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Review

Autoimmune disorders affecting both the central and peripheral nervous system

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ABSTRACT

Various case series of patients with autoimmune demyelinating disease affecting both the central and peripheral nervous system (CNS and PNS), either sequentially or simultaneously, have been reported for decades, but their frequency is considerably lower than that of the "classical" neurological autoimmune diseases affecting only either CNS or PNS, such as multiple sclerosis (MS), chronic inflammatory demyelinating polyneuropathy (CIDP) or Guillain–Barré-Syndrome (GBS), and attempts to define or even recognize the former as a clinical entity have remained elusive. Frequently, demyelination started with CNS involvement with subsequent PNS pathology, in some cases with a relapsing–remitting course. Three potential mechanisms for the autoimmune etiology of these conditions can be discussed: (I) They could be caused by a common autoimmunological reactivity against myelin antigens or epitopes present in both the central and peripheral nervous system; (II) They could be due to a higher general susceptibility to autoimmune disease, which in some cases may have been caused or exacerbated by immunomodulatory treatment, e.g. b-interferon; (III) Their co-occurrence might be coincidental. Another example of an autoimmune disease variably involving the central or peripheral nervous system or both is the overlapping and continuous clinical spectrum of Fisher syndrome (FS), as a variant of GBS, and Bickerstaff brainstem encephalitis (BBE). Recent data from larger patient cohorts with demonstration of common autoantibodies, antecedent infections, and results of detailed clinical, neuroimaging and neurophysiological investigations suggest that these three conditions are not separate disorders, but rather form a continuous spectrum with variable central and peripheral nervous system involvement. We herein review clinical and paraclinical data and therapeutic options of these disorders and discuss potential underlying common vs. divergent immunopathogenic mechanisms.

Contents

Abbreviations: ADEM, acute disseminated encephalomyelitis; AIDP, acute inflammatory demyelinating polyneuropathy; BBE, Bickerstaff brainstem encephalitis; CSF, cerebrospinal fluid; CNS, central nervous system; CIDP, chronic inflammatory demyelinating polyneuropathy; FS, Fisher syndrome; GBS, Guillain–Barré-syndrome; ICU, intensive care unit; IFN, interferon; MBP, myelin basic protein; MRI, magnetic resonance imaging; MS, multiple sclerosis; NCS, nerve conduction studies; PNS, peripheral nervous system.

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1. Introduction

Multiple sclerosis (MS) is an autoimmune disease characterized by chronic inflammation, demyelination and gliosis affecting the central nervous system (CNS) but usually not the peripheral nervous system (PNS), although subclinical PNS involvement has occasionally been described. Evidence has emerged in recent years that CNS atrophy and axonal damage may also play a role in MS pathology and especially in determining clinical outcome [1–3]. In contrast, chronic inflammatory demyelinating polyneuropathy (CIDP) is considered a typical example of an autoimmune disease restricted to the PNS because it is apparently caused by an autoimmune response against one or several antigen(s) on peripheral nerves (reviewed in [4]). Several single cases or small series of patients with combined demyelination of both CNS and PNS, occurring either sequentially or simultaneously, have been reported (see Table 1), but there have been as of yet no clear definitions or even clear recognitions of this entity in the literature. Further it is currently unclear whether CNS and PNS involvement is due to a common immunopathogenic mechanism or whether either CNS or PNS damage, depending on the course of the disease with variable sequential appearance of symptoms, may occur secondary as a consequence of immune dysregulation, either caused by the disease itself or possibly as a consequence of immunomodulatory or immunosuppressive treatment, or may be coincidental.

Another example of an autoimmune disease affecting both the central and peripheral nervous system is the overlapping clinical spectrum of Miller–Fisher–/Fisher–Syndrome (FS), Bickerstaff brainstem encephalitis (BBE) and Guillain–Barré-Syndrome (GBS). It is hypothesized that all three entities are not separate conditions but may share a common etiology, as supported especially by the presence of common autoantibodies and antecedent infections, and form a continuous spectrum with variable clinical and anatomical involvement of PNS and CNS, even leading some authors to suggest a new eponymic terminology of "Fisher–Bickerstaff syndrome" which includes as yet unclassified conditions as well as FS and BBE, or may be better described as "anti-GQ1b–IgG-antibody syndrome" [5]. However, it is generally difficult to determine whether the lesions responsible for ophtalmoplegia, ataxia and areflexia in the latter conditions are located in the central or peripheral nervous system.

2. Reports of patients with autoimmune demyelination of both CNS and PNS

Given the comparatively high prevalence of multiple sclerosis (between 1 and 300/100,000 worldwide with considerable regional variability, approximately 2 million patients worldwide [6]) and CIDP (between 1.2 and 7.7/100,000 [7]), reports of patients with autoimmune demyelination of both CNS and PNS have been scarce. For a brief overview with emphasis on clinical findings and the temporal course of the disease, see Table 1. A detailed overview of further clinical and paraclinical characteristics including neuroimaging, neurophysiological and laboratory findings of most of these patients is given in [8].

In both MS and CIDP, the combination of a genetic predisposition and an environmental trigger factor is proposed as immunopathogenic mechanism [7,9]. In conditions with combined demyelination of both CNS and PNS, it is conceivable that reactive T-cells and/or antibodies may cross the blood-brain-/blood-nerve-barrier and activate an inflammatory process after being re-exposed to the autoantigen, but presently it cannot be determined whether the same antigenic target occurs in both PNS and CNS. Although PNS myelin is produced by Schwann cells and CNS myelin by oligodendrocytes, the majority of PNS myelin proteins are also present in the CNS [10]; for example, myelin P1 expressed in peripheral nerves is identical to central myelin basic protein (MBP) (Fig.1). Therefore, the concept of a common autoantigen shared between both CNS and PNS is generally conceivable.

Clinical evidence for demyelinating lesions of the CNS is considered uncommon in typical CIDP, whereas subclinical involvement may be present in a considerable proportion of patients [11–14]. Likewise, there is currently only little evidence for PNS involvement in typical MS, at least in clinical terms; one retrospective study of 150 patients with MS found clinical and neurophysiological signs of PNS involvement in 13 patients, including four with a demyelinating neuropathy [15], whereas a more recent study in 54 patients found evidence for only minor PNS affection with subtle alterations by standard nerve conduction velocity and without hints for small fibre pathology [2]. In accordance with these findings, another recent study found significantly lower CMAP amplitudes of four different motor nerves, but no significant differences in motor and sensory conduction velocities and distal motor latency in 69 MS patients compared to 75 healthy controls, suggesting possible lower motor neuron damage without peripheral neuropathy in these patients [1]. Taken together, these findings support the hypothesis that the case series of patients with combined demyelination of both CNS and PNS discussed above and summarized in Table 1 probably represent a separate clinical entity apart from both typical MS and CIDP. This is further supported by the absence of oligoclonal bands but the presence of elevated protein levels in the CSF of many of those patients where adequate data is available.

However, another important aspect to be considered is the temporal succession of symptoms, i.e. whether there is simultaneous involvement of both CNS and PNS, or whether a "temporal dissociation" of lesions between CNS and PNS can be observed, and whether CNS involvement precedes PNS involvement or vice versa. In the majority of cases reported [8,16–22], (see Table 1), CNS involvement preceded PNS involvement in the form of peripheral demyelinating neuropathy, in many cases after a diagnosis of MS was established and in some after immunomodulatory treatment with interferon-β (IFN-β) was initiated. In many of the latter cases, peripheral demyelinating neuropathy was responsive to subsequent intravenous immunoglobulin (IVIG)-treatment [17]. This raises the possibility that treatment with IFN-β, by an as yet undefined mechanism, contributed to the development of CIDP, which is supported by other reports of peripheral demyelinating neuropathy after treatment with IFN-α [23,24]. Further, the fact that IVIG-treatment was ineffective in treating CNS symptoms in these patients suggests distinct immunopathogenic mechanisms of central vs. peripheral demyelination, even if a shared antigen is assumed.

Several clinical, CSF and MRI features in these patients were atypical for MS, including bilateral optic neuropathy, absence of oligoclonal bands from CSF, and grey matter involvement, mass effect and multiple enhancing lesions on brain MRI, several of which are rather reminiscent of relapsing variants of acute disseminated encephalomyelitis (ADEM). Since it is increasingly recognized from the data gathered recently by larger patient series that a considerable proportion of patients with ADEM show atypical features with a relapsing course and PNS involvement [25], the possibility should be considered that at least a subset of the patients discussed above may represent atypical ADEM variants complicated by peripheral nervous system involvement. In line with this hypothesis, a recent retrospective analysis of a large series of children with central or peripheral nervous system demyelination revealed a significant proportion (13/93 = 14% of children with acute demyelination) of pediatric patients with acute combined (simultaneous) demyelination of both CNS and PNS [26]. Compared with children with acute demyelination of either only CNS ($n = 37$) or only PNS ($n = 43$) demyelination, patients in the first subgroup had more frequently infectious prodromi (85%), were slightly older and more severely affected with more frequent admission to a pediatric intensive care unit (ICU),