Blockade of Blocking Antibodies in Guillain-Barré Syndromes: "Unblocking" The Mystery of Action of Intravenous Immunoglobulin†

The Guillain-Barré syndrome(s) (GBS[s]) comprises various forms of acute flaccid paralysis caused by an autoimmune attack against components of the peripheral nerve.[1,2] The most common pattern is the acute inflammatory demyelinating polyneuropathy (AIDP), in which the putative target antigens are on the myelin sheath. The least common, but better understood forms, are the acute motor (or motor-sensory) axonal neuropathy (AMAN or AMSAN) and the Miller-Fisher syndrome (MFS) with target antigens on motor nerve terminals and axons. Humoral and cell-mediated mechanisms participate in the cause of GBS(s) probably triggered by molecular mimicry between bacterial or viral glycoconjugates and nerve gangliosides.[3,4] In AIDP, autoreactive T cells may initiate the lesion, but the effector mechanisms are complement deposits and macrophages invading the myelin sheath. In AMAN and MFS, immunoglobulin G (IgG) antibodies against specific gangliosides (GM_1, GM_{1a}, GalNac-GD_{1a}, and GM_{1b} in AMAN; GQ_{1b} in MFS) block functionally relevant epitopes for nerve conduction[5–8] or neuromuscular transmission[9,10] resulting in axonal injury by an antibody-dependent cellular cytotoxic process. Furthermore, rabbits immunized with GM_1 develop AMAN.[11]

Therapeutically, the self-limiting course of GBS(s) is significantly shortened by intravenous immunoglobulin (IVIg) or plasmapheresis. The results from these therapies are gratifying, but the mode by which they exert their immunomodulatory action remains a fascinating immunological puzzle. Although plasmapheresis removes circulating immune factors responsible for conduction block, IVIg manipulates the immune system to modify or neutralize these factors either in situ or in the circulation.[12,13] In this issue, Buchwald and colleagues insightfully demonstrate that in patients with GBS, IVIg exerts a neutralizing effect on the activity of blocking antibodies.[14] They showed, by means of a perfused macropatch clamp electrode in a mouse nerve-muscle preparation, that serum from AMAN and MFS patients contains IgG antibodies that "block" quantal release, confirming their own work.[9] These "blocking" antibodies were neutralized in the serum obtained after IVIg therapy, or in a mixture of pre-IVIg with post-IVIg serum. Furthermore, the $F(ab')_2$, but not the Fc portion of IgG extracted from the same IVIg lots, neutralized the "blocking" antibodies in a dose-dependent manner. Four patients had AMAN and 2 patients had MFS with GM_1 or GQ_{1b} antibodies, which cause conduction block in vitro.[15] Because IVIg blocks the antigen-binding sites of anti–GM_1 antibodies and inhibits their binding to GM_1,[16,17] the inhibition of neuromuscular blockade noted after IVIg is most likely related to neutralization of GM_1 or GQ_{1b} antibodies.

In AMAN and AMSAN, the anti-GM_1–specific IgG enters freely through the roots and distal nerve terminals, which lack blood-nerve barrier, and recognizes GM_1 epitopes at the nodes of Ranvier.[18] The infused IgG molecules also should enter freely at the roots and distal nerve terminals and may quickly neutralize these antibodies even in situ, like the neutralization described in vitro by Buchwald and colleagues. Such antibody blockade supports the fast recovery of patients with AMAN who have IgG GM_1 antibodies, compared with those without antibodies,[5,19] and the reported superiority of IVIg compared with plasmapheresis in this group of patients.[5,20] The observations of Buchwald and colleagues are novel and significant in elucidating the mode by which IVIg manipulates pathogenic autoantibodies but also call for additional studies.

How does IVIg neutralize the blocking antibodies in GBS? Normal humans make IgG antibodies against a wide spectrum of normal proteins and "anti-idiotypic antibodies," defined as antibodies against the Fab′, the antigen-binding region (idiotype), of these antibodies. Because IVIg preparations are derived from large pools of human donors, they contain a wide range of idiotypic and anti-idiotypic antibodies that form dimeric pairs.[12,13,21] The larger the pool of donors, the higher the number of the $F(ab')_2$ dimers and the wider the expected spectrum of idiotypic–anti-idiotypic specificities. The anti-idiotypic antibodies supplied by IVIg have the potential to bind and neutralize pathogenic autoantibodies, thereby preventing their interaction with the autoantigen. In AMAN and MFS, IVIg can neutralize the blocking activity of GM_1 or GQ_{1b} antibodies because (1) normal human serum, and the various IVIg preparations, contains anti-idiotypic antibodies that recognize anti-GM_1[22,23]; and (2) the $F(ab')_2$, but not Fc fragments of IVIg, blocks within minutes the functional activity of sera containing GM_1 or GQ_{1b} antibodies.[11,14,16]

Are there differences in neutralizing activity between brands of IVIg? The repertoire of idiotypic and anti-idiotypic antibodies within the IVIg preparations and their capacity to neutralize idiotypes does not differ significantly between the various IVIg brands because all of them originate from large pools of 3 to 10,000 donors. However, the *content* of anti-idiotypes directed against a specific idiotype (or a set of idiotypes) of a given autoantibody, might vary among IVIg preparations owing to different exposures of donors to a specific antigen. This is pertinent to autoantibodies against GM_1 or other glycoconjugates because they often are produced after exposure to certain bacterial or viral infections, including cytomegalovirus, Epstein-Barr virus, *Hemophilus influenza*, or *Campylobacter*.[22] Consequently, the content of specific idiotypes against glycoconjugates may differ from one IVIg brand to another, or even from lot to lot, according to the donors' exposure to natural infections. Such variations in the content of specific idiotypes could explain the differences in neutralizing activity between the brands of IVIg noted by Buchwald and colleagues[14] and justify the varying degree of response to IVIg observed even among GBS patients with the same disease severity.

Is manipulation of autoantibody the main mechanism of action of IVIg in all forms of GBS? Apart from affecting autoantibodies, IVIg exerts a combined effect on complement, cytokines, and Fc receptors. Blocking antibodies are detected only in AMAN and MFS but not in AIDP, in which complement and macrophages are the main effector mechanisms. Consequently, in AIDP, IVIg may act predominantly by blocking complement activation and intercepting MAC formation,[12,13,24] or blocking Fc receptors on macrophages intercepting an antibody-dependent cell-mediated cytotoxic process.[12,13] It is frustrating that AIDP, the classic and most common form of GBS, remains the least understood in reference to pathogenesis and mechanism of action of applied therapies.

What are the clinical correlates of blocking antibodies and their neutralization? The rapid reversal of conduction block in vitro, should correspond to a fast resolution of clinical symptoms. Although after 4 weeks, most of the patients studied by Buchwald and colleagues had improved, the temporal relationship of clinical improvement to the natural evolution of blocking antibodies or their neutralization by IVIg have not been determined. Such bench-to-bedside correlations are needed to assess the practical significance of the described blockade. It will be of great practical value to explore if neutralization of the in vitro blockade serves as prognostic biomarker that predicts response to IVIg or confers superiority of an IVIg brand for a given patient. We should expect more from this novel model in the years to come.

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DOI: 10.1002/ana.10259

Hereditary Spastic Paraplegia: The Pace Quickens†

For more than 100 years after Seeligmüller's 1876 description of a family with progressive lower extremity spastic weakness,[1] hereditary spastic paraplegia (HSP) remained a poorly understood syndrome characterized clinically by progressive lower extremity spastic weakness[2] and pathologically by axonal degeneration involving the distal ends of long axons in the spinal cord. Twenty years ago, Harding[3] recognized that HSP was a group of disorders and classified HSP as *uncomplicated* if symptoms were limited to lower extremity spasticity and weakness and as *complicated* if the heritable syndrome included other neurological deficits. The development of diagnostic criteria and the ability to study homogeneous HSP kindreds permitted genetic investigations that have expanded our understanding of HSP at a rapid and accelerating pace.

We have learned, for example, that HSP, like the spinocerebellar ataxias and hereditary motor sensory neuropathies, exhibits extreme genetic heterogeneity: mutations in separate genes cause similar syndromes of lower extremity spastic weakness, urinary urgency, and mild vibratory sense impairment. The report by Valente and colleagues[4] (in this issue) of a locus for autosomal dominant, uncomplicated HSP on chromosome 9q33-q34 brings the total number of known HSP loci to 18. This includes 10 dominant, 5 recessive, and 3 X-linked forms (Table).

Although lower extremity spastic weakness is remarkably similar between different genetic types of uncomplicated HSP, there are clinical differences that have important implications. Symptoms in uncomplicated HSP linked to chromosomes 12 (SPG10), 14 (SPG3), and 19 (SPG12) begin on average before 11 years of age. In contrast, symptoms begin on average after 20 years in patients with HSP linked to chromosomes 2p (SPG4), 2q (SPG13), 8q (SPG8), 15 (SPG6), and 9q33 (SPG19) (reviewed by Fink and Hedera[5]). Furthermore, although individuals with adult-onset HSP generally show progressive worsening, it is not uncommon for individuals with early childhood–onset HSP to show very little worsening even over many years.

Genes have been discovered for 6 types of HSP (see Table). In 1999, Hazan and colleagues[6] discovered mutations in a novel gene (*SPG4*) as the cause of chromosome 2p–linked HSP, the single most common form of HSP. *SPG4* mutations are predicted to be pathogenic through haploinsufficiency (a deficiency of functional spastin), rather than through a dominant negative mechanism. Recent evidence indicates that spastin is distributed within the cytoplasm and interacts with microtubules.[7,8] These observations raise the possibility that spastin abnormalities may be pathogenic by disturbing the function or distribution of microtubules, essential factors in axonal morphology and axonal transport.

Zhao and colleagues[9] recently reported that mutations in a novel gene (*SPG3A*) cause autosomal dominant HSP linked to chromosome 14q. In this issue, Muglia and colleagues[10] provide the first confirmation of this finding. *SPG3A*'s encoded protein (designated *atlastin*) contains a conserved GTPase domain. The *SPG3A* mutation reported by Muglia and colleagues disrupts a conserved element of the predicted GTPase domain. This observation lends further support to the importance of atlastin's GTPase domain and the concept that *SPG3A* mutations are pathogenic through haploinsufficiency.

Atlastin bears structural homology with guanylate binding protein 1, a member of the dynamin family of large GTPases. Dynamins play essential roles in a wide variety of vesicle trafficking events that are important for neurotransmission and the action of neurotrophic factors (see Zhao and colleagues[9] for dynamin referenc-

Table. Genetic Types of Hereditary Spastic Paraplegia

Spastic Gait (SPG) Locus	Chromosome	Gene/Protein: Function	HSP Syndrome
Autosomal dominant heat shock protein HSP			
SPG4	2p22	SPG4/spastin: cytosolic protein, with AAA domain that binds to microtubules	Uncomplicated
SPG13	2q24-34	Heat shock protein 60 (Hsp60), mitochondrial chaperonin (Cpn60)	Uncomplicated
SPG8	8q23-q24		Uncomplicated
SPG9	10q23.3-q24.2		Complicated: spastic paraplegia associated with cataracts and gastroesophageal reflux, and motor neuronopathy
SPG17	11q12-q14		Complicated: spastic paraplegia associated with amyotrophy of hand muscles (Silver syndrome)
SPG10	12q13		Uncomplicated
SPG3A	14q11-q21	SPG3A/atlastin: predicted to be GTPase similar to dynamins	Uncomplicated
SPG6	15q11.1		Uncomplicated
SPG12	19q13		Uncomplicated
SPG19	9q33-q34		Uncomplicated
Autosomal recessive HSP			
SPG14	3q27-28		Complicated: spastic paraplegia associated with mental retardation and distal motor neuropathy
SPG5	8q		Uncomplicated
SPG11	15q		Uncomplicated or complicated: variably associated with HSP associated with thin corpus callosum, mental retardation, upper extremity weakness, dysarthria, and nystagmus
SPG7	16q	SPG6/paraplegin: mitochondrial protein	Uncomplicated or complicated: variably associated with mitochondrial abnormalities on skeletal muscle biopsy and dysarthria, dysphagia, optic disc pallor, axonal neuropathy, and evidence of "vascular lesions," cerebellar atrophy, or cerebral atrophy on cranial MRI
SPG15	14q		Complicated: spastic paraplegia associated with pigmented maculopathy, distal amyotrophy, dysarthria, mental retardation, and further intellectual deterioration
X-linked HSP			
SPG1	Xq28	L1 cell adhesion molecule (L1CAM)	Complicated: associated with mental retardation, and variably, hydrocephalus, aphasia, and adducted thumbs
SPG2	Xq28	Proteolipid protein (PLP): Intrinsic myelin protein	Complicated: variably associated with MRI evidence of CNS white matter abnormality
SPG16	Xq11.2		Uncomplicated Complicated: associated with motor aphasia, reduced vision, mild mental retardation, and dysfunction of the bowel and bladder

CNS = central nervous system; MRI = magnetic resonance imaging.

es). For example, dynamins are essential for rapid and efficient recycling of synaptic vesicles, associate with cytoskeletal elements such as actin and microtubules, and have been implicated in the maintenance and distribution of mitochondria. The mechanism by which *SPG3A*/atlastin mutations cause HSP is unknown.

The discovery by Casari and colleagues[11] of *SPG7* mutations as the cause of a rare form of autosomal recessive HSP (chromosome 16q–linked) expanded our concepts of HSP. First, individuals with *SPG7* gene mutations may exhibit either uncomplicated HSP or complicated HSP in which spastic paraplegia is associ-

ated with dysarthria, dysphagia, optic disc pallor, axonal neuropathy, and evidence of vascular lesions, cerebellar atrophy, or cerebral atrophy on cranial magnetic resonance imaging.[12] This observation raises the possibility that some other forms of complicated HSP may be allelic variants of uncomplicated HSP. Second, *SPG7*'s encoded protein (designated *paraplegin*) has been shown to be a mitochondrial protein. Some but not all HSP subjects with *SPG7* mutation have ragged red fibers and cytochrome-*c* oxidase negative fibers in skeletal muscle biopsy. Several months ago, Hansen and colleagues[13] showed that another form of HSP (uncomplicated autosomal dominant HSP linked to chromosome 2q) was caused by mutations in another nuclear-encoded mitochondrial protein (heat shock protein 60 [Hsp60], also known as mitochondrial chaperonin Cpn60). The observations that nuclear-encoded mitochondrial protein abnormalities (paraplegin and Hsp60) may manifest as progressive spastic paraplegia expands our knowledge of pathophysiological mechanisms in HSP and our appreciation of the neurological manifestations of mitochondrial disorders.

Although 2 HSP proteins, paraplegin and Hsp60, may cause HSP through related biochemical mechanisms (disturbances in mitochondrial function), other proteins implicated in HSP appear to have quite separate mechanisms of action. Mutations in the proteolipid protein gene cause both Pelizaeus-Merzbacher disease, an X-linked infantile-onset dysmyelinating disorder, and a childhood-onset slowly progressive spastic gait disorder (X-linked HSP; reviewed by Fink[2]). Proteolipid protein is an intrinsic myelin protein in contrast with paraplegin and Hsp60, which are distributed to mitochondria. Neural cell adhesion molecule (L1CAM) gene mutations cause one form of X-linked spastic paraplegia and developmental neurological disorders, including X-linked hydrocephalus, MASA syndrome (mental retardation, aphasia, shuffling gait, adducted thumbs), and CRASH syndrome (corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraparesis, and hydrocephalus).[2] L1CAM is involved in neuron-neuron interaction and plays an important role in neuronal migration, neuronal differentiation, and axon growth.

In summary, there have been great strides in our understanding of HSP in the past several years. We have learned that HSP shows extreme genetic heterogeneity, that the most common forms of uncomplicated HSP involve the disturbance of motor (corticospinal tract) and sensory (dorsal column) fibers, and that cognitive impairment may be a feature of at least 1 type of uncomplicated HSP.[14] Although most forms of complicated and uncomplicated HSP are genetically distinct, some forms of complicated and uncomplicated HSP may be allelic. Although most HSP subjects experience progressive worsening, for some individuals the disorder is nonprogressive. This suggests that some forms of HSP are truly neurodegenerative disorders (eg, those due to the *SPG4* mutation) and that other forms of HSP are developmental disorders (eg, HSP due to the *L1CAM* gene and possibly HSP due to the *SPG3A* mutation). Although some HSP proteins may disturb a common biochemical pathway (eg, paraplegin and Hsp60, both of which are mitochondrial proteins), other HSP proteins may participate in widely divergent biochemical pathways.

Until recently, HSP was a clinical diagnosis based on family history, neurological signs, and careful exclusion of alternate diagnostic possibilities. Genetic testing for the *SPG4* gene mutation is currently available, and testing for the *SPG3A* mutations is expected soon. Together, *SPG4* and *SPG3A* testing can be used to confirm the diagnosis and for prenatal diagnosis in 50 to 60% of individuals with dominantly inherited HSP.

Information and support for HSP patients and their families are increasingly available. This year in the United States, the Spastic Paraplegia Foundation was established to promote research and treatment for HSP, primary lateral sclerosis, and related disorders (http://www.hspinfo.org). Similar organizations exist in France (Association Strumpell Lorraine, http://perso.wanadoo.fr/asl.spastic/) and Germany (Tom Wahlig Foundation, http://www.fsp-info.de).

These are exciting times for HSP research. In addition to the progress cited, efforts are underway to create animal models of HSP by targeted disruption of *SPG7*/paraplegin, *SPG4*/spastin, and *SPG3A*/atlastin genes. Such animals will facilitate investigations of HSP's molecular pathophysiology. The rapid pace of HSP investigations, together with the emergence of HSP patient organizations, offers the real hope that insights into HSP biochemical pathophysiology may soon be at hand and, with this information, the possibility of treatment.

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This research was supported by grants from the Veterans Affairs Merit Review and the National Institutes of Health (National Institute of Neurological Disorders and Stroke; R01NS33645, R01NS36177, and R01NS38713, J.K.F.).

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DOI: 10.1002/ana.10258