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Guillain-Barré Syndrome Induced by *Campylobacter jejuni*

Hamidreza Honarmand[1] and Masoumeh Ahmadi Jalali Moghadam[2*]

[1]Department of Microbiology, Guilan University of Medical Sciences, Rast, Iran.
[2]Cellular and Molecular Research Center, Faculty of Medicine, Guilan University of Medical Sciences, Rasht, Iran.

Authors' contributions

This work was carried out in collaboration between both authors. Author HH designed the study and wrote the first draft of the manuscript. Author MAJM managed literature searches. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Purpose of Review: Guillain-Barré syndrome (GBS) is a neurologic disease that produces ascending paralysis that affects people all over the world. Several infectious agents have been associated with GBS and many reports suggest that infection with *Campylobacter jejuni*, a common enteric pathogen, may cause GBS by triggering demyelination of peripheral nerves. This review provides an update on the *C. jejuni* infections engaged in the developing of GBS.
Summary and Results: Guillain–Barré syndrome is the most common cause of acute neuromuscular paralysis, yet its cause and pathogenesis are unknown. In approximately two thirds of patients, neuropathic symptoms follow an infection — often a mild, undiagnosed respiratory or gastrointestinal illness. The organism that has most frequently been described in association with GBS is *C. jejuni,* a gram-negative rod that is now the most common cause of bacterial gastroenteritis in developed countries. Although there has been a plethora of case reports and studies documenting the association, the specific clinical and epidemiologic features are not well

**Corresponding author: E-mail: Masoumehjalaly@gmail.com;*

known. In addition, there is controversy about whether those with preceding *C. jejuni* infection have a more severe form of the GBS. *C. jejuni* can cause the disease by a mechanism called molecular mimicry. *C. jejuni* contains ganglioside-like epitopes in the lipopolysaccharide (LPS) moiety that elicit autoantibodies which can react with peripheral nerve targets. It seems that heterogeneity in the LPS structure determines the specificity of the antiglycolipid response and thereby the clinical features in patients with a post-*campylobacter infection* neuropathy.

Keywords: Campylobacter jejuni; Guillain-Barré syndrome; autoantibody; autoimmunity.

1. INTRODUCTION

In developed countries, *Campylobacter jejuni* is a leading cause of acute gastroenteritis. In 1982, Rhodes and Tattersfield [1] reported the first case of a patient who developed GBS after *C. jejuni* enteritis. Actually *C. jejuni* infection frequently precedes GBS, but it is far more common than GBS. The risk of developing GBS after *C. jejuni* infection actually is considerable. In the USA, it is estimated that about 0.1% of *C. jejuni* infection is followed by GBS [2]. In Ireland, three populations in which outbreaks of *C. jejuni* infection had occurred were investigated, involving an estimated 8000 cases [3]. No cases of GBS were detected in the 6 months following the outbreaks in those local populations. The point estimate for the risk of GBS following *C. jejuni* infection was 0 in 8000. GBS-related *C. jejuni* is reported to be associated with the specific Penner serotypes O:19 in Japan and O:41 in South Africa, but the association is not as strong in other countries. There are some reports of the association of GBS after *C. jejuni* infection with certain Human Leukocyte Antigen (HLA) types, but no specific immune response genes have been reported.

2. BACTERIOLOGY

Campylobacter species are gram-negative curved bacilli. Among this species complete genome sequence has been characterized for *C. jejuni*. It contains hypervariable regions that might be important in the survival of the organism [4]. *Campylobacter* species have unipolar or bipolar flagella and grow slowly; 72–96 h is required for primary isolation from stool samples, but isolation from blood can take even longer. They grow best at 42°C in selective media with microaerophilic condition. Most *Campylobacter* species are resistant to cephalothin while other stool flora are susceptible, so using a medium that contains cephalothin is an effective method for isolation this bacterium from stool samples [5].

Outbreaks have been associated with drinking raw milk or contaminated water and eating poultry. There are several other sources including pets and other animals, and sewage contamination. Chicken is a natural reservoir of *C. jejuni* where it colonizes in the mucosal layer of the gastrointestinal tract and can transfer between chickens through the faecal-oral route. Actually *C. jejuni* infection is one of the most commonly identified bacterial causes of acute gastroenteritis worldwide. In developing countries, *C. jejuni* is an important cause of childhood morbidity due to diarrheal illness and also is among the most common causes of diarrhea in travelers from developed countries. In the United States and other industrialized countries, *Campylobacter* infections were found to cause diarrheal disease >2–7 times more frequently than infections by *Salmonella* species, *Shigella* species, or *Escherichia coli* O157:H7 [6,7]. In the United States >99% of reported infections with *Campylobacter* are with *C. jejuni* [8].

In tropical developing countries, *Campylobacter* infections are hyperendemic among young children, especially those aged <2 years and asymptomatic infections occur in both children and adults. In developed countries, asymptomatic *Campylobacter* infections are not usual. In addition, outbreaks of infection in developing countries are not common and the illness lacks the marked seasonal nature observed in industrialized countries. It should be noted that in both developed and developing countries, *Campylobacter* is one of the most common bacterial causes of diarrhea [9,10]. Some type of *C. jejuni* strains (Eg: serotype O:19, O:41) has been more frequently associated with GBS. More studies are necessary in characterize the strains.

3. GUILLAIN-BARRÉ SYNDROME

The most common disorders of the nervous system are peripheral nerve diseases. Study on neuropathies has played an important role in

developing our understanding of basic mechanism of nervous system injury and repair because the peripheral nervous system is more accessible to direct physiological and pathological investigations. Studies on peripheral nervous system are providing new insight into the mechanisms of immune injury to the nervous system. Peripheral nervous system disorders are now suspected to be immune-mediated, and the molecular and cellular targets of immune attack are known.

GBS is an autoimmune disorder in which peripheral nerves are damaged and cannot transmit signals efficiently. The immunological attack consists of deposits of immunoglobulins and complement on the axon and Schwann cell surface accompanied by macrophage and T-cell infiltration of the nerve [11]. The disease typically progresses from the legs up the body to the trunk and may even affect the respiratory system, causing almost complete paralysis. In GBS, the myelin sheath protecting the nerves is mainly damaged and because nerves cannot transmit signals to muscles, muscles will not function properly, thus causing paralysis. No one knows exactly what causes GBS or why some people get it and other do not. Most people who get GBS do so after having a bacterial or viral infection. In some cases, it has been connected to certain immunizations, such as the flu vaccine [11].

Because GBS is a syndrome and not a disease, it might be difficult to diagnose. The symptoms are not always the same in different persons, but typically reflexes will be lost and the process is typically symmetric. Other important features are elevated CSF protein without significant inflammatory cells. The nadir of clinical worsening should occur within one month of onset. Patients recover spontaneously and their recovery is accelerated by immunomodulating therapies, such as plasma exchange and intravenous immunoglobulins [12]. Even when patients are treated in well-equipped intensive care units, mortality rates still range from 3–7% [13]. Acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN) are main clinical features of GBS and AIDP is the most common subtype of GBS.

4. EPIDEMIOLOGY OF GUILLAIN-BARRÉ SYNDROME

Since the eradication of polio in most parts of the world, GBS has become the most common cause of acute flaccid paralysis with an annual incidence of 0.6–4 cases per 100,000 populations. Actually GBS has now become the most common cause of acute flaccid paralysis worldwide [14,15]. Males are more frequently affected than females (1.25 : 1). It occurs in all age groups but the incidence appears to increase with age. In developed countries, AIDP appears to affect an older population, while in northern China AMAN affects primarily children and young adults [16]. No consistent geographical variations have been reported and most studies have failed to identify the seasonal variation in GBS.

5. PATHOGENESIS OF GUILLAIN-BARRÉ SYNDROME

GBS is self-limiting, muscle weakness with partial or complete recovery occurring over weeks to months. The rate of recovery is facilitated by plasma exchange, and its therapeutic effect presumably is related to the removal of circulating factors. GBS is caused by attacking the body's immune system to the peripheral nerves. The syndrome may comes on after an infection. It seems that at a molecular level, some infectious agents look like parts of the nervous system. This results in mistake of the immune system to the identity of peripheral nerves, thinking that parts of the nerve are an infectious agent. So, the immune system releases antibodies that can attack the peripheral nerves. GBS is perhaps best thought of as a family of disorders, which can cause different kinds of problems. In AIDP, antibodies don't attack the nerve cells directly. They make damage to the glial supporting cells that surround the axon of the nerve which leads to sensory changes and weakness that starts in the lower limbs. Common symptoms of GBS are deep aching pain in their weakened areas and back. In AIDP, both sides of the body tend to be equally affected.

Immunopathological studies suggest that the target of immune attack differs with the GBS subtype. As it is noted, in AIDP, the attack appears to be directed against a component of Schwann cells. In AMAN, attack appears to be against the axolemma and nodes of Ranvier [17]. These findings indicate that the presence of IgG, which binds effectively with complements and macrophages, is the most important factor in the development of GBS. Rees et al. [18] revealed that anti-GM1-positive patients were more likely to have axonal degeneration and less sensory

disturbance than were anti-GM1 antibody-negative patients. Walsh et al. [19] reported that 14 of 95 (15%) patients with GBS had anti-GM1 antibodies and that the predominant immunoglobulin class was IgG not IgM. Kusunoki et al. [20] found antibody to the minor monosialosylganglioside GM1b to be a useful diagnostic marker of GBS.

Patients with the anti-GM1b-positive were distinguished by more rapidly progressive, more severe, and predominantly distal weakness. Cranial nerve involvement and sensory deficits are less common in the patients with anti-GM1b antibodies. The presence of these antibodies was associated with slower recovery. Clinical manifestations predominantly were associated with anti-GM1b antibodies of the IgG isotype [21]. Gangliosides are sialic acid-containing glycolipids, expressed abundantly in the nervous system. They are composed of a ceramide tail inserted in the lipid bilayer and a highly variable oligosaccharide moiety protruding externally. More than 100 different types of gangliosides have been identified. Gangliosides are implicated in cell growth and differentiation but they also serve as receptors for bacterial toxins and have a function in signal transduction.

6. MECHANISM OF THE SYNDROME

It is believed that a susceptible human host generates autoantibodies that target both the bacterial ganglioside-like lipooligosaccharide (LOS) structures and human peripheral nerve gangliosides, which triggers axonal degeneration and demyelination of the peripheral nerves. It should be noted that the paralysis usually occur because attacking the immune system to the protective Schwann cells surrounding the nerves and breaking down the myelin [22].

Contrary to what is expected from an antibody response against carbohydrate antigens, the isotype of the ganglioside antibodies in GBS patients is not only IgM but also IgA and IgG [10]. Furthermore, the IgG antibodies have a high titer and are of the IgG1 and IgG3 subclass [10], pointing to an isotype switch involving T-cell help. Interestingly, activated T cells have been identified in the affected nerves and acute phase blood samples from GBS patients. These activated cells are $CD4^+$ and $CD8^+$ and express αβ or γδ TCRs [23]). Until now, there have been no reports describing glycolipid reactive T cells in GBS patients, although γδ T cells reacting with non-peptidic *Campylobacter* antigens have been recovered from nerves and peripheral blood of GBS patients [24].

Frequently, an impaired γδ T-cell response towards non-peptidic antigens has been described in GBS patients with an antecedent *C. jejuni* infection, perhaps underlying the deviant antibody response [25]. The wide range of gangliosides to which antibodies have been reported in GBS patients include GM1, AsialoGM1, GM1b, GD1a, GD1b, GD3, GT1a, GT1b, GQ1b, LM1, GalC, and sulfated glucuronyl paragloboside (SGPG). Gas-liquid chromatography-mass spectrometric analysis showed that the purified LPS has galactose (Gal), *N*-acetylgalactosamine (GalNAc), and *N*-acetylneuraminic acid (NeuAc), ie, the sugar components of the GM1 ganglioside [26].

A single strain of *C. jejuni* may have several ganglioside-like LPSs. A patient with *C. jejuni*-associated GBS could have several types of antiganglioside IgG antibodies. Infection by such a *C. jejuni* strain may induce a single anti-ganglioside IgG in some patients and a combination of antibodies in others [26]. In Chinese patients with GBS, 24% of those with AMAN, but none of those with AIDP, had anti-GD1a IgG antibody, indicating that this antibody is closely associated with AMAN but not AIDP [27].

The presence of antibodies to the main epitops of LPS (Fig. 1) was shown to be related to antecedent *C. jejuni* infection. GBS patients with them had a more rapidly progressive, more severe and predominantly distal weakness, but less sensory loss, paraesthesia, and cranial nerve involvement [21].

The GD1a epitope is present in *C. jejuni* LPSs isolated from patients with GBS [28]. The GM1b and GalNAc-GD1a epitopes also are expressed in *C. jejuni* LPSs isolated from patients with AMAN who had anti- GM1b and anti-GalNAc-GD1a IgG antibodies [21].

Actually antibodies to >20 different glycolipids have now been associated with different types of acute and chronic neuropathy syndromes. Now we know more about the link between acute motor axonal neuropathy and antibodies to GM1, GD1a, GM1b and GalNAc-GD1a. Many clinical and serological studies support this theory. Advances in animal modelling of antiglycolipid antibody-associated diseases made advances in

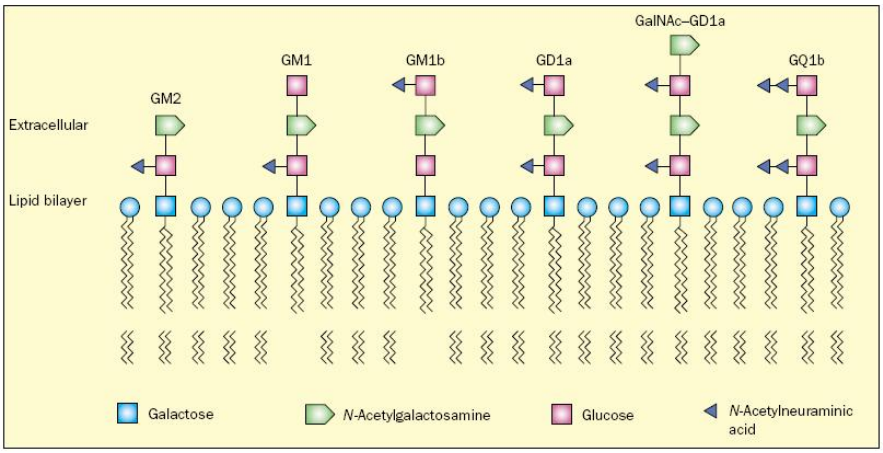

Fig. 1. Gangliosides may have a role as antigens in GBS. In AMAN, GM1, GM1b, GD1a, and GalNAc-GD1a can be target molecules for IgG antibodies and in AIDP, GM2 may be a possible target for IgM antibody after cytomegalovirus infection. GQ1b can be a target molecule for IgG antibody in Miller Fisher Syndrom. (Reprinted from Yuki N [21])

our understanding of the role of anti-GQ1b antibodies in Miller Fisher syndrome respecting to the motor nerve terminal as a potential site of injury. Considering such information, it is possible to determine the precise mechanisms by which antibodies injure the different compartments of peripheral nerve [21].

7. SEROLOGICAL AND CULTURE STUDIES

In 1982, Rhodes and Tattersfield were the first to report on a patient who developed GBS 10 days after *C. jejuni* infection [28]. Then various electrodiagnostic and pathologic studies have shown that *C. jejuni* infection is significantly associated with primary axonal dysfunction [29,30] and several reports are also available suggesting role of *C. jejuni* infection in the demyelinating process [31,32].

GBS is now recognized as a post-infectious complication of *C. jejuni* infection, but its incidence is <0.1% infections [9]. Many evidences have supported *Campylobacter* infection as a trigger of GBS. Some serologic surveys have demonstrated that sera from GBS patients contain anti-*C. jejuni* antibodies, consistent with recent infection. And also a culture study showed that many GBS patients have *C. jejuni* in their stools at the time of onset of neurologic symptoms [33].

Actually there are numerous reports described patients who developed GBS following *C. jejuni* infections [34–38]. It is also believed that GBS following *C. jejuni* infection may be more severe, for instance, having fulminating disease with quadriplegia and requiring ventilator support within 24–48 h of onset [38,39]. Neurologic symptoms typically occur 10 days to 3 weeks after onset of diarrhea. The longest reported interval between onset of *C. jejuni* enteritis and onset of GBS symptoms is 23 days [11]. Actually the median interval from the onset of diarrhea to the onset of neuropathic symptoms for most *C jejuni*-positive patients is 10 days, evidence that indicates GBS is a consequence of an immune response to *C jejuni* rather than the direct effect of the organism or one of its toxins [39].

Some researchers believe that the risk of developing GBS after *C. jejuni* infection is actually quite small [40] and other researchers believe that the risk of developing GBS is increased after infection with certain *Campylobacter* serotypes. In the United States, Penner type O:19 is most commonly associated with GBS [41,42] and in South Africa, Penner type O:41 is the serotype associated with GBS frequently.

Almost 25%–40% of GBS patients worldwide suffer from *C. jejuni* infection 1–3 weeks prior to the illness [43]. The short interval between the acute infection and the development of symptoms enables identification of the triggering infectious agents and even their culture *in vitro* for further microbial investigations. Culture [41] and serological [42, 43] studies have proved that

C. jejuni cause infections in GBS patients. The isolation rate of *C. jejuni* from stool culture of GBS patients' ranges from 8% to 50% [41] and seropositivity ranges from 24% to 76% [42,43,44].

Campylobacter is not a part of normal, stool flora, and detection of the organism would not be expected in the absence of recent infection. However, obtaining culture confirmation of an association with GBS and preceding *C. jejuni* infection is difficult because most patients with *Campylobacter* infection would have already cleared the bacteria when their GBS symptoms began. Nevertheless several investigators have succeeded in isolating *C. jejuni* from the stools of patients with GBS at the onset of their neurologic symptoms. Kuroki et al. [45] isolated *C. jejuni* from 30% of GBS patients, whereas Rees et al. had a isolation rate of 8% [46]. In a similar study, *Campylobacter* was recovered from 4 (44.9%) of 9 GBS patients with diarrhea [47]. In a prospective study, *C. jejuni* and *C. upsaliensis* were detected in patients having AIDP and AMAN type, respectively [48]. Other researchers identified *C. jejuni* infections in GBS cases with culture (2.5%) and with PCR (22.5%), respectively [49].

In a large study conducted in North America and Europe involving 229 GBS patients, 52 (22.7%) patients had positive serology for *C. jejuni*, and 56% of them showed demyelinating neurophysiology [50]. A study in Japan investigating 86 GBS patients showed that of the 20 (23.3%) *C. jejuni*-positive patients, 70% had AMAN and 15% had AIDP [30]. These results raise the possibility that *C. jejuni* infection can elicit both axonal and demyelinating subtypes of the disease.

A high prevalence of antibodies to *C. jejuni* in the serum of patients with GBS have documented in other studies too [43,50–55].

In a large, blinded, case-control study of 118 GBS patients and 113 controls in the United States, GBS patients were more than five times as likely to have serologic evidence of a recent *Campylobacter* infection [56]. The association was detected using all three immunoglobulin classes, and it was observed in all age groups and in all seasons. However, it was most pronounced in those > 60 years old and during summer months. In this study, male patients also were more likely than female GBS patients to have evidence of preceding *C. jejuni* infection.

In a retrospective serologic study, Kaldor and Speed found that 38% of patients with GBS had a recent *C. jejuni* infection [48]. Saida et al. [56] showed among 205 Japanese GBS patients in their study, 44% had serologic evidence of recent *C. jejuni* infection, compared with 1% in healthy controls. Rees et al. [46] subsequently made a prospective case-control study of 96 patients with GBS and systematically examined all the patients and controls for evidence of *C. jejuni* infection. There was evidence of recent *C. jejuni* infection in 26% of the patients with GBS, compared with 2% of the household controls (a member of the patient's household) and 1% of the age-matched hospital controls. In a British prospective study, 14 of 99 (14%) patients with GBS had serological evidence of *C. jejuni* infection, compared with only 2% of the controls [52] and finally Anti-GM1b antibody was present in 22 of 104 cases investigated by Yuki et al. [57]. Of 132 patients with GBS, 25 (19%) had anti-GM1b antibodies. IgM antibodies were present in 14, IgG antibodies in 15, and both in four patients. The 25 patients with anti-GM1b antibodies had a clinical pattern distinct from that of the other 107 GBS patients, more frequently showing serological evidence of recent infection by *C. jejuni* [57].

8. OTHER EXPERIMENTS

Numerous reports showed developing of GBS after injecting bovine brain ganglioside. This indicates that an antecedent infectious agent with a ganglioside-like structure can causes this syndrome. The lipopolysaccharide which was extracted from the *C. jejuni* isolated from a patient with GBS who had anti-GM1 IgG antibody reacted with cholera toxin [9]. It could be purified by column chromatography [58]. The oligosaccharide structure (Gal _1-3 GalNAc _1-4 [NeuAc _2-3] Gal_) protrudes from the LPS core was showed by nuclear magnetic resonance. This terminal structure is similar to the terminal tetrasaccharide of the GM1 ganglioside. This was the first report that showed the molecular mimicry between human nerve tissue and an infectious agent isolated from a patient with GBS [21].

The oligosaccharide structures of GM1-like and GD1a-like LPSs were clarified in a *C. jejuni* strain from an enteritis patient [59-61]. The *C. jejuni* LPS induced anti-GM1 IgM antibody in rats, but they did not show muscle weakness [62]. Ang et al. [63] immunized rabbits with *C. jejuni* LPS from GBS-associated strains bearing a GM1 epitope.

All the animals produced high anti-GM1 IgG antibody titres, but none developed overt signs of muscle weakness.

Clinical symptoms in animals are induced by immunization with gangliosides or with purified *Campylobacter* lipo-oligosaccharides. The experiment providing ultimate proof for the molecular mimicry hypothesis in GBS would consist of the induction of cross-reactive antibodies and clinical symptoms following experimental oral infection with a *Campylobacter* strain bearing a ganglioside mimic, whereas infection with a mutant strain lacking only the ganglioside mimic leaves the animals unaffected.

Other animal studies have also shown that immunization and infection with *C. jejuni* or purified LOS result in a cross-reactive anti-ganglioside and LOS response [63,64]. As expected, the specificity of the anti-ganglioside antibodies in the animals was similar to the specificity in GBS patients from whom these *Campylobacter* strains were derived [63]. This forms strong evidence that the ganglioside autoantibodies in humans can be induced by molecular mimicry between *Campylobacter* LOS and gangliosides. The immunized and infected animals did not develop neuropathy but the anti-ganglioside antibodies generated in animals share pathogenic properties with human GBS sera [64]. Rabbits sensitized with a bovine brain ganglioside mixture containing GM1, GD1a, GD1b, and GT1b, developed high anti-GM1 IgG antibody titres and flaccid limb weakness of acute onset; moreover, they had a monophasic illness course [65,66].

In an animal experiment, the production of paralytic neuropathy in chickens experimentally fed *C. jejuni* isolated from a patient is reported. An average of 33% of the chickens became paralyzed. The median time after inoculation to paralysis was 12 days [67], indicating that the experimental inoculation with *C. jejuni* may provide a new model for understanding different forms of GBS.

9. ROLE OF *C. jejuni* INFECTION IN GBS

Gangliosides are highly expressed in nervous tissues and are considered as cell surface molecules implicated in various biologic cellular functions. There have been several reports of motor neuron disease and multifocal motor neuropathy associated with IgM antibody to GM1 ganglioside [68,69]. The molecular mimicry between infectious agents and gangliosides may function in the production of anti-ganglioside antibodies. This sugar mimicry is one possible cause of the GBS and MFS; however, unidentified host factors may contribute to the development of these syndromes [70]. GBS is suggested to be provoked by molecular mimicry between sialylated lipooligosaccharide (LOS) structures on the cell envelope of these bacteria and ganglioside epitopes on the human peripheral nerves, resulting in autoimmune-driven nerve destruction [70]. Earlier, the *C. jejuni* sialyltransferase (Cst-II) was found to be linked to GBS and demonstrated to be involved in the biosynthesis of the ganglioside-like LOS structures. Apart from a role in pathogenicity, it seems that *Cst-II*-generated ganglioside-like LOS structures confer efficient bacteriophage resistance in *C. jejuni* [71].

Terminal structure of *C. jejuni* LPS is identical to the terminal tetrasaccharide of the GM1 ganglioside. Aspinall et al. [59] firstly demonstrated the existence of molecular mimicry between nerve tissue and the infectious agent isolated from a GBS patient in 1994. Later, a hyaluronic acid–like repeat unit of LPS was reported as an antigenic determinant of PEN 19 [72]. Glycosaminoglycans, including hyaluronic acid, may play an important role in the development of autoimmune diseases [73].

MFS, a variant form of GBS, is characterized by ophthalmoplegia, ataxia, and areflexia. Sera from patients with MFS have IgG anti-GQ1b antibody during the acute phase of the illness [74–76]. The existence of molecular mimicry between GM1 and lipopolysaccharide of *C. jejuni* isolated from a GBS patient and that between GQ1b and *C. jejuni* lipopolysaccharides from patients with MFS are shown by Yuki [77]. Ang et al. [78] also showed that *C. jejuni* isolated from GBS patients more frequently had a GM1-like epitope than isolates from MFS patients. GQ1b-like epitopes were present in all MFS-associated isolates and was associated with anti-GQ1b antibody reactivity and the presence of oculomotor symptoms. These results demonstrate that the expression of ganglioside mimics is a risk factor for the development of post-*Campylobacter* neuropathy [78].

It seems that antibody reactivity against GM1, GM1b, and GalNAc-GD1a is associated with pure motor GBS [79-81] and as it is noted that anti-GQ1b antibody reactivity showed a strong association with oculomotor symptoms and

ataxia [81]. Polymerase chain reaction–based restriction fragment length polymorphism analysis of an *flaA* gene showed that all HS-19 isolates, regardless of a GBS association, had an identical and distinguishable pattern, *Cj-1*, suggesting that HS-19:Cj-1 isolates are distinctive among *C. jejuni* isolates. Lectin typing showed that all GBS-associated HS-19 isolates contained terminal b-*N*-acetylglucosamine residues on their cell surface, but HS-19 isolates from patients with enteritis did not [56].

Kuroki et al. [45,82] reported a possible association between GBS and Penner's heat-stable diagnostic (HS) O serotype HS-19, a rare serogroup in diarrheic patients without neurologic disease. In Beijing, 62% of 46 GBS patients had serologic evidence of *C. jejuni* infection, compared with 9% of healthy controls [83], and in Shijiazhuang, Hebei Province, 66% of 38 GBS patients had serologic evidence of *C. jejuni* infection, compared with 16% of village controls. Studies from Australia [43] and the United States [84] also found high frequencies (38% and 36%, respectively) of *C. jejuni* infection in patients with GBS.

A model of AMAN associated with anti-GM1 IgG antibody has been established. Inoculation with GM1 may induce high anti-GM1 IgG antibody titres, the autoantibody thereafter binding to the GM1 expressed on rabbit peripheral nerve axons, thereby producing dysfunction of the motor nerves followed by Wallerian-like degeneration [85]. A similar mechanism may function in the development of AMAN subsequent to *C. jejuni* enteritis, but animal models showing limb weakness produced by sensitization with the GM1-like LPS are required to validate the molecular mimicry theory [21].

Serologic evidence of *C. jejuni* infection in 55 Chinese patients with clinically defined GBS was correlated with anti-GM1b and anti-GalNAc-GD1a IgG antibodies [86]. Ogawara et al. [32] showed that *C. jejuni* infection is frequently associated with AMAN or anti-ganglioside IgG antibodies. These findings suggest that three phenomena—axonal dysfunction, IgG antibodies against GM1, GD1a, or GalNAc-GD1a, and *C. jejuni* infection—are closely associated.

GM(1)- and GD(1a)-like ganglioside mimicry in *C. jejuni* lipooligosaccharide (LOS) has a significant role in the pathogenesis of Campylobacter-induced GBS. It seems that GBS-related *C. jejuni* isolates are more related to the expression of GD(1a)-like mimicry comparing to gastroenteritis-related isolates. The presence of some genes involved in LOS ganglioside mimicry, *cst*-II, *cgt*A, and *cgt*B, thought to be associated with GBS-related strains. It should be noted that expression of GD(1a)-like epitope may be an important virulence phenotype related to the risk of developing GBS after campylobacter infection.

Sialylated LOS are main antigen recognized by the immune system and it is very important to better understand the immune events leading to GBS. Heikema et al. [86] showed that GBS-associated *C. jejuni* strains bind to human sialoadhesin (hSn) that is a macrophage-restricted I-type lectin. They showed that *C. jejuni* strains with α(2,3)-sialylated LOS, especially strains expressing GM1a- and GD1a-like epitopes, bind to hSn. These results are important because these epitopes are the main targets of the cross-reactive antibodies detectable in GBS patients. It must be noted that the Sn binding domains are not constitutively exposed on the surface of *C. jejuni*. Food-borne *C. jejuni* usually encounter with extreme environmental conditions during its passage through the intestinal tract, such as low pH and contact with bile constituents. In this condition, Sn binding process can enhances bacterial uptake and increases the production of interleukin-6 (IL-6) by macrophages compared to control conditions, when nonsialylated *C. jejuni* was used. It is reported that Sn-mediated uptake can enhance humoral immune responses and Sn binding may be a promoting event in the production of cross-reactive antibodies and the development of GBS [86].

Heikema et al. [87] also showed that GBS-related *C. jejuni* strains usually bind to sialoadhesin (Sn) which is a sialic acid receptor found on group of macrophages. By using a whole-cell enzyme-linked immunosorbent assay (ELISA), they found that *C. jejuni* strains with sialylated LOS bound exclusively to soluble Sn. Study by mass spectrometry showed that binding was sialic acid-linkage specific with a preference for alpha(2,3)-linked sialic acid attached to the terminal galactose of the LOS chain (especially GD1a, GM1b, and GM3). This type of molecular interaction may also relate to the functional consequences as a GBS-associated *C. jejuni* strain that bound Sn in a whole-cell ELISA. This was the first report of the preferential binding of GBS-associated *C. jejuni* strains to the Sn immune receptor ($P = 0.014$). It must be noted

that this binding is dependent on sialylated LOS and is the main pathogenic factor in GBS progression. These findings bring us closer to unraveling the mechanisms of formation of cross-reactive antibodies in GBS disease [87].

Carbohydrate mimicry was seen between the lipo-oligosaccharide of *C. jejuni* isolated from an AMAN patient and human GM1 ganglioside and sensitization with the lipo-oligosaccharide of *C. jejuni* induces AMAN in rabbits as sensitization with GM1 ganglioside does. In addition, paralyzed rabbits showed pathological changes in their peripheral nerves similar to changes seen in human GBS [88,89].

10. CONCLUSION

Causal relationship between *C. jejuni* and GBS was hypothesized in 1982 based on a serial of case reports. Isolation of *Campylobacter* from the stool of GBS patients also supported this relationship, but it was assumed to underestimate bacterial presence because the lag time between initial infection to culture and also because of culture methodology that could influence recovery of the bacterium. Different methods of detection antibodies to *C. jejuni* have also been used to demonstrate presence of the organism in GBS patients, but cross-reaction with closely related bacteria is a main problem. Animal models have also supported the association of *C. jejuni* and GBS. High titers of antibodies that react against nerve cells have developed in rabbits and mice following injection of molecules similarly shaped to those of *C. jejuni* LPS and gangliosides. Now there are strong supports for the hypothesis that molecular mimicry between *C. jejuni* LPS and gangliosides plays a key role in the induction of antiganglioside antibodies and neurological symptomes in patients with GBS. The timing of GBS following *C. jejuni* infection suggests a humoral immunopathogenic mechanism.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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