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JOURNAL OF NEUROLOGY AND NEUROSCIENCE

2012
Vol. 3 No. 1:1
doi: 10.3823/325

Campylobacter jejuni-mediated Guillain-Barre Syndrome, an overview of the molecular mimicry and vaccine development approaches

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Abstract

Guillain-Barre syndrome (GBS) is an autoimmune disease in which body's immune system attacks the nervous system that leads to nerve inflammation causing muscle weakness. This syndrome affects people of both sexes between ages 25 and 50 years. It is not clear what exactly triggers GBS. However, *Campylobacter jejuni* is found to be the most common pathogenic factor that is found to trigger GBS and this is widely reported. Several of these studies have shown that surface lipopolysaccharide (LPS) present in *C. jejuni* may act as an antigenic factor that induces GBS. In addition, some of these reports have also suggested that in addition to the host cell and bacterial antigenic factor interactions, the molecular mimicry between *C. jejuni* LPS and peripheral nerve gangliosides may play a significant role in the development of GBS. Although LPS was recognized as a potent antigen by different studies, nevertheless, the antigenic diversity and the lack of clearly defined protective epitopes are major constraints in developing vaccines against *C. jejuni*. In this review, we will briefly overview the molecular mimicry mechanism, potential vaccine development strategies, the current successes and pitfalls in developing vaccines against *C. jejuni*-induced GBS.

Key words: *Campylobacter jejuni*; Guillain-Barre syndrome, Motor neuron, Vaccine development

Introduction

Guillain-Barre syndrome (GBS) is an autoimmune disorder of peripheral nerves and is characterized by ascending paralysis. In spite of several studies due to its clinically importance and worldwide distribution, the etiology of this disease is still not clear. This syndrome was first described in 1892 by Sir William Osler as "acute post infectious polyneuritis" [1]. There are three different extreme patterns of clinically defined GBS, as described by van der Meche [2]. It was observed that two third of the GBS patients developed the syndrome following a pathogenic infection. The pathogens that been ascribed to leading to this syndrome include bacteria such as *Cam-*

pylobacter jejuni, *Mycoplasma pneumoniae;* viruses such as hepatitis B virus, cytomegalovirus, various varicella-zoster virus, Epstein-Barr virus, rubeola and human immunodeficiency virus [3-7]. Interestingly, certain studies have suggested that vaccines against rabies, influenza, and swine flu vaccine may also cause GBS-associated conditions [8-10]. However, in response to the study by Hurwitz et al (1981), Lehmann et al (2010) suggested that there was no clear association between GBS and immunization [11]. Their justification was based on rationale that the Hurwitz et al (1981) study lacked a longitudinal epidemiological data involving both active or passive surveillance, monitoring the vaccine safety similar to the one following mass immunization programmes during and after the 2009 H1N1 pandemic [11].

The recent systematic review by Poropatich et al (2010) further strengthened the findings of previous reports on *Campylobacter jejuni* (*C. jejuni*) infection as the most recognized causative factor of GBS [12]. All the available reports have suggested *C. jejuni* to be a potential predictor of poor outcome in patients suffering from GBS, as this pathogen induce a severe autoimmune response leading to greater axonal damage [12-18]. This is in lines with the findings shared by scientists of different disciplines and clinicians from all over the world in the workshop on "Development of GBS following *Campylobacter* infection" in Bethesda, Maryland on August 26-27, 1996. Until now, no effective measures have come into effect to regulate *C. jejuni*-mediated GBS. However, certain learned school of thought believes that an effective vaccine development programme may provide a unique and successful preventive measure against *C. jejuni*-mediated GBS. They have been partially successful in this direction; however a safe and efficient vaccine programme for humans is still elusive. In this review, we briefly describe the *C. jejuni*-induced GBS, critically review the molecular mimicry hypothesis of *C. jejuni* mediated GBS, explore potential vaccine development approaches and discuss the impeding factors involved in the pursuit of safe and efficient vaccine development.

Guillain Barre Syndrome (GBS): symptoms and clinical spectrum

As mentioned earlier in this report that GBS is a neurological disease characterized by ascending paralysis, which can lead to respiratory muscle compromise and even death. Several reports have suggested a multitude of symptoms associated with GBS. These symptoms include muscle weakness and dysesthesias in the legs, which may subsequently spread to the arms and upper body. The spectrum of GBS can be described at least three levels: the clinical level, the level of antecedent infections and the level of immunologic disturbances [2,19,20]. The spectrum of clinical symptoms ranges from classical, largely motor, acute inflammatory demyelinating polyneuropathy (AIDP) to purely motor form called acute motor axonal neuropathy (AMAN), acute sensory neuropathy (ASN), and acute motor and sensory axonal neuropathy (AMSAN) and to the Miller Fisher syndrome (MFS) manifesting opthalmoplegia, ataxia and areflexia. [20]

Epidemiology and Economic impact of *C. jejuni* associated GBS

C. jejuni infection is much more common in developing countries than in developed countries. In almost all reported cases, males were commonly affected by GBS than females [19,67]. The age distribution is bimodal, with peaks in elderly as well as young adults between 15 and 30 years old and elderly [21]. The incidence is lower in children than in adults, with the highest incidence in the elderly [22]. The youngest patient reported was a 2 years old girl and the oldest patient was 83 years old woman [9]. Summer time outbreaks of GBS with primary axonal involvement (acute motor axonal neuropathy) are well described in China and also reported in Mexico, Spain and Korea. Familial cases of GBS are almost unknown [29]. The US Centers for Disease Control and Prevention estimates that there are 1000 cases of *C. jejuni* infection per 100,000 every year [23]. The number of symptomatic *C. jejuni* infections has been estimated to be ~2.5 million per year in the United States. The incidence of reported infections is slightly higher in males than in females [24]. The annual percentage of *C. jejuni*-associated GBS cases among the total GBS population in Japan was found to be in the range of 35-59% in 1990-1996, with the male to female ratio for all GBS patients was 2.2:1 [25].

Currently, the world statistics on economic burden of Campylobacter-associated GBS is not available. However, the epidemiological reports on Campylobacter-associated GBS suggest a significant economic burden to the healthcare system within the countries of European Union, United States of America and Australia [26]. In United States alone, the total medical costs associated with Campylobacter-associated GBS, is estimated to be $57.7-$420.5 million/year. According to the survey conducted in USA during 1995, the total lifetime medical and lost productivity costs due to Campylobacter-associated GBS have further inflated the estimates to $247.3-$1,799.2 million each year [16].

C. jejuni and the route of transmission in humans

C. jejuni is a microaerophilic, gram-negative, non-spore-forming bacterium with a characteristic S-shaped or spiral morphology. *C. jejuni* transmission to humans occurs by oral route and direct contact with infected animals, especially pets

[23]. The *C. jejuni* infection is zoonotic and the main route of infection is through ingestion of uncooked poultry, contaminated milk and water [23].

The association of *C. jejuni* with GBS and the role of lipopolysaccharide mediated autoimmune responses

The typing studies proved to be critical in our understanding of the epidemiology and pathogenesis of Campylobacter-associated GBS. Currently, two major serotyping schemes are employed worldwide, viz. Lior serotyping [27] and Penner serotyping [28]. These molecular typing studies have helped us answer the questions about genetic diversity of strains associated with GBS and determine whether certain pathogenic "clones" are responsible for eliciting GBS. By molecular typing, it was possible to determine the differences between strains, even with the same serotype, and help our understanding of the association of different pathologic forms of GBS. In this section we will explore some of the reports that provided us an insight into the C. jejuni-associated GBS and the role of LPS/LOS in eliciting autoimmune responses.

The N-acetylneuraminic (Neu5Ac, sialic acid),a characteristic component of many mammalian glycolipids and glycoproteins, was discovered in *C. jejuni* strains by Moran *et al.* in 1991 [31]. A recent study have also reported the strong association of *C. jejuni* lipopolysaccharides in conferring virulence and colonization potential, in humans and pets, by their ability to mimic a wide range of mammalian glycans [30]. The chemical studies on *C. jejuni* have revealed that structures in the terminal regions of the core oligosaccharides (OSs) of specific serotypes may mimic the structures of human gangliosides. Recently, Houliston et al (2011) have also reported that the lipopolysaccharides, Paragloboside (LNnT) and P-blood group related antigens were found in up to 10 – 15% of *C. jejuni* strains based on the abundance of class 'D' and 'F' loci, while sialylated non-ganglioside lipopolysaccharides expression were observed in less than 5% of strains [30]. The mimicry of gangliosides by *C. jejuni* LPS has been proposed as a mechanism of disease whereby the immune-mediated response to *C. jejuni* epitopes elicits the production of cross-reactive anti-ganglioside antibodies which target and damage the neural cells and tissues bearing gangliosides. The supportive findings for the hypothesis of molecular mimicry suggest that the most frequently isolated LPS/LOSs of *C. jejuni* associated GBS were GM_1 and GD_{1a}-bearing structures [32] and that the anti-GM_1 antibodies are the most frequently observed antibodies in GBS. In addition, other *C. jejuni* LPS/LOSs bear structural resemblances to that of GD_3, GM_2, GM_3, and GT_{1a} gangliosides. In addition, there is a strong, combined clinical and serologic evidence that suggests anti-ganglioside antibodies are significantly associated with GBS [33]. So it has been hypothesized that GBS may arise as a result of the production of antibodies to *C. jejuni* LPS due to molecular mimicry, cross-reaction with gangliosides or other structure present in peripheral nerves [32]. The serological studies appear to consistently support and contest the molecular mimicry hypothesis. However, studies have documented high prevalence of antibodies to *C. jejuni* in the serum of patients with GBS [17] as well as high prevalence of antibody (IgG anti-GM_1) to *C. jejuni* in the serum of GBS patients in acute phase of the illness [34]. Interestingly, these antibodies were not detected in patients with *C. jejuni* enteritis that was not followed by GBS [35-37]. In addition, patients with the pure motor form of GBS had more anti-GM_1 antibodies present in their blood stream, preceding *C. jejuni* infection, as opposed to patients with other neurological diseases or normal control [38]. These contrary findings may be an understatement of the molecular mimicry, as triggering factors for GBS initiation, suggesting that a highly complex mechanism of antibody generation in GBS patients. Oomes *et al* (1995) demonstrated that anti-ganglioside antibodies in GBS sera recognized surface epitopes on whole *C. jejuni* bacteria in a strain-specific fashion [39]. While Schwerer *et al.*(1995), and Moran *et al* (1996) showed that IgA antibodies from the *C. jejuni*-infected patients recognized GM_1 and *C. jejuni* HS:2, HS:4, and HS:19 LPS [40-41].Serum IgG from a patient who developed GBS after parenteral administration of gangliosides cross-reacted with the serotype HS: 2, HS: 4, HS: 19 and HS: 41 LPSs and this was absent in a preceding infection with *C. jejuni*. This clearly demonstrates that gangliosides and LPS from *C. jejuni* GBS-associated serotypes may cross-reactive.

Earlier studies including Hughes and Rees (1997) reported with a strong statement that while *C. jejuni* infection is not the only etiologic factor, however it is responsible for about one-fourth of all reported cases of GBS [9]. Moreover, Kaldor and Speed (1984) found that 38% of patients with GBS have had a recent *C. jejuni* infection [13]. In support of this study, Kuroki *et al.* (1991) and Yuki *et al.* (1992) have shown that a specific Penner's serotype (PEN) PEN19 (HS: 19 or O: 19) was frequently isolated from GBS patients [14, 15]. The strongest association of *C. jejuni* O:19 infection and GBS is also reported by Lang *et al.* (1997) [16]. Besides the clonality of HS: 19, a clonal population of HS:19 strains, reported by Nachamkin *et al.* (2001) and the great diversity in thermostable antigens of *C. jejuni* may suggest that the species were unique in the microbial world [66]. Initial studies on the cross-reactivity of anti-ganglioside antibodies with *C. jejuni* LPSs demonstrated that anti-GM_1 antibodies reacted with *C. jejuni* HS: 19. The presence of GT_{1a} and GD_3-like epitopes in HS: 19 LPS were also confirmed serologically. Moreover, IgM anti-GM_1 monoclonal antibodies (mAbs) from patients with chronic motor neuropathy were found to react with LPS of *C. jejuni* HS: 4, HS: 19 and HS: 50 serostrains. In addition, these exclusive

antibody reaction with the core OS were demonstrated, providing us the first conclusive evidence that it is the core OS of LPS, not the lipid A or polysaccharide moiety, to which these antibodies bind [16, 21]. High levels of anti-GQ_{1b} antibodies were detected in most patients suffering from Miller Fisher syndrome (MFS), a variant of Gullian-Barre Syndrome [43]. There are reports suggesting the cross-reactivity of GQ_{1b} ganglioside and LPS/LOSs from *C. jejuni* HS: 2 and HS: 23 strains [64]. However, no neuropathy associated LPS were chemically characterized to date that bears resemblances to a full GQ_{1b} structure. The finding of GD_2/GD_3 ganglioside mimicry in a *C. jejuni* HS: 23 may be relevant because GD_3 bears the terminal trisaccharide Neu5Acα2- 8NeuAcα2-3Gal, and this is identical to the terminal of GQ_{1b} ganglioside, a moiety that is repeated internally. Thus, the repeated finding of ganglioside epitopes in *C. jejuni* LPS/LOS by their cross-reactivity with GBS anti-ganglioside serum may be interpreted as further justification of the findings that molecular mimicry may determine the neuritogenicity of *C. jejuni*.

Molecular mimicry of gangliosides by *C. jejuni* LPS/LOS moieties

Penner and Aspinall (1997) classified the LPS antigens into 3 major classes, Class 1- complete LPS molecule; sialylated core oligosaccharide with covalently linked O chain, (O:4, O:19, O:23 and O:36), Class 2-lipooligosaccharide(LOS) type molecule, sialylated core oligosaccharide(OS); no O chain (O:1,O:2) and Class 3-nonsialylated core OS with polysaccharide polymer not linked to core oligosaccharide, (O:3). In addition, further structural analysis studies have shown that the outer core of *C. jejuni* O:19 LPS, including those from GBS-associated isolates, contain terminal tetra- and pentasaccharide moieties identical to those of GM_1 and GD_{1a} gangliosides, respectively (see **Figure 1**) [32,44-47]. In addition, the terminal hexasaccharides and trisaccharides of the LPS from some GBS-associated *C. jejuni* O:19 isolates were observed to have molecular mimicry to GM_1, GT_{1a} and GD_3 gangliosides [46, 64].

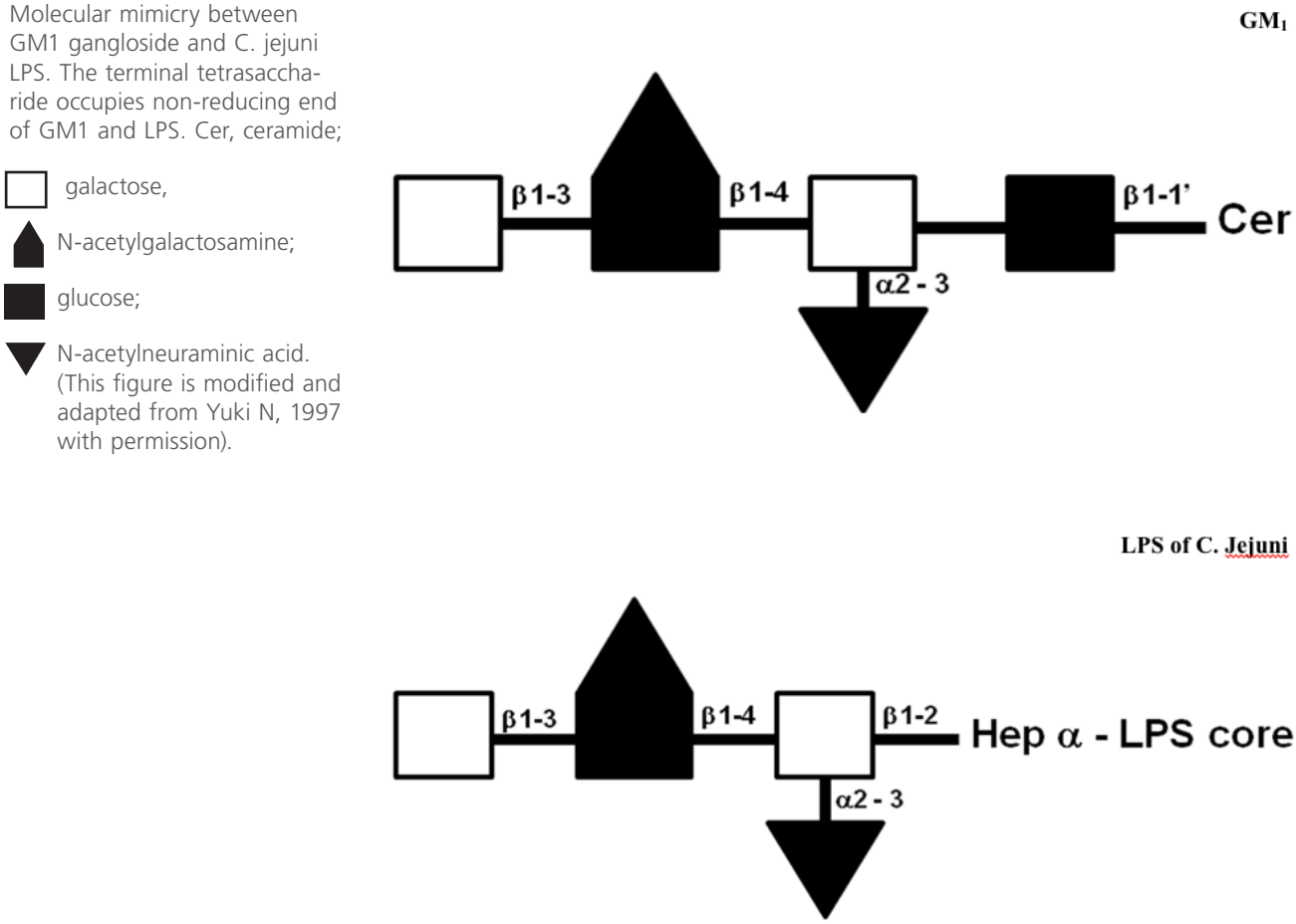

Figure 1. Molecular mimicry between GM1 gangloside and C. jejuni LPS. The terminal tetrasaccharide occupies non-reducing end of GM1 and LPS. Cer, ceramide;

- galactose,
- N-acetylgalactosamine;
- glucose;
- N-acetylneuraminic acid.

(This figure is modified and adapted from Yuki N, 1997 with permission).

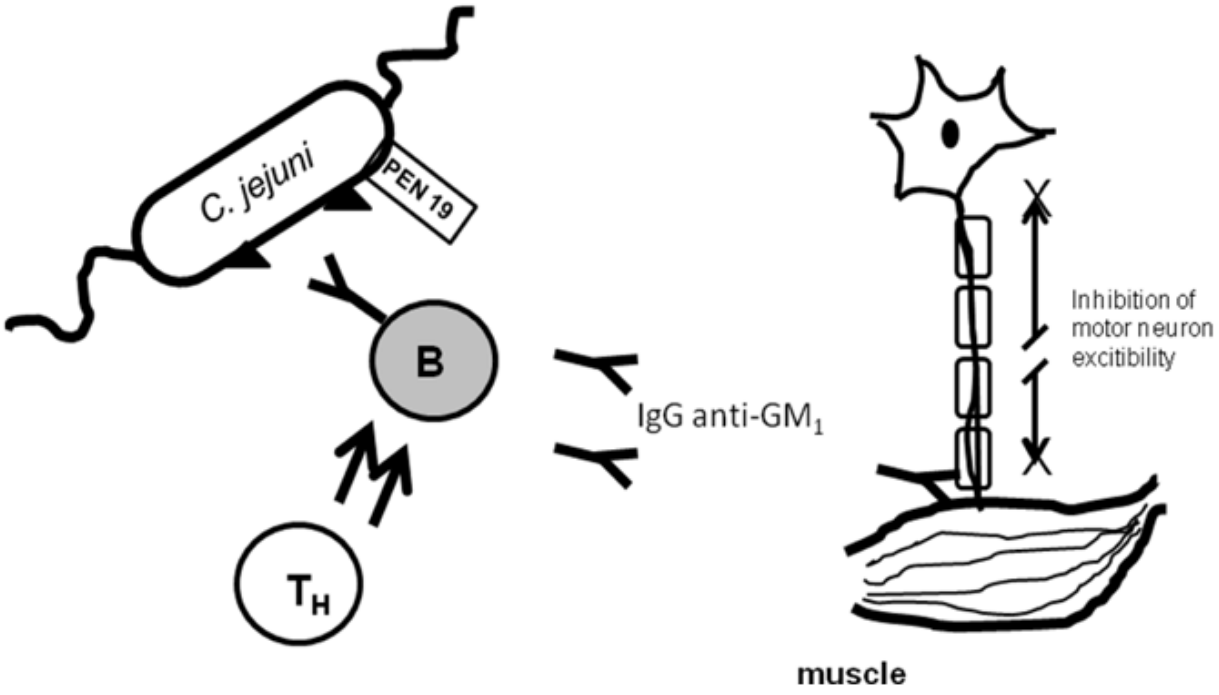

Figure 2. Pathogenesis of GBS associated with IgG anti-GM1antibody subsequent to C. jejuni enteritis. C. jejuni that bears GM1- like LPS associated with antigenic determinant of Penner's serotype 19 (PEN 19) induces higher production of IgG anti-GM1 antibodies through the aid of helper T cells (TH). The IgG anti-GM1 antibodies then bind to motor nerve terminal axons inhibiting motor neuron excitability which in turn cause muscular weakness. (This figure was adapted and modified from Yuki, 1997 with permission)

Mechanism of the development of GBS after *C. jejuni* infection

In this section we will elaborate on the mechanism involved in the development of *C. jejuni* associated GBS. This is based on the earlier studies on the molecular mimicry between the surface components of peripheral nerves (gangliosides) and infectious agents isolated from patients of GBS. Yuki *et al* (1992) showed that the purified LPS contained galactose and N-acetylgalactosamine(GalNAc) and N-acetylneuraminic acid (NeuAc), which are sugar components of GM_1 ganglioside. Also the terminal structure (Gal β1-3 GalNAc β1-4 [NeuAc α2-3] Gal β) is identical to the terminal tetrasaccharide of the GM_1 ganglioside (**Figure. 1**) [15]. Yuki (1997) placed the hypothesized that this molecular mimicry between gangliosides and lipopolysaccharides (LPSs) of *C. jejuni* plays the vital role in the pathogenesis of GBS [32]. GBS may arise as a result of the production of antibodies to *C. jejuni* LPS, which through molecular mimicry results in generating antibodies against GM_1, these then cross-reacts with gangliosides or other structures present in the peripheral nerves (see **Figure 2**). In the same report, his research team has also shown the mechanism of antibody production against ganglioside epitope and the role of T helper cells in the production of anti-GM_1 antibody [32]. Molecular mimicry between LPS of *C. jejuni* and GM_1 ganglioside and the presence of a hyaluronic acid-like repeat unit of *C. jejuni* LPS helps this GM_1 -like LPS to induce the production of the IgG anti- GM_1 antibody and the subsequent development of GBS (**Figure 1**) [32,48,45]. Specific Penner serotype PEN19 (O:19 or HS:19) was most frequently isolated from GBS patients [14, 15]. Isolation of LPS from O: 19 showed that the LPS has the GM_1 epitope [32,49]. It has been reported that presence of anti-ganglioside antibody in blood after *C. jejuni* infection in GBS patients and bovine ganglioside infection may also cause GBS [49].

In contravening the hypothesis of Yuki 1997, Moran and Prendergast (1998) argued specifically that high expression of the hyaluronic-like O chain may be more important for the development of GBS rather than the molecular mimicry per se [51]. Moran and Prendergast (1998) examined the expression of the O chain in 2 enteritis and 2 GBS isolates of *C. jejuni* O:19. They showed that the chemical liberation and purification of O chains gave higher yields from LPS of GBS than of enteritis-associated isolates [51]. In addition, Moran and O'Malley (1995) showed that the LPS core of a *C. jejuni* O:19

isolate from a patient with enteritis without GBS, exhibited mimicry of GM_1 and GD_{1a} oligosaccharides. Moreover, the molecular mimicry is not restricted to *C. jejuni* O:19, isolates of other *C. jejuni* serotypes obtained from GBS patients exhibit mimicry of GM_1 and other gangliosides [41]. Thus they proclaimed that since both the GBS-and enteritis-associated isolates in their study exhibited ganglioside mimicry, differences in the extent of expression of the hyaluronic acid-like O chain, may play the vital role in the development of *C. jejuni*-associated GBS.

However, a seminal report by Yuki et al (2004) supporting his previous hypothesis on molecular mimicry and GBS initiation in an animal model was published [50]. In their study, when the Japanese white rabbits were sensitized with *C jejuni* lipooligoasaccharides containing GM1 epitope, it induced the production of pathogenic autoantibodies that can lead to peripheral neuropathy similar to GBS-associated condition. The same study also found indirect evidence to the fact that the nature of GM1-oligosaccharide structure may be important in the development of GBS. It is this finding that may have some relevance to the earlier report of Moran et al (1996) in which the difference in the extent of expression of oligosaccharide structure in *C jejuni* associated GBS rather than molecular mimicry mechanism postulated by Yuki et al (1991) that form the basis of GBS initiation. In lines with Moran et al (1996), Caporale et al (2006) appeared to suggest that only 1/1000 of *C jejuni* enteritis developed GBS, also contesting the hypothesis that molecular mimicry between glycolipid antigens expressed in *C jejuni* and human peripheral nerve may induce GBS [52]. However, Caporale et al (2006) emphasized on the importance of host-related factors in the development of the disease and proposed an alternate hypothesis that the polymorphism of CD1 molecule, a MHC-like glycoproteins specialized in capturing and presenting the glycolipid to antigen-specific T-Cells, may determine the susceptibility to develop GBS. However, another research group could not conclusively prove this hypothesis as they found no correlation between CD1 polymorphism, antecedent infection and GBS [53]. In spite of the several studies that support and disproves the molecular mimicry hypothesis, the common consensus is that an intricate highly complex molecular pathway in lines with molecular mimicry may be involved in *C jejuni* initiated GBS. However, the recent advances in glycobiology, proteomic, kinomic and genomic analysis method, along with a more multidisciplinary approach may help determine the exact mechanism of *C. jejuni*-associated GBS and other GBS-related conditions.

Current treatment or prevention measures

So far, the possible symptomatic treatments of *C. jejuni*-associated enteritis include extensive antibiotic based therapy, mechanical ventilation, plasma exchange (PE) and intravenous immunoglobulin injection (IVIG). The antibiotics are only effective during the primary stages of the infection for the symptomatic treatment of diarrhoeal illness. However, they are not effective in preventing GBS following an antecedent infection. PE and IVIG treatment were reported to be equally effective in hastening the recovery from GBS. Though PE is found to carry greater risk of side-effects and the American Academy of Neurology (AAN) does not recommend combining both these treatment options. However, studies have shown that there are differences between the treatment effects of PE and IVIG within a cluster of patients who suffer from pure motor syndrome. In these group of patients, IVIG treatment with anti-GM1 antibody or *C. jejuni* antibody were more effective than PE treatment alone [37,38].

Other possible preventive measures from infection with *C. jejuni* and GBS induction include avoiding uncooked poultry, contaminated water, unpasteurized milk, direct contact with pets, infected person, maintaining proper sanitation and taking precaution while traveling to *Campylobacter* endemic areas. However, successful vaccine development may still be an unique and effective preventive measure against *C. jejuni* associated GBS.

C. jejuni vaccine development, strategies and major constraints

The development of vaccine against *C. jejuni* may be feasible due to number of epidemiological reports, its economic impact and current lack of effective treatment. However, the development of vaccine may be complicated by the tremendous antigenic diversity of *C. jejuni* and by the fact that the protective epitopes are yet to be clearly defined.

It is widely believed that for a vaccine to be effective against an enteric agent such as *C. jejuni*, it must be able to stimulate intestinal immunization [54-57, 68]. Historically, several approaches to develop an oral based vaccine were explored.

Live attenuated vaccines: Using genetic approach to develop a live attenuated Campylobacter vaccine is an attractive approach [58]. But this approach is complicated by the paucity of information on pathogenesis and physiology of this organism. Interestingly, Buckley et al (2010) demonstrated that this approach could be possible, as they tested this approach by vaccinating Light Sussex chickens with *Salmonella enterica* serovar Thyphimurium DeltaaroA vaccine expressing the *C jejuni* amino acid binding proteins CjaA, Peb1A, GlnH or ChuA as a plasmid-borne fusion to the C-terminus of fragment C of tetanus toxin (TetC-CjaA, TetC-Peb1A, TetC-GlnH or TetC-ChuA) [59]. They found that vaccine with DeltaaroA strain of a TetC fusion to Peb1A (TetC-Peb1A) elicited protection against intestinal colonisation by *C. jejuni*.

Sub-unit vaccines: Two Campylobacter antigens, flagellin and a protein called PEB1, have been suggested as subunit vaccine candidates for use either as purified recombinant proteins or by expression in carrier vaccine strains, such as live attenuated Salmonella or Shigella species [60,61] . The antigenic diversity of *Campylobacter* flagellins, coupled with the fact that these eubacterial proteins are glycosylated, may make the development of flagellin subunit-based vaccines highly problematic, as several studies (as discussed earlier) have shown how glycosylated proteins such as hyaluronic acid may elicit different immune responses in humans.

The other protein that has been suggested as potential subunit-based vaccine target is PEB1, a highly immunogenic protein conserved among *C. jejuni* isolates that has also been suggested to function as an adhesion to eukaryotic cells [62]. As more is understood about the pathogenesis of *Campylobacter* species, it is likely that additional conserved subunit targeted proteins will be identified.

*Killed WC vaccine*s: Inactivated microorganisms offer several advantages as potential vaccines for mucosal immunization [61]. They should enhance interactions between their surface and mucosal lymphoid tissues. As vaccines, they are inexpensive to produce and possess multiple antigens that can be important for conferring protection. The formulations can be modified to enhance protection against prevalent serotypes over time as is done for influenza virus vaccines. The presentation of multiple antigens may be particularly important for pathogen like *Campylobacter* species, for which protective antigens are yet to be known or these antigens are not available in recombinant forms. The Enteric program at Navy Medical Research Institute (NMRI) have studied the hypothesis that a killed WC vaccine against *Campylobacter* species could be safe, immunogenic, and protect against disease, particularly if combined with an effective mucosal adjuvant , such as *E.coli* heat-labile toxin (LT) [18,63].

Future exploration

Current animal models of *Campylobacter* enteritis with ensuing GBS may help understand the pathophysiological mechanism of GBS and may help pave the way to define or discover protective epitopes that confer *C. jejuni*'s virulence capacity, the killed WC (whole cell) vaccine of *C. jejuni* 19 may be used to study vaccine development approaches. The molecular mimicry hypothesis/theory has been proven by Yuki and his team using animal models. However it is absolutely necessary that a through structural studies of surface antigens of all causative agents for GBS in human neuronal cell gangliosides is still to be determined. A large-scale investigation is imminent to establish the hypothesis that the high expression of hyaluronic like O chain may play an important role in the development of *C. jejuni* associated GBS, however the genetic diversity of both host immune system and antigenic factors of the pathogens is yet to be established.

Interestingly, the development of GBS is rare in children < 2 years of age despite their susceptibility to *C.jejuni* infection. This may indicate that particular maturation of the immune system or neural antigens or receptors are needed for GBS to manifest itself. Since, the trisaccharide is a feature that distinguishes neuropathic from non-neuropathic strain and it is conceivable that the trisaccharide could be an important epitope in pathogenesis [42]. Hence, more investigation is needed to determine the acquisition of the enzyme α-2,-8-sialyltransferase and its activation and regulation. Since O:19 (PEN19 or HS-19) is the main target of GBS neuropathic manifestation because of its ability to generate anti- GM_1 antibodies, clonality potential and its reported involvement with GBS being maximal [33]. However, the presence of anti- GM_1 antibodies is not only concentrated with *C. jejuni* alone [33] but also in presence of other infectious agents such as CMV, *M .pneumoniae* as reported by Hao *et al.* [65]. Therefore, the comparative structural studies of O:19 antigen with others may correlate the both hypothesis discussed earlier. Further research is necessary to clarify the mechanism of immune-mediated nerve damage which is still poorly understood.

Concluding remarks

A concrete multidisciplinary approach incorporating advance proteomic, kinomic and genomic techniques may help further explore the molecular mimicry hypothesis and characterize the *C. jejuni* LPS/LOS, the genetic diversity of the organism, and host immune components that trigger autoimmune response following infection. Though *Campylobacter* vaccine development will be a unique measure to prevent *C. jejuni*-induced GBS. A common and clearly defined antigenic determinant that facilitates development of a stable vaccine against *C. jejuni*-induced GBS is yet to be characterized. This may hinder the development of safe and effective vaccines against *C. jejuni* infection in humans.

Acknowledgements

The authors are grateful to Dr. Debabrata Biswas, Department of Animal and Avian Sciences, University of Maryland for his fruitful discussion and critical reading of this manuscript.

Conflict of interests

The authors declare that they have no conflict of interest.

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