



Reversible Conduction Failure in Guillain-Barré Syndrome

Byeol-A Yoon^{1,2}, Jong Kuk Kim^{1,2}

¹Department of Neurology, Dong-A University College of Medicine, Busan, Korea

²Peripheral Neuropathy Research Center, Dong-A University College of Medicine, Busan, Korea

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Corresponding author:

Jong Kuk Kim

Department of Neurology, Dong-A
University College of Medicine, 26
Daesingongwon-ro, Seo-gu, Busan
49201, Korea

Tel: +82-51-240-5266

Fax: +82-51-244-8338

E-mail: advania9@chol.com

Gangliosides are the primary antigenic target in acute motor axonal neuropathy. When anti-ganglioside antibodies bind to gangliosides near the motor axon node of Ranvier, complement system activation and Wallerian degeneration occur. Nevertheless, debate persists regarding the impact of anti-ganglioside antibodies on Guillain-Barré syndrome (GBS). Certain patients with these antibodies experience a swift recovery or exhibit conduction abnormalities indicative of demyelination in nerve conduction studies. The concept of reversible conduction failure was introduced by Kuwabara et al. in 1998. They proposed that this could result from compromised physiological conduction at the node of Ranvier. Auto-antibodies that bind to GM1 or GD1a gangliosides at this node can activate the complement system and disrupt sodium channel and axo-glial junctions, causing conduction failure. In 2003, Cappaso et al. described two cases of rapidly improving flaccid paralysis following *Campylobacter jejuni* infection. Initial nerve conduction studies indicated motor conduction block, which resolved quickly within 2 to 5 weeks. The authors termed this phenomenon acute motor conduction block neuropathy and considered it a form of arrested or partial acute motor axonal neuropathy. Since acute motor conduction block neuropathy could be misclassified as acute inflammatory demyelinating polyneuropathy based on existing electrophysiological criteria, several suggestions were made to refine the classification of GBS subtypes.

Keywords: Guillain-Barre syndrome; Gangliosides; Acute inflammatory polyneuropathy

Introduction

Guillain-Barré syndrome (GBS), a type of acute immune-mediated neuropathy, is a monophasic disease that typically has a good prognosis insofar as recovery occurs with appropriate treatment [1]. However, outcomes in real-world scenarios are not always favorable. The Erasmus group has identified several factors that can influence prognosis, including advanced age, a history of diarrhea, and a low Medical Research Council sum score at the time of hospital admission [2]. Traditionally, the axonal variant of GBS is associated with comparatively poor clinical outcomes, since it is more often linked to diarrhea caused by *Campylobacter*

jejuni infection and is frequently characterized by Wallerian degeneration [3]. However, among patients with axonal GBS who present with severe symptoms, some individuals recover quickly and others very slowly; thus, a wide range of outcomes are possible [4]. In cases of axonal GBS with rapid recovery, nerve conduction studies (NCS) display a distinctive feature: initial conduction block that shows marked improvement in the reduced proximal compound muscle action potential (CMAP) during short-term follow-up, a phenomenon known as reversible conduction failure [5,6]. It is widely recognized that the key factor for this phenomenon is located at the node of Ranvier.

Chinese Paralytic Syndrome

Following the identification of GBS in two soldiers by Georges Charles Guillain, Jean Alexandre Barré, and André Strohl in 1916 during World War I, GBS has been associated with acute inflammatory demyelinating polyneuropathy (AIDP) for nearly a century [7]. In 1964, a pathological review of 97 patients with GBS identified predominantly demyelinating neuropathy features, noting secondary axonal degeneration in certain severe cases [8]. In 1986, Feasby et al. [3] described five patients with GBS who exhibited severe axonal degeneration without prominent demyelination, hinting at an alternative mechanism for GBS. This suggestion, however, did not gain immediate acceptance within the academic community. A pivotal event soon challenged this traditional view. In the early 1990s, reports emerged from rural northern China of dozens of severe limb paralysis cases in children occurring annually following infection [9,10]. These cases presented with ascending symmetric paralysis and respiratory weakness, reaching their nadir approximately 6 days after the onset of symptoms. Cerebrospinal fluid analysis revealed albuminocytologic dissociation. While these clinical features aligned with the classical presentation of GBS as AIDP, NCS of these patients differed substantially. Motor NCS revealed a marked reduction in CMAPs while maintaining relatively normal conduction velocities and sensory studies. These patients are now recognized as having had a subtype of GBS termed acute motor axonal neuropathy (AMAN). Consequently, GBS is now understood as a syndrome that includes acute onset immune-mediated neuropathies with a spectrum of clinical and electrophysiological manifestations.

Gangliosides and the Node of Ranvier

Gangliosides are a type of glycosphingolipid that contain one or more sialic acid residues and are integral to the composition of cell membranes, including those in the central and peripheral nervous systems [11]. They are known to perform critical functions in the nervous system, such as stabilizing its structure and facilitating the rapid transmission of neural information. The velocity of nerve impulse conduction is influenced by the extent of myelination provided by Schwann cells. Through axo-glial interactions between these cells and axons, several polarized domains are established, including the node of Ranvier, paranode, juxtaparanode, and internode (Fig. 1). The node of Ranvier is characterized by a high concentration of voltage-gated sodium channels, whereas the juxtaparanode contains voltage-gated potassium channels that help maintain the resting membrane potential

[12]. Additionally, the formation of a robust axo-glial junction at the paranode is facilitated by contactin/contactin-associated protein (Caspr) and neurofascin 155 (NF155); this structure also serves to prevent the intermingling of sodium channels from the node of Ranvier with potassium channels from the juxtaparanode. The generation of an action potential is driven by these differences in electrolyte distribution, leading to saltatory conduction that is primarily centered around the node of Ranvier [13]. Gangliosides are predominantly located along the axonal membrane at the node of Ranvier and to a lesser extent at the paranode. Mice lacking the enzyme beta-1,4 N-acetylgalactosaminyltransferase, which is vital for ganglioside synthesis, exhibited disrupted axo-glial junctions in their nerves [14]. This finding suggests that gangliosides play a crucial role in maintaining the structural integrity of the node of Ranvier and may also be involved in the pathogenesis of GBS.

In 1989, Yuki et al. [15] described two cases in which patients developed acute limb paralysis following gastrointestinal infection with *C. jejuni*. These individuals presented with clinical symptoms that were consistent with AIDP, yet they did not exhibit any sensory deficits. NCS indicated that the axonal damage

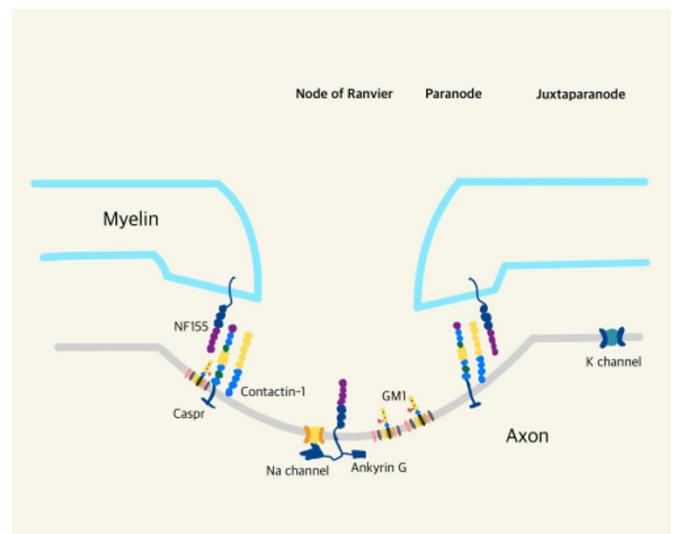


Fig. 1. Gross and molecular structure of the node of Ranvier. The myelinated fibers of the peripheral nerves can be divided into four domains: the node of Ranvier, the paranode, the juxtaparanode, and the internode. Within the paranode, contactin/contactin-associated protein (Caspr) and neurofascin 155 (NF155) contribute to the formation of an axo-glial junction. The node of Ranvier is characterized by a high concentration of voltage-gated sodium (Na) channels, whereas voltage-gated potassium (K) channels are primarily found in the juxtaparanode. Gangliosides present at the node of Ranvier and the paranode are instrumental in maintaining the stability of these structures.

was confined to motor nerves, which aligns with the present classification of AMAN. In sera collected during the acute phase, immunoglobulin G (IgG) antibodies against ganglioside monosialotetrahexosyl ganglioside (GM1) ganglioside were identified in these patients, prompting recognition of the link between GM1 gangliosides and the axonal variant of GBS. In the early 1990s, mixtures of gangliosides extracted from bovine brains were commonly employed as a treatment for central nervous system disorders, including stroke, Parkinson disease, and amyotrophic lateral sclerosis, in several European countries [16-18]. However, a significant number of patients discontinued this treatment due to drug-induced GBS [19,20].

Subsequent research revealed that the lipooligosaccharides in the outer membrane of *C. jejuni*, especially those of the O:19 serotype, possess epitopes structurally resembling those of ganglioside GM1. This similarity is referred to as molecular mimicry theory [21]. Animal experiments have substantiated this concept, and it is currently considered a prominent pathomechanism for AMAN [22].

Reversible Conduction Failure

In 1998, Kuwabara et al. [5] categorized patients with GBS into two groups: those with and those without IgG anti-GM1 antibodies. This classification was designed to clarify the role of GM1 ganglioside in neural function [5]. In patients with IgG anti-GM1 antibodies, initial NCS revealed a reduction in the distal CMAP or prominent conduction block in motor nerves. Contrary to what is observed in AIDP, these abnormalities were not prolonged. Follow-up NCS frequently demonstrated a rapid recovery of CMAP, a pattern that led to the characterization of this response as so-called reversible conduction failure. While the resolution of conduction block in AIDP typically occurs over approximately 6 to 10 weeks, patients exhibiting reversible conduction failure associated with anti-GM1 antibodies often recover within a 2-week timeframe.

In 2003, Capasso et al. [23] described two notable cases of axonal GBS. The patients involved exhibited only conduction block without temporal dispersion on NCS, and they demonstrated rapid recovery of both clinical and electrophysiological features. The author termed this condition acute motor conduction block neuropathy (AMCBN) and considered it to be a form of arrested or partial AMAN. These patients presented with high titers of IgG anti-GD1a and/or anti-GM1 antibodies, in conjunction with *C. jejuni* infection [23]. The emergence of this phenomenon is ascribed to the binding of anti-ganglioside antibodies to the nodes of Ranvier, which inflicts nerve damage that

extends to the paranode, potentially prompting axonal degeneration. Rapid recovery of the damaged node results in the swift resolution of reversible conduction failure. However, if the damage is sustained, it can lead to axonal degeneration and the progression of AMAN [24].

Electrodiagnostic Criteria of GBS

The Hadden criteria, established in 1998, are currently the most widely accepted electrodiagnostic standards for GBS [25]. These standards stipulate that the presence of a conduction block exceeding 50% in at least two nerves is indicative of AIDP. However, this can result in the erroneous categorization of patients with reversible conduction failure as AIDP in AMCBN. This is particularly relevant in South Korea, where the incidence of axonal GBS is significantly greater than that observed in Western countries. Consequently, a broader range of electrodiagnostic criteria is essential to ensure the accurate classification of GBS subtypes in this population [26,27]. In a study applying the Hadden criteria to the initial NCS of 55 patients—comprising 32 with AIDP, 21 with axonal GBS, and two with indeterminate GBS—only 10 patients were identified as having axonal GBS. Seven patients were mistakenly classified as having AIDP, and four were incorrectly diagnosed as exhibiting equivocal GBS [28].

In 2014, Rajabally et al. [29] introduced new electrodiagnostic criteria that considered AMCBN. They applied a stringent definition of conduction block (70%) and recommended that AIDP be diagnosed only if additional demyelinating criteria are met, explicitly excluding the presence of conduction block in two nerves [29]. When the Rajabally criteria were applied to a previous cohort of 55 patients, 19 were reclassified as having axonal GBS; however, a significant proportion of patients with AIDP were reclassified as having equivocal GBS [28]. Consequently, Uncini et al. [30] advocated for follow-up NCS to be conducted between 3 and 8 weeks after the onset of GBS symptoms to ensure adequate interpretation.

Conclusion

Conduction block has traditionally been associated with demyelinating neuropathy. However, advances in knowledge regarding gangliosides and the node of Ranvier have revealed that conduction block can also occur in axonal neuropathy. At present, our understanding is evolving based on the types of gangliosides and their distribution patterns. A notable example is N-acetylgalactosaminyl GD1a (GalNAc-GD1a), which is locat-

ed in the inner part of compact myelin and in the periaxonal axolemma-related region of the ventral root [31]. Patients with IgG antibodies against GalNAc-GD1a typically exhibit symptoms of pure axonal GBS, whereas those with IgM antibodies are more likely to display the pure motor demyelinating subtype of GBS [32,33].

In real-world scenarios, it is hypothesized that various carbohydrate structures from two or more gangliosides, or gangliosides combined with certain types of lipids, may interact to form entirely new epitopes. One example is the phosphatidic acid/GM1 ganglioside complex. When target antibodies bind to these complex epitopes, novel forms of GBS may emerge. Antibodies that target these structures are referred to as complex antibodies. In cases of AMAN caused by IgG anti-GM1/GalNAc-GD1a complex antibodies, reversible conduction failure is observed more frequently than among patients with antibodies targeting only GM1 or GalNAc-GD1a. It is believed that the gangliosides GM1 and GalNAc-GD1a are positioned near the surface of the axolemma, particularly in regions that interact with the node of Ranvier or paranode. The complex structure of GM1/GalNAc-GD1a may be located in areas of the axolemma that are relatively distant from the node of Ranvier [34].

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

ORCID

Byeol-A Yoon, <https://orcid.org/0000-0002-4350-3551>

Jong Kuk Kim, <https://orcid.org/0000-0001-9204-3718>

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