Clinica Chimica Acta 449 (2015) 37–42

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Autoimmune peripheral neuropathies

Pierre R. Bourque [a], Jodi Warman Chardon [a,b], Rami Massie [c]

[a] Division of Neurology, The Ottawa Hospital, 1053 Carling Avenue, Ottawa, ON K1Y 4E9, Canada
[b] Department of Genetics, The Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, ON, K1H 8L1, Canada
[c] Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, 3801 University Street, Montreal, QC H3A 2B4, Canada

ARTICLE INFO

Article history:
Received 23 February 2015
Accepted 23 February 2015
Available online 4 March 2015

Keywords:
Neuropathy
Antiganglioside antibodies
Guillain-Barré syndrome
Myelin
Multifocal motor neuropathy

ABSTRACT

Peripheral nervous system axons and myelin have unique potential protein, proteolipid, and ganglioside antigenic determinants. Despite the existence of a blood–nerve barrier, both humoral and cellular immunity can be directed against peripheral axons and myelin. Molecular mimicry may be triggered at the systemic level, as was best demonstrated in the case of bacterial oligosaccharides.

The classification of immune neuropathy has been expanded to take into account specific syndromes that share unique clinical, electrophysiological, prognostic and serological features.

Guillain-Barré syndrome encompasses a classical syndrome of acute demyelinating polyradiculoneuropathy and many variants: axonal motor and sensory, axonal motor, Miller-Fisher, autonomic, and sensory. Similarly, chronic immune neuropathy is composed of classic chronic inflammatory demyelinating polyradiculoneuropathy and variants characterized as multifocal (motor or sensorimotor), sensory, distal symmetric, and syndromes associated with monoclonal gammopathy.

Among putative biomarkers, myelin associated glycoprotein and several anti-ganglioside autoantibodies have shown statistically significant associations with specific neuropathic syndromes. Currently, the strongest biomarker associations are those linking Miller-Fisher syndrome with anti-GQ1b, multifocal motor neuropathy with anti-GM1, and distal acquired symmetric neuropathy with anti-MAG antibodies. Many other autoantibody associations have been proposed, but presently lack sufficient specificity and sensitivity to qualify as biomarkers. This field of research has contributed to the antigenic characterization of motor and sensory functional systems, as well as helping to define immune neuropathic syndromes with widely different clinical presentation, prognosis and response to therapy. Serologic biomarkers are likely to become even more relevant with the advent of new targeted forms of immunotherapy, such as monoclonal antibodies.

Advances in pathophysiology, biomarkers and specific treatment approaches have transformed our understanding of immune disorders of the peripheral nervous system (PNS).The original syndromic classification simply categorizing acute (Guillain-Barré syndrome or GBS) and chronic (chronic inflammatory demyelinating polyradiculoneuropathy or CIDP) autoimmune neuropathies has been vastly expanded to include many subtypes. This article will review key clinical and laboratory aspects of GBS and CIDP subtypes, emphasizing the role of autoantibodies, notably against gangliosides, that show promise as potential biomarkers. Other forms of immune neuropathy, notably systemic vasculitis, presynaptic neuromuscular junction disorders and paraneoplastic neuropathy, are beyond the scope of this discussion.

1. The peripheral nervous system

The PNS is composed of cranial nerves (with the notable exception of the optic nerve), nerve roots, plexuses and peripheral nerve branches, including the peripheral axons and ganglia of the autonomic nervous system. A fundamental histologic specificity is PNS myelination of axons by Schwann cells. Along a single axon, the transition from oligodendroglia to Schwann cells, occurs within millimeters where cranial nerves arise from the brainstem and where spinal roots emerge from the spinal cord [1].

At a biochemical level, the most significant potential antigenic targets of the axonal membrane include gangliosides and ion channels. Sodium channels are largely limited to the region of the node of Ranvier, whereas potassium channels are concentrated in the paranodal regions (Fig. 1). PNS myelin is rich in proteolipids and specific proteins, and is formed of compact and non-compact domains. There are substantial differences in protein subtypes or proportions compared to the CNS myelin. Compact myelin, devoid of residual Schwann cell cytoplasm, forms the vast majority of PNS myelin. Its dominant protein subtypes are myelin protein zero (MPZ), myelin basic protein (MBP) and peripheral myelin protein-22 (PMP22). Non-compact myelin, localized in the paranodes and Schmidt-Lanterman incisures, is rich in myelin-associated glycoprotein (MAG), Connexin 32 and gangliosides. Interestingly, there has been little overlap between the preponderant antigenic determinants of inherited neuropathy and acquired immune neuropathy. Common forms of Charcot-Marie-Tooth disease

http://dx.doi.org/10.1016/j.cca.2015.02.039
0009-8981/

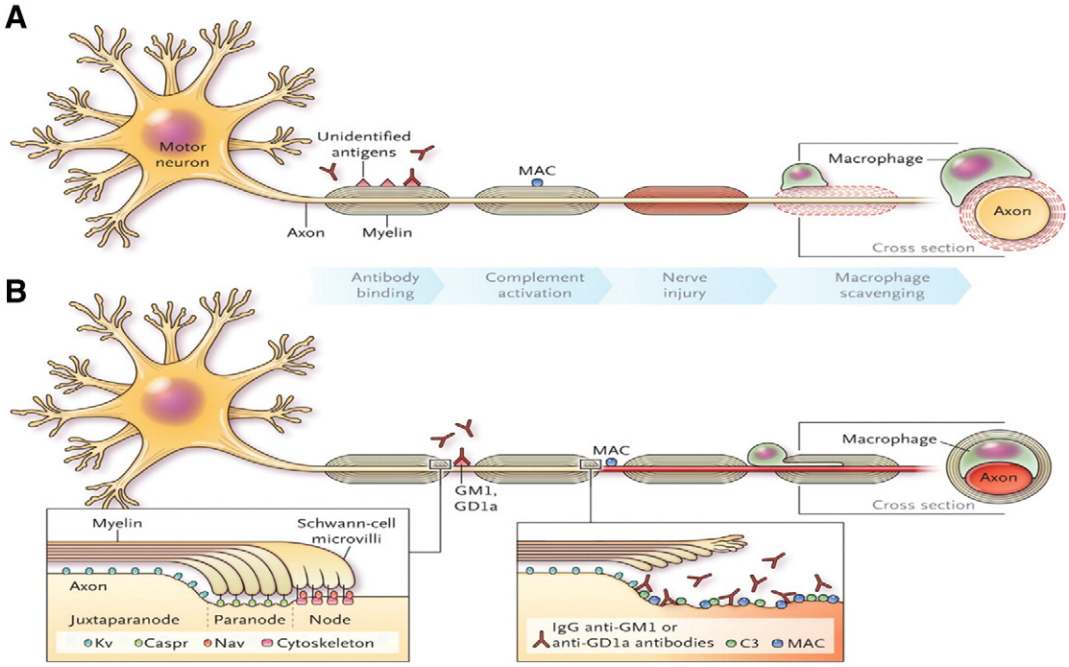

Fig. 1. Panel A shows the proposed immune attack in AIDP. Autoantibodies are suspected to bind to myelin antigens and activate complement.The formation of a membrane attack complex (MAC) on the outer surface of Schwann cells leads to vesicular degeneration, with subsequent removal of myelin debris by macrophages. Panel B shows a different pathogenesis proposed for AMAN. Anti-GM1 or anti-GD1a antibodies are shown binding to the nodal axolemma. This may affect voltage-gated sodium (Nav) channels. Additional disruption of paranodal myelin may also contribute to conduction failure. Macrophages may subsequently invade the periaxonal space [5].

have been associated with mutations in genes coding for PMP22, MPZ, Connexin 32 and other structural proteins. In contrast, immune mediated neuropathies have so far been more closely associated with antibodies that recognize gangliosides, much less frequently myelin proteins, with the exception of MAG.

Gangliosides are glycosphingolipids present in large amounts on the plasma membranes, anchored in the lipid bilayer by a ceramide moiety and exposed to the extracellular space and hence accessible to the immune system [2]. In addition to ceramide, gangliosides contain an oligosaccharide (for the majority, a glucose molecule attached to a combination of galactose and N-acetylgalactosamine) with one or more sialic acids linked to the sugar chain. In the accepted ganglioside nomenclature, the first letter, G, stands for ganglioside, while the second letter refers to the number of sialic acid residues – M = 1, D = 2, T = 3, Q = 4. The following number refers to the number of complete tetrasaccharide chains and the final lower-case letter to its isomeric position (Fig. 2). In addition, several other glycolipids are sulfated, the most common being sulfatide, and represent another potential immunogenic target. Gangliosides act as receptors, receptor modulators or signaling molecules.

2. Mechanisms of PNS autoimmune attack

The PNS, like the CNS, is relatively isolated from the systemic circulation by the blood–nerve barrier. The chief structural determinant of this filter for large molecules (including antibodies) is the presence of tight junctions between endoneurial capillary endothelial cells and between the perineurial cells that ensheath individual nerve fascicles. The blood–nerve barrier is more permeable in proximal (spinal roots) and distal (neuromuscular junction) segments of the PNS. Similar to immune disorders in the CNS such as multiple sclerosis, cellular and humoral immune responses can still successfully target relatively shielded PNS antigens. The initial step in immunopathogenesis is postulated to involve molecular mimicry and antigen processing at a systemic level. This leads to activation of autoreactive T cells, which penetrate the blood–nerve barrier with the help of cell adhesion molecules [3]. At the level of the endoneurium, T cells may directly execute the cytotoxic attack, or recruit local macrophages through the production of cytokines and chemokines. Some immune neuropathies may be mediated directly by systemic B-cell production of autoreactive antibodies that are able to traverse a leaky blood–nerve barrier. At the endoneurial level, such antibodies may produce either a direct humoral, complement-mediated attack, or recruit macrophages expressing Fc receptors.

The pathophysiology of immune neuropathies is often described as “axonal” or “demyelinating”. This distinction was formerly based on nerve biopsies, which almost exclusively were limited to the sural nerve, chosen because of ease of access and low procedural morbidity. Sural nerve specimens represent a very selective sampling of a purely cutaneous distal nerve branch, devoid of motor axons. Most modern evaluations of immune neuropathy rely instead on nerve conduction studies. Axonal loss is inferred if the predominant abnormality is reduction of motor or sensory potential amplitude. In contrast, demyelination is reflected in prominent slowing of conduction velocity or focal conduction block. A wide sampling of nerve conduction studies is required to determine if there is diffuse or distally accentuated neuropathy, selective involvement of motor or sensory axons, unifocal or multifocal conduction block, and involvement of proximal nerve segments.

Compared to demyelinating neuropathies, axonal neuropathies identified on nerve conduction studies were originally expected to have a poorer prognosis, based on inferences made from classical studies of nerve trauma. This traditional binary subdivision has been questioned recently with the proposal of a new pathophysiological entity, nodo-paranodopathy [4]. This would explain how some acute neuropathies, previously classified as axonal, and may have an excellent prognosis. Their rapid recovery could not be accounted for by axonal regrowth, but is better explained by reversible conduction failure, mediated by antibody binding at the nodal/paranodal region. Such nodo-paranodopathies are strongly associated with the presence of serum anti-ganglioside antibodies [4].

3. The Guillain-Barré syndrome

The acute immune-mediated polyneuropathies are traditionally grouped under the eponym Guillain-Barré syndrome (GBS). By