The role of antibodies to peripheral nerve antigens in pathogenesis and laboratory evaluation of immune-mediated neuropathies

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Abstract

Detection of antiganglioside autoantibodies and their association with clinically defined subtypes implicate an autoimmune mechanism of peripheral and cranial nerve damage in peripheral neuropathies.

Increased titer of antibodies that react with human peripheral nerve antigens have been reported in patients with motor neuropathy including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and sensory motor neuropathy. This study represents review of the data related to increased titers of anti-glycoconjugate antibodies in different autoimmune neuropathies and their correlation with existence of structural homology between bacterial and glycoconjugated structures, as a basis for understanding the immune pathological response to glycoproteins and glycolipids present in the human peripheral nerve as target antigens in autoimmune neuropathies.

Evaluation of presence and increased level of autoantibodies against peripheral nerve antigens could be an important parameter in laboratory evaluation, diagnosis and prognosis of autoimmune neuropathies and contribute in more efficient therapeutic approaches in treatment of these pathological conditions.

Keywords: anti-glycoconjugate antibodies, anti-ganglioside antibodies, peripheral nerves, autoimmune neuropathies

Introduction

Peripheral neuropathies are heterogeneous group of diseases affecting peripheral nerves, occurring as a component of several common and many rare diseases which diverse in pathology and varying in severity. Peripheral neuropathies are characterized by motor,

sensor or autonomic dysfunctions. Several different types of autoimmune diseases can cause autoimmune neuropathies and produce symptoms of nerve pain and nerve damage. According to their etiology, peripheral neuropathies are divided in two groups: hereditary neuropathies, mainly dysmyelinating and acquired neuropathies, mainly demyelinating neuropathies with autoimmune origin (Martyn and Hughes, 1997). Inflammatory neuropathies include several syndromes

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with different pathological and clinical features including Guillain-Barré syndrome (GBS) and its variants (motor, sensory and Miller-Fisher syndrome (MFS)), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and Multifocal motor neuropathy (MMN) (Dalakas, 2013).

The most typical acute autoimmune neuropathy is *Polyradiculoneuritis acuta* known as Guillain-Barré syndrome. It has been established that GBS is an inflammatory demyelinating polyneuropathy in which the T-lymphocytes and the macrophages attack the peripheral nerves (Prineas, 1981). Moreover, studies have proven that GBS is usually preceded by respiratory, as well as gastrointestinal infections, with following pathogens *Hepatitis C*, *Mycoplasma*, *Campylobacter jejuni* (*C.jejuni*), *Cytomegalovirus* (CMV), *Epstein-Barre virus* (EBV), but can also occur after surgery, injuries, or may be associated with malignant diseases (Yuki, 1997). Much additional knowledge has been gained from additional studies where according to the histologic characteristics GBS is classified in demyelinating and axonal subtypes: acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN), both associate with antibodies to gangliosides on the axolemma that target macrophages to invade the axon at the node of Ranvier (Hughes and Cornblath, 2005; Kuwabara and Yuki, 2013; Yuki and Hartung, 2012).

Chronic inflammatory demyelinating neuropathy (CIDP) is demyelinating autoimmune polyneuropathy which is characterized by the presence of number of different antibodies to the constituents of the peripheral nerve and presence of the antiganglioside antibodies in patient serum (Willison and Yuki, 2002).

Other autoimmune neuropathies are multifocal motor neuropathy and anti-MAG (myelin-associated glycoprotein) neuropathy and both affect sensory and motor nerves (Herrendorff et al., 2017). In recent study, increased antibody titers against multiple gangliosides have been reported in multifocal acquired sensory and motor neuropathy, possibly implicating immune mechanisms in their pathogenesis (Suturkova et al., 2014).

This review focuses on the correlation of the increased titers of anti-glycoconjugate antibodies in different autoimmune neuropathies and existence of structural homology between bacterial and glycoconjugated structures, as an important parameter for understanding the immune pathological response to glycoproteins and glycolipids present in the human peripheral nerve as target antigens in autoimmune neuropathies.

Autoimmune response to peripheral nerve antigens in autoimmune neuropathies

Identification and characterization of autoantigens present at the human peripheral nerve represents a great

challenge in the field of neuroimmunology, especially in demyelinating disorders. A number of studies indicate that myelin specific proteins present in peripheral nervous system including myelin protein zero (P0), myelin-associated glycoprotein (MAG), peripheral myelin protein 2 (P2), peripheral myelin protein 22 (PMP22) have an important role in myelin formation and in mediating autoimmune peripheral nerve disease (Allen et al., 2005; Gabriel et al., 2000; Hughes and Cornblath, 2005).

The latest investigations are focused on understanding of biology of glycoconjugates present at the peripheral nerve, and their immunological reactivity. There is a considerable cross-reactivity among these anti-glycoconjugate antibodies, resulting from shared oligosaccharide epitopes, possibly explaining the overlap in syndromes observed in many affected patients (Suturkova et al., 2014).

Anti-MAG neuropathy is caused by monoclonal IgM auto-antibodies that recognize the carbohydrate human natural killer-1 (HNK-1) epitope which is highly expressed on adhesion molecules, such as MAG, present in myelinated nerve fibers (Quarles, 2007). Results from nerve biopsy has also confirmed that anti-MAG neuropathy is characterized with demyelinating lesions and deposits of anti-MAG IgM on myelin sheaths (Lombardi, 2005; Monaco et al., 1990).

Many pathogens associated with the development of GBS, such as *C.jejuni*, *CMV*, *EBV*, *Mycoplasma pneumonia* and *Hemophilus influenza*, are supposed to share homologous carbohydrate epitopes with peripheral nerve components (Rinaldi, 2013). It was shown that antiganglioside antibodies in serum from patients with GBS recognize galactosyl (β 1-3) N-acetylgalactosamine (Gal(β 1-3)GalNAc) epitope, a carbohydrate determinant shared by several gangliosides (GM1, GD1a, GD1b, GT1b and asialoganglioside GA1), peripheral nerve glycoproteins and glycoconjugate antigens present in bacterial cell wall (Aspinall et al., 1994; Thomas et al., 1989). In line with this finding, high titers of anti-ganglioside antibodies to GM1, GM1b, GD1a have been found in the serum of a number of patients with AMAN following infection with *C. jejuni*. (Kusunoki, 2000). Additionally, anti-GQ1b and anti-GT1b antibodies were detected in serum from patients with MFS (Chiba et al., 1993; Chung et al., 2014) while anti-GM1 IgM antibodies were associated with development of MMN (Cats et al., 2010; Willison and Yuki, 2002).

Bacterial lipopolysaccharides units are considered to induce the production of anti-ganglioside antibodies, due to the presence of terminal tetrasaccharides, identical to those in the gangliosides GM1, GD1a and GQ1b (Yuki et al., 1993). Later it was suggested that due to molecular similarity the immune response to bacterial oligosaccharides can be diverted to their own neuronal antigens, which strongly explains the pathological point of view of an axonal variant of GBS associated with *C. jejuni* infection (Schwerer et al., 1995).

Another study demonstrates the possible molecular mimicry between cross-reactive glycoproteins in which was concluded that molecular mimicry may have a potential role in the development of GBS in patients with previous infection with *C. jejuni* (Brezovska et al., 2011). This reactivity indicates on presence of shared epitopes in glycoproteins from the human peripheral nerve and *C. jejuni* (O:19), recognized by PNA and by GM1-positive serum from patient with GBS, associated with *C. jejuni* infection (Brezovska et al., 2011).

In recent study positive reactivity with several Gal(1-3)GalNAc bearing glycoproteins from human peripheral nerve and from *C. jejuni* O:19 isolates was shown in serum from patients with MMN (Suturkova et al., 2013). One of these patients had a previous history of *C. jejuni* infection which suggests the possibility that *C. jejuni* may be also involved in the pathogenesis of MMN (Suturkova et al., 2013). Higher frequency of the presence of anti-ganglioside and anti-glycoprotein antibodies in patients with MMN compared to healthy controls and to patients with other neuropathies point out their pathogenic significance in the inducing and propagation of the nerve damage and development of neurological symptoms (Suturkova et al., 2014).

The etiological factors of several autoimmune diseases can be mediated by proteins belonging to the HSP (heat shock proteins), a family of highly conserved proteins present in all prokaryote and eukaryote cells (Arispe et al., 2002; Yonekura et al., 2004). Yonekura et al. (2004) showed that GBS patients shared higher IgG antibody titers against several families of HSP (HSP 27, HSP 60, HSP 70) in their cerebrospinal fluid. Immuno-reactive proteins present in human peripheral nerve (HPN) tissue were also identified in GBS patients, including HSP, intermediate filaments (vimentin and desmin) and other proteins and enzymes such as troponin/tropomyosin complex and ATP synthase subunit beta and the keratan sulfate proteoglycan, lumican (Loshaj-Shala et al., 2018). These findings suggested that the neuronal autoimmune damage is specifically directed to intermediate neuronal (vimentin) and neuromuscular IF, probably localized nearby cell surface, affording increased accessibility to autoantibodies, and shows that the post-infectious development of GBS may be also associated to additional concomitant immune factors that lead to nerve damage generated by auto-immune trigger(s) different from molecular mimicry (Loshaj-Shala et al., 2018).

Table 1. Target antigens and class of antibodies involved in immune-mediated neuropathies and their clinical features

Clinical features	Class of antibody (immunoglobulin)	Antigen	Reference
Anti-MAG neuropathy	IgM	MAG	Quarles, 2007; Monaco et al., 1990; Lombardi, 2005.
GBS	IgG and IgM	GM1, GD1a, GD1b, GT1b and GA1	Thomas et al., 1989. Aspinall et al., 1994; Brezovska et al., 2011.
GBS	IgG	HSP (HSP 27, HSP 60, HSP 70)	Yonekura et al., 2004. Loshaj-Shala et al., 2015.
AMAN	IgG	GM1, GM1b, GD1a	Kusunoki, 2000;
MFS	IgG	GQ1b	Chiba et al., 1993; Chung et al., 2014.
MMN	IgM	GM1	Cats et al., 2010; Willison and Yuki, 2002; Suturkova et al., 2013;

AMAN, acute motor axonal neuropathy; GBS, Guillain-Barré syndrome; MAG, myelin-associated glycoprotein; MFS, Miller Fisher syndrome.

The positive correlation with disease remission in two patients with GBS carrying the highest HSP 70 concentrations, although limited to a low number of patients, are supportive of a peripheral neuroprotective role of extracellular HSP 70, in good accordance to the results from several studies reported in the literature (Loshaj-Shala et al., 2015). Target antigens and class of antibodies involved in immune-mediated neuropathies and their clinical features are summarized in Table 1.

Laboratory evaluation of autoimmune peripheral neuropathy

There are several approaches in diagnosis of patients with peripheral neuropathy including laboratory testing, electrodiagnostic studies, nerve biopsy or even cerebrospinal fluid analysis. A systematic approach begins with clinical history and neurological examination (type of nerve fiber involvement and distribution of symptoms), identification of the underlying etiology and exclusion of potentially treatable causes (Lehmann et al., 2020).

Until recently no standardized tools for the determination of antiganglioside autoantibodies were available. Enzyme immunoassays with highly purified gangliosides have been introduced in the routine diagnostic of peripheral neuropathy but the determination of antibody profiles with this method is not cost-effective. Provided that the optimal binding of gangliosides on membranes can be achieved, dot or line immunoassays may be a good alternative for the multiparametric determination of antiganglioside autoantibodies (Conrad et al., 2007).

Currently, the enzyme-linked immunosorbent assay (ELISA) is a standard immunoassay used in measuring antibody reactivity (expressed as titers) for glycosphingolipids (GSLs) such as gangliosides and sulfoglycolipids in the serum of patients with GBS, variants of GBS, and CIDP. ELISA detects serum antibody binding to ganglioside-coated microwells. The ELISA system, however, requires two days to complete and measures antibodies to individual gangliosides in its present format (Alaadini et al., 2002).

The Bühlmann anti-MAG ELISA is used as the most common and very sensitive platform for MAG testing, but in some cases low and intermediate levels of positivity may not be associated with typical anti-MAG neuropathy (Lunn, 2017).

Human anti-MAG antibodies can be also detected in the patient's serum with Western blots by electrophoresing purified MAG, isolated myelin or whole brain homogenates. Because serum positive for anti-MAG antibodies almost always recognize the SGPG glycolipid, the assay has been performed by certain laboratories using SGPG as antigen instead of human MAG. It is clearly preferable to use MAG instead of SGPG because the IgM antibodies bind to MAG 10-100 times more strongly than

to SGPG; consequently, low-affinity anti-MAG antibodies may be missed if SGPG is used as antigen (Dalakas, 2018).

Determination of the level of antibodies against these cross-reactive antigens in serum from patients, may help in the diagnosis of these conditions. Production of monoclonal antibodies against cross-reactive epitopes on glycoconjugates present in human peripheral nerves remain as one of the biggest challenges for development of simple and specific methods for laboratory evaluation of the level of autoantibodies as an important step in diagnostic approaches and prognosis of autoimmune neuropathies.

Conclusion

Increased titer of antibodies that react with human peripheral nerve antigens have been reported in patients with motor neuropathy including GBS, CIDP, multifocal motor neuropathy and sensory motor neuropathy.

Identification and localization of the GalGalNAc binding glycoproteins and determination of the structure of their immunodominant determinant could help in understanding the mechanisms by which autoantibodies are produced and how they bind to the target antigens on peripheral nerves. Laboratory evaluation of the level of autoantibodies to these cross-reactive glycoprotein antigens could be an added value in diagnosis and prognosis of autoimmune neuropathies.

Resolving the mechanisms which regulate the immune system to produce anti-glycoconjugate antibodies in patients with neuropathies, will give an opportunity to develop specific and effective strategy for targeted immunotherapy in order to prevent or limit the processes that result in autoimmune neuropathy.

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Резиме

Улогата на антитела насочени кон антигени на периферни нерви во патогенезата и лабораториската дијагностика на автоимуни невропатии

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Клучни зборови: гликокоњуѓатни антитела, антиганглиозидни автоантитела, периферни нерви, автоимуни невропатии

Детекцијата на антиганглиозидни автоантитела и нивната поврзаност со клинички дефинирани подтипови имлицираат автоимун механизам на оштетување на периферните кранијални нерви кај периферна невропатија.

Забележан е зголемен титар на антитела кои реагираат со човечки антигени на периферните нерви кај пациенти со моторна невропатија, вклучувајќи Guillain-Barré синдром, хронична инфламаторна демиелинизирачка полиневропатија, мултифокална моторна невропатија и сензорна моторна невропатија. Овој труд е преглед на литература за зголемен титар на анти-гликокоњуѓатни антитела во различни автоимуни невропатии и нивната поврзаност со присуство на структурна хомологија помеѓу бактериски и гликокоњуѓатни структури, како основа на разбирање на имунопатолошкиот одговор на гликопротеини и гликолипиди присутни во човековите периферни нерви како таргет антигени во автоимуните невропатии.

Евалуација на присуство и зголемено ниво на автоантитела насочени кон антигени на периферни нерви може да претставува важен параметар во лабораториска евалуација, дијагноза и прогноза на автоимуни невропатии и да придонесе за терапевтски пристап со поголема ефикасност кај овие патолошки состојби.