Biochimica et Biophysica Acta xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Pathogenesis of immune-mediated neuropathies ☆

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ARTICLE INFO

Article history:
Received 15 May 2014
Accepted 9 June 2014
Available online xxxx

Keywords:
Autoimmune neuropathy
Node of Ranvier
Immunotherapy

ABSTRACT

Autoimmune neuropathies occur when immunologic tolerance to myelin or axonal antigens is lost. Even though the triggering factors and the underling immunopathology have not been fully elucidated in all neuropathy subsets, immunological studies on the patients' nerves, transfer experiments with the patients' serum or intraneural injections, and molecular fingerprinting on circulating autoantibodies or autoreactive T cells, indicate that cellular and humoral factors, either independently or in concert with each other, play a fundamental role in their cause. The review is focused on the main subtypes of autoimmune neuropathies, mainly the Guillain–Barré syndrome(s), the Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), the Multifocal Motor Neuropathy (MMN), and the IgM anti-MAG-antibody mediated neuropathy. It addresses the factors associated with breaking tolerance, examines the T cell activation process including co-stimulatory molecules and key cytokines, and discusses the role of antibodies against peripheral nerve glycolipids or glycoproteins. Special attention is given to the newly identified proteins in the nodal, paranodal and juxtaparanodal regions as potential antigenic targets that could best explain conduction failure and rapid recovery. New biological agents against T cells, cytokines, B cells, transmigration and transduction molecules involved in their immunopathologic network, are discussed as future therapeutic options in difficult cases. This article is part of a Special Issue entitled: Neuromuscular Diseases: Pathology and Molecular Pathogenesis.

1. Introduction

Autoimmune Peripheral Neuropathies (APN) develop when immunologic tolerance to key antigenic sites on the myelin, axon, nodes of Ranvier or ganglionic neurons is lost [1,2]. Current evidence supports the notion that in APN the autoimmunity is mediated by antibodies directed against myelin antigens, along with autoreactive T cells and macrophages that invade myelin sheath, axonal membranes or the nodes of Ranvier. In some APN the triggering factors have been identified and progress has been made in understanding the key players involved in the immunopathogenic network; in several others however, the exact immunopathologic mechanisms remain still unclear, but autoimmunity is suspected based on the presence of antibodies, sensitized T cell infiltrates in the peripheral nerves, response to immunotherapies or coexistence with another autoimmune disease or viral infections. The APN are clinically important because they respond to immunotherapies based on controlled studies, or have the potential to respond if more effective agents are used. The review addresses the autoimmune pathways involved in the pathogenesis of the most common autoimmune neuropathies and highlights the rationale for target-specific immunotherapies.

1.1. Main clinicopathologic features of common APN

The common autoimmune neuropathies include: 1) Acute Inflammatory Polyneuropathy [the Guillain–Barré Syndrome(s)]; 2) Chronic inflammatory demyelinating polyneuropathy (CIDP) and its variants; 3) Multifocal motor neuropathy with conduction block; and 4) Polyneuropathies associated with IgM monoclonal gammopathies and anti-MAG antibodies [1,2]. Other less common immune-mediated neuropathies that will not be addressed here because their pathogenesis is less clear include: the paraneoplastic neuropathies associated with anti-Hu antibodies, vasculitic neuropathies due to isolated peripheral nerve vasculitis, certain diabetic demyelinating or inflammatory neuropathies where an immune component appears prominent, and the neuropathies associated with systemic autoimmune disorders.

As discussed below and elaborated previously [1,2], in some APN, like certain GBS variants and the anti-MAG neuropathy, the main target antigens have been identified and the antibodies against them are well characterized; in the most common neuropathies however, like the demyelinating variant of GBS and the CIDP, the target antigens remain still

☆ This article is part of a Special Issue entitled: Neuromuscular Diseases: Pathology and Molecular Pathogenesis.

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http://dx.doi.org/10.1016/j.bbadis.2014.06.013
0925-4439/

elusive in spite of the progress made in understanding their molecular immunopathology.

Q10 The Guillain–Barré syndrome(s) (GBS) presents with an acute (within 1–3 weeks) ascending motor weakness, areflexia, and mild to moderate sensory abnormalities [1–5]. The neuropathy is *inflammatory*, with perivascular and endoneurial lymphoid cell infiltrates throughout the nerves, roots or plexuses, and *demyelinating* with signs segmental demyelination induced by complement-fixing antibodies and macrophages as the final effector cells. GBS represents several syndromes – or variants – according to whether the main clinicopathologic involvement is centered on motor or sensory nerve fibers and whether it affects predominantly the myelin or the axon [1–4]. Accordingly, the GBS syndromes comprise the following subtypes: i) the *acute inflammatory demyelinating polyneuropathy* (AIDP), where the main target appears to be the myelin and accounts for the majority of GBS patients; ii) the *acute, motor axonal neuropathy* (AMAN), where the primary pathology is in the axon, either due to massive acute demyelination and inflammation, as occurs in experimental allergic neuritis when animals are immunized with a high dose of myelin antigens [1,2,6], or due to a primary attack on the axons and the nodes of Ranvier mediated by macrophages and antibodies. A number of these cases have high GM1 antibodies and, as discussed later, report an antecedent infection with *Campylobacter jejuni* [2,3,7]; iii) the *acute motor–sensory axonal neuropathy* (AMSAN), which is like AMAN but with concurrent involvement of the sensory axons; iv) the *Miller-Fisher syndrome*, characterized by ophthalmoplegia, gait ataxia, and areflexia [1–5], a rather distinct variant because of the unique clinical phenotype and the presence of IgG antibodies against GQ1b ganglioside [1–4,7,8]; vi) the *sensory ataxic GBS*, probably due to involvement of dorsal roots and ganglionic neurons; some of these patients have also IgG antibodies to GQ1b or GD1b ganglioside and may be forming a continuum with Miller-Fisher syndrome or share autoantibodies with the same sialic groups [1,2,8,9]; and vii) the *acute pandysautonomic neuropathy* where the target antigen is probably in the sympathetic ganglionic neurons [1,2].

1.1.1. Chronic inflammatory demyelinating polyneuropathy (CIDP)

This is the most common APN with prevalence as high as 9/100,000 [2,10,11], and the most gratifying neuropathy because it is treatable in the majority of the cases [2]. CIDP is viewed as the chronic counterpart of GBS [1,2] because it shares with GBS certain clinical, electrophysiologic, histologic, laboratory and autoimmune features. It differs from GBS predominantly by its tempo, mode of evolution, prognosis, and responsiveness to steroids or immunosuppressants [1,2,10,12,16]. On electrophysiological grounds, CIDP demonstrates features of demyelination in motor and sensory fibers with slow conduction velocity, dispersion of the compound muscle action potentials, conduction block in at least one nerve, prolonged distal motor or sensory latencies and prolonged F wave latencies. On histological grounds, there is evidence of demyelination associated with macrophages, complement and activated T cells [10,12–16]. The demyelination in CIDP is also multifocal, like the one seen in GBS, affecting spinal roots, plexuses and proximal nerve trunks [13–15], accounting for the variable distribution of symptoms and signs, which are clinically expressed as CIDP variants [10]. The most notable CIDP variables are *the asymmetric, unifocal or multifocal motor–sensory form (the Lewis-Sumner syndrome)*; *the pure motor form*; the *pure sensory form*; the *sensory ataxic form*; and *the pure distal* [1,2,10,12,16].

1.1.2. Multifocal motor neuropathy (MMN) with conduction block

MMN has distinct clinical and electrophysiologic criteria, namely, weakness in the distribution of individual motor nerves and multifocal conduction block limited to motor but sparing the sensory nerves [1,2,17]. In contrast to CIDP, where conduction in the sensory nerves is also affected and sensory responses may not be elicited, in MMN the sensory conduction remains normal across the nerve segments that have the motor block. The reasons for such a selective motor involvement remain unclear. Differences in the myelin composition, leading to distinct antigenic specificities between motor and sensory fibers, have been implicated mainly because the ceramide content within the gangliosides differs between sensory and motor fibers [1,2,8]; the reasons however may be more complex and relate to the uniqueness of the targeted antigens not within the compact myelin but rather in the nodal regions and axonal membrane at the nodes of Ranvier. Up to 50% of MMN patients have high IgM anti-GM1 antibody titers, but the pathogenic role of these antibodies remains unclear [1,2,17], in spite of recent evidence that GM1 antibodies fix complement and may induce a complement-mediated nodal dysfunction that reverses after IVIg therapy [18]. The suggestion that GM1 antibodies bind to GM1 and interfere with saltatory conduction, has not been confirmed and GM1-binding sites have not been co-localized with voltage-gated sodium channels at the nodes of Ranvier. Even though the immunopathology remains uncertain, MMN patients respond remarkably well to immunotherapy with IVIg.

1.1.3. IgM MGUS polyneuropathies with anti-MAG or ganglioside antibodies

The majority of these patients present with a chronic, slowly progressive, large-fiber, sensory polyneuropathy of insidious onset, manifested as sensory ataxia [1,2,19–21]. Other times, it presents as sensorimotor polyneuropathy with mixed features of demyelination and axonal loss. Conduction velocity is slow with a rather characteristic prolonged distal motor and sensory latencies consistent with distal demyelination. The serum protein electrophoresis shows a monoclonal IgM spike that recognizes antigenic components on the compact myelin, most of the times the Myelin Associated Glycoprotein (MAG) [21], as discussed later. Sural nerve biopsy demonstrates diminished number of myelinated axons with a characteristic splitting of the outer myelin lamellae, linked to deposition of IgM that recognizes MAG in the same area of the split myelin [1,2,21].

1.2. Immunopathogenesis

In general, complement-fixing antibodies, macrophages and T cells are the main effector mechanisms in all APN. In vitro and in vivo studies, including immunization of animals with myelin proteins, disease transfer experiments with the patients' serum or with intraneural injections, immunocytochemical studies on the patients' nerves, and T cell profiling studies in the peripheral blood, have provided evidence that both cellular and humoral factors, either independently or in concert with each other, play a central role in their pathogenesis [1,2].

1.3. GBS

1.3.1. Cellular factors

In autopsy cases of GBS patients, perivascular and endoneurial inflammatory infiltrates are observed throughout the nerves, roots or plexuses along with segmental demyelination mediated by macrophages, especially in areas with lymphoid infiltrates [1–4]. The macro- Q11 phages break through the basement membrane of healthy Schwann cells and make direct contact with the outermost myelin lamellae, leading to destruction of the superficial myelin sheath [1–5]. Cytokines and chemokines released by the activated T cells or complement activation, may increase capillary permeability and facilitate transmigration of additional macrophages or T cells. Increased levels of IL-2 and soluble IL-2 receptors are also noted in the serum during the acute phase of GBS suggesting ongoing T-cell activation [3]. Further, lymphocytes from GBS patients exert myelinotoxic activity when applied to cultures of myelinated axons [1,2]. The involvement of a T cell-mediated process in GBS has been strengthened by observations in the experimental allergic neuritis (EAN) model induced in animals immunized with the whole human nerve or with various peripheral nerve myelin proteins, such as Po, P2, or galactocerebroside. These animals develop EAN with segmental demyelination and mononuclear cell infiltrates consisting of

Please cite this article as: M.C. Dalakas, Pathogenesis of immune-mediated neuropathies, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbadis.2014.06.013