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Expert Review of Neurotherapeutics

ISSN: 1473-7175 (Print) 1744-8360 (Online) Journal homepage: informahealthcare.com/journals/iern20

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To cite this article: Benjamin R Wakerley & Nobuhiro Yuki (2015) Guillain–Barré syndrome, Expert Review of Neurotherapeutics, 15:8, 847-849, DOI: 10.1586/14737175.2015.1065732

To link to this article: https://doi.org/10.1586/14737175.2015.1065732

Published online: 08 Jul 2015.

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Expert Rev. Neurother. 15(8), 847–849 (2015)

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Over the past three decades much has been elucidated about the pathogenesis and clinical manifestations of Guillain–Barré syndrome, the most common cause of acute flaccid paralysis worldwide. Cross-reactivity between surface epitopes on the bacterium *Campylobacter jejuni* and peripheral nerve gangliosides has been shown to induce antibody-mediated axonal-type neuropathy in some patients. Understanding the molecular mechanisms that cause nerve damage in these patients has led to the development of novel therapies, which specifically target the complement cascade and prevent formation of the membrane attack complex. The most promising, eculizumab, is a humanized monoclonal antibody, which blocks formation of human C5a and C5b-9, and has been shown to prevent antiganglioside antibody-induced neuropathy *in vitro* and in a mouse model and is currently in Phase II clinical trials.

Next year marks 100 years since the first description of Guillain–Barré syndrome (GBS), which is now recognized as the most common cause of flaccid paralysis worldwide [1]. Since the first report by Guillain, Barré and Strohl of postinfectious neuropathy in association with cerebrospinal fluid albuminocytological dissociation, the GBS family has expanded to include a number of related disorders [2]. Of these Miller Fisher syndrome (MFS) is the most notable [3], but other subtypes including Bickerstaff brainstem encephalitis and pharyngeal–cervical–brachial weakness also remain clinically very relevant. Identification of antiganglioside antibodies in some patients with GBS and MFS, especially following infection with *Campylobacter jejuni* has furthered our understanding of disease pathogenesis and phenotypic differences between subtypes [1]. Currently, GBS and related disorders are treated with intravenous immunoglobulins or plasma exchange with the primary aim of removing or neutralizing neurotoxic antibodies. In this editorial, we briefly summarize the pathogenesis of GBS and highlight the next generation of immunotherapies that target the complement cascade and therefore have the potential to reduce neuronal damage at the all important node of Ranvier, the immune target in axonal-type GBS.

GBS represents a continuous spectrum of related disorders that vary significantly in terms of their phenotypic appearance and severity [2]. The most common subtype, referred to as classic GBS or just GBS, is principally characterized by ascending weakness with glove-and-stocking type sensory disturbance. A significant proportion of these patients may also develop respiratory weakness and require mechanical ventilation. Three regional subtypes (e.g., pharyngeal-cervical-brachial weakness) also exist and are named according to the pattern of weakness. Developing novel treatments that can be commenced early and prevent disease progression therefore remains essential in these patients. GBS has one main variant, known as MFS, which is characterized by ophthalmoplegia and cerebellar-like ataxia [3]. Typically, these patients do not develop respiratory weakness, and the outcome is generally good. Incomplete subtypes of MFS, for example, acute ataxic neuropathy, have also been described in patients who develop ataxia in the absence of ophthalmoplegia. Some patients with ophthalmoplegia and ataxia also display hypersomnolence, and these are described as having Bickerstaff brainstem encephalitis. More limited forms in patients who only develop isolated ptosis or mydriasis are also recognized as

Keywords: anti-ganglioside antibodies • complement cascade • Guillain–Barré syndrome • miller fisher syndrome • molecular mimicry

EXPERT REVIEWS

 10.1586/14737175.2015.1065732 ISSN 1473-7175

members of the GBS family. Although all of these subtypes may occur as discrete syndromes, sometimes there is an overlap. For example, patients with bulbar, neck and upper limb weakness associated with ophthalmoplegia and ataxia are said to have pharyngeal–cervical–brachial weakness overlapping with MFS. All these disorders share core clinical features [2] that, in the majority of cases, are supported by the presence of cerebrospinal fluid dissociation and abnormal nerve conduction studies.

GBS can be caused by either demyelinating or axonal-type neuropathy [4,5]. Precise electrodiagnosis is best achieved following at least two sets of nerve conduction studies [6]. Classic GBS, causing tetraparesis, can be caused by axonal or demyelinating neuropathy, whereas MFS and its subtypes are exclusively axonal. The pathogenesis of axonal and demyelinating neuropathy differs, although in both cases antecedent infectious symptoms are reported in the majority of patients prior to development of neurological symptoms. *C. jejuni*-associated gastroenteritis is the most common cause and identified in up to one-third of patients. Other common microorganisms, including cytomegalovirus, Epstein–Barr virus and *Mycoplasma pneumoniae*, have also been implicated [7]. The exact mechanism underling neuropathy in GBS remains unknown. Pathological studies indicate that demyelinating-type neuropathy is associated with cellular infiltrates, whereas axonal-type neuropathy is associated with nerve damage at the nodes of Ranvier by the complement membrane attack complex [8]. The latter occurs following activation of the complement cascade by IgG antiganglioside antibodies. This, in part, can be explained by molecular mimicry. Mistaken identity between microbial surface antigens and peripheral nerve gangliosides in some patients may induce generation of IgG antibodies against gangliosides (GM1, GD1a, GT1a and GQ1b) and lead to axonal-type neuropathy [9–11]. Neuronal expression of gangliosides is anatomically determined and therefore specific serological profiles are associated with different patterns of neurological weakness. For example, ganglioside GQ1b has been shown to be concentrated in nerves that innervate the extraocular muscles [12], and therefore the presence of anti-GQ1b antibodies may explain ophthalmoplegia in these patients. Frustratingly the molecular target in patients with demyelinating-type neuropathy remains unknown, and these patients do not display antiganglioside antibodies.

Treatment options for GBS have remained unchanged for almost three decades. Unlike most other neurological conditions with an autoimmune basis, patients with GBS do not respond to corticosteroids [13]. Instead intravenous immunoglobulin or plasma exchange are favored [14,15]. Although the exact mechanism of action of intravenous immunoglobulin is unknown, its therapeutic effect in GBS is thought to occur by neutralizing pathogenic autoantibodies and inhibiting autoantibody-mediated complement activation. In contrast, plasma exchange is thought to remove pathogenic autoantibodies and complement. The use of intravenous immunoglobulin is commonplace and generally accepted as safe, although there is increased risk of fluid overload, anaphylaxis and thromboembolism [14]. Plasma exchange is more invasive and only available in specialist units, the main complications being that of hypocalcemia and hypotension [15]. Both treatments are associated with immunosuppression, and increased risk of opportunistic infections as they are non-specific and their effects on the immune system are widespread.

Knowledge of the interaction between antiganglioside antibodies and the complement system in the pathogenesis of axonal-type GBS has provided a potential target in the treatment of GBS [1].

One approach has been the direct modulation of the complement system with monoclonal antibodies and synthetic serine protease inhibitors. Eculizumab (trade name Soliris) is a humanized monoclonal antibody that binds to plasma C5 and selectively prevents enzymatic cleavage into C5b, an important component of the complement membrane attack complex. Eculizumab was first shown to be of benefit in patients with paroxysmal nocturnal hemoglobinuria [16], and more recently atypical hemolytic uremic syndrome [17], which are both characterized by uncontrolled activation of the complement system. Although generally well tolerated and safe, long-term use has since shown to increase the risk of certain infections, including *Neisseria meningitides*. Recently, in a Phase II study, it was shown to be safe and improve clinical outcomes in patients with refractory myasthenia gravis [18]. Other potential benefits being explored include treatment of certain immune-mediated neuropathies. *In vitro* and murine *in vivo* models of anti-GQ1b antibody-mediated neuropathy indicated that eculizumab completely prevented complement-mediated neuropathy [19], and a Phase II trial in GBS is currently underway. Although safe when used in conjunction with intravenous immunoglobulin for the treatment of multifocal motor neuropathy, clinical benefit was minimal and only in selected patients [20]. Nafamostat mesilate, a synthetic serine protease inhibitor, has also been shown to attenuate important elements of the complement cascade. In one animal model of anti-GM1 antibody-associated acute axonal motor neuropathy, complement deposition was significantly reduced following intravenous administration of nafamostat mesilate [21]. In a novel approach, a bacterial virulence factor has been used to inhibit complement-activation mediated by antiganglioside antibodies [22]. The virulence factor in question, immunoglobulin G-degrading enzyme is produced by *Streptococcus pyrogenes* and is able to cleave pathogenic autoantibodies in $F(ab')_2$ and Fc fragments. A recent *in vitro* study demonstrated that immunoglobulin G-degrading enzyme efficiently cleaved IgG and blocked complement activation mediated by anti-GM1, anti-GD1a and anti-GQ1b IgG antibodies.

Many important questions remain unanswered about the pathogenesis of GBS and related disorders. For example, what are the molecular targets that drive cell-mediated immunity in demyelinating-type GBS and how do these relate to specific infectious organisms? Unraveling the molecular mechanisms that trigger demyelinating-type GBS is likely to lead to development of more specific immunotherapies, akin to those already under

investigation for axonal-type disease. Early diagnosis of GBS also remains problematic. Nerve conduction studies and cerebrospinal fluid analysis are frequently nondiagnostic in the first week, and antiganglioside antibodies are not always present or easily tested for. Although we believe that, in the majority of cases, diagnosis can be made based on clinical features alone [2], sometimes this may be difficult and therefore development of laboratory assays that are highly specific early in disease course may be useful.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript

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