considered the clinical phenotype that is associated with a strong involvement of the peripheral adaptive immune system. Not surprisingly, all approved agents, and almost all agents that are currently in development, are anti-inflammatory and immunomodulatory, or immunosuppressive. Also not surprisingly, some of these agents are associated with substantial adverse events. While the first generation of therapeutics was modestly effective, they were also considered relatively well tolerated and safe. Newer agents are often more effective, as sometimes shown by head-to-head comparison studies, but some of them also have more serious potential side effects. Natalizumab, for instance, has a very high risk of progressive multi-focal leucoencephalopathy (PML), a potentially lethal infection with the human polyomavirus John Cunningham (JC). The reason for this side effect remains incompletely understood, but given the mechanism of action of natalizumab there is probably an impairment of CNS immunosurveillance. Other agents have less common, but equally serious, potential side effects, reviewed by Winkelmann and colleagues. They provide an update on the current knowledge of infectious issues that should be considered when using MS therapeutics [3]. While infectious side effects of pharmacotherapies for MS are clearly relevant when devising a treatment plan, there are other issues to consider. Rommer *et al.* discuss all known side effects of approved agents and those about to be approved, as well as currently recommended laboratory monitoring [4]. In addition, pregnancy ratings for each agent are provided. This is very useful information for neurologists and patients who are attempting to identify the most suitable drug.

Cerebral vasculitis is a rare disorder of the CNS. It is also a rare cause of juvenile stroke, which makes it highly relevant. As in MS, afflicted individuals are often left with substantial neurological disability if not diagnosed and treated early. Cerebral vasculitis is either a primary angiitis of the central nervous system (PACNS) or a manifestation in the setting of systemic vasculitis. Due to the rarity of the disease, the exclusion of more frequent entities will often lead to its diagnosis. Berlit and Kraemer summarize the diagnostic steps that lead to the diagnosis of cerebral vasculitis [5]. Importantly, the dilemma of angiography-negative vasculitis and false-negative brain biopsy are discussed.

An even more rare CNS inflammatory disorder than cerebral vasculitis is chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). CLIPPERS was only recently defined through an anatomical involvement of the pons, and a combination of clinical symptoms attributable to brainstem pathology. Also, there is a characteristic magnetic resonance imaging (MRI) appearance with punctate and curvilinear gadolinium enhancement of the pons. Another key feature of CLIPPERS is its clinical and radiological responsiveness to glucocorticosteroid (GCS)-based immunosuppression. Because there is no known biomarker associated with CLIPPERS, its diagnosis is challenging and requires careful exclusion of alternative diagnoses. A review by Dudesek and co-workers will provide many insights in this regard [6].

There are three neurological autoimmune disorders in which autoantigens have been identified: myasthenia gravis (MG), neuromyelitis optica (NMO) and the group of paraneoplastic disorders. The identification of autoantigens is a critical step in identifying disease-specific therapies. Sieb provides a thorough overview of the current advances in diagnosis and therapy of MG [7]. While a post-synaptic defect of neuromuscular transmission is the main pathophysiological feature of MG, the disorder can now be classified according to the antibody specificity [acetylcholine, muscle-specific receptor tyrosine kinase (MuSK), low-density lipoprotein receptor-related protein 4 (LRP4), seronegative, thymus histology (thymitis, thymoma, atrophy)], age at onset and clinical phenotype. Despite the fact that autoantigens have been identified, the mainstay of therapy remains glucocorticosteroids and steroid-sparing non-specific immunosuppressants. Research initiatives in this regard clearly appear indicated.

Cancerous cells frequently express protein self-antigens on their cell surface that become the targets of self-directed humoral immunological events. Paraneoplastic neurological syndromes are immune-mediated erroneous attacks on the central or peripheral nervous systems, or both. More recently, the discovery of new subgroups of paraneoplastic encephalitis syndromes with a remarkably good response to immune therapy has ignited an enormous clinical and scientific interest. The sheer abundance of new autoantibodies and syndromes can be confusing, and a review paper by Leypoldt and Wandinger neatly summarizes current knowledge and new developments in this field [8].

The final functional component of a motor response is the skeletal muscle. Inflammatory myopathies, including dermatomyositis (DM), polymyositis (PM), necrotizing myopathy (NM) and inclusion body myositis (IBM), are four distinct subtypes of myositis. Recent observations suggest a unique pathogenesis of each entity. Carstens and Schmidt provide an up-to-date outline of the pathogenesis and diagnostic approach, and present a guide towards therapeutic and general management [9].

In summary, this issue of *Clinical and Experimental Immunology* provides a comprehensive overview of recent work in inflammatory disorders of the CNS and PNS. The authors provide novel information on pathogenesis, diagnosis and therapy for many of the disorders that neuroimmunologists frequently encounter. It is reasonable to expect the field to move forward rapidly over the coming years, and that disease phenotypes will ultimately be defined as mono-genetic or mono-molecular.

Disclosure

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