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Current focus

Chronic effects of *Campylobacter* infection

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Abstract

Campylobacter jejuni is one of the most common causes of bacterial gastroenteritis and chronic sequelae, such as reactive arthritis and Guillain-Barré syndrome (GBS), are known to follow uncomplicated infections. While little is known about reactive arthritis following *Campylobacter* infection, our knowledge on the pathogenesis of *Campylobacter*-induced GBS is expanding rapidly and is summarized in this review.

Keywords: *Campylobacter*; Guillain-Barré syndrome; Post-infectious polyneuropathy; Gastrointestinal infections; Autoimmune diseases

1. Introduction

Despite over 25 years of research, we still have little understanding of how the extremely common gastrointestinal pathogen, *Campylobacter jejuni*, causes disease. Clinically, *C. jejuni* causes gastroenteritis that is generally indistinguishable from other infections caused by common enteropathogens, such as *Salmonella* and *Shigella*. However, *Campylobacter* appears to have developed a unique set of pathways in its pathogenesis that make this an interesting bug to study. Recent surveillance data suggest that nearly 2.4 million infections occur annually in the US, surpassing salmonellosis and shigellosis [1].

Chronic sequelae following *Campylobacter* infection manifest as either rheumatologic disorders (i.e. reactive arthritis) or peripheral neuropathies. Reactive arthritis following infection has been reported in numerous case reports or series and was recently reviewed by Skirrow and Blaser [2]. Little is known about the pathogenesis of *Campylobacter*-induced rheumatologic disease and therefore, will not be discussed in this review.

In addition to causing acute gastroenteritis, *Campylobacter* is now recognized as the most identifiable infection preceding Guillain-Barré syndrome (GBS), an acute, post-infectious immune-mediated disorder affecting the peripheral nervous system. In the post-polio era, GBS is now considered to be the most common form of acute flaccid paralysis [3]. Research into this association has received wide attention during the past few years, and the National Institutes of Health convened a special conference devoted to this topic in 1996 [4]. Advances in our understanding of *Campylobacter*-induced GBS have enabled far reaching insights into the biology of the organism as well as offering opportunities to better understand host factors and autoimmunity. This review will summarize some of the major concepts in our current understanding of *Campylobacter* and GBS, and is not meant to be an exhaustive review.

2. *Campylobacter* is the most identified infection preceding the development of GBS

GBS is frequently preceded by a number of infectious processes including bacterial and viral infections in the majority of cases. The recognized agents involved in infection or immunization preceding GBS are the following: *C. jejuni*, *Mycoplasma pneumoniae*, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, and vaccines (rabies, swine influenza) [5]. Although numerous microbial agents have been reported to be associated with the development of GBS, only *Campylobacter* is firmly established as a trigger of GBS based on case-control studies and biologic evidence. *C. jejuni* has been isolated from approximately 15% of patients with GBS (range 6–100%) [6]. Combined with serologic evidence of infection, 30–40% of patients with GBS have evidence of *Campylobacter* infection. Several studies suggest that patients with *Campylobacter* infection preceding GBS have a particularly serious

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outcome, even after taking into account other prognostic factors [5].

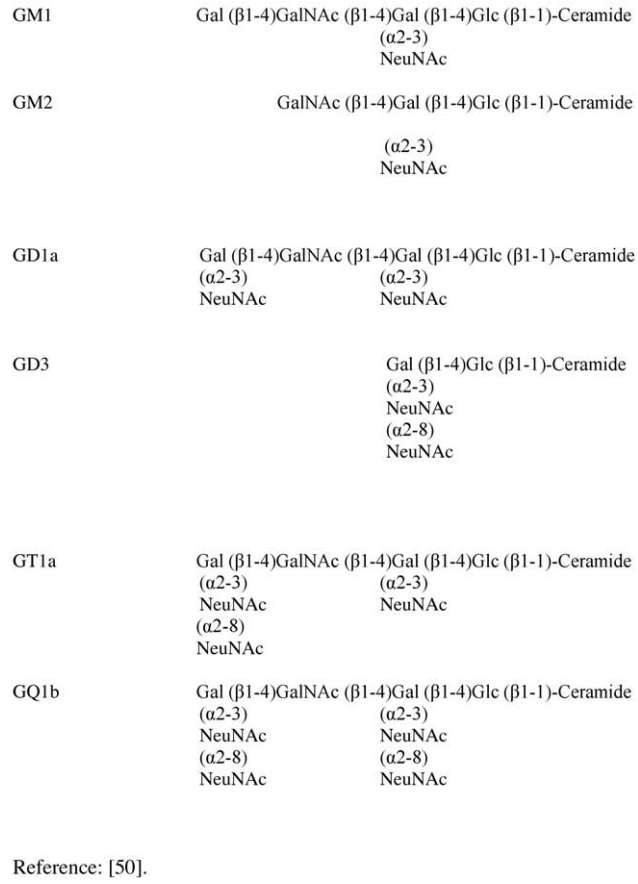
3. Development of GBS following *Campylobacter* is linked to certain strains

In addition to clinical studies, there is strong biologic evidence supporting the role of *Campylobacter* in the pathogenesis of GBS. In 1993, Kuroki et al. [7] described a prospective study of 46 Japanese patients with GBS, in which *C. jejuni* was isolated from 14 patients (30.4%). Only 1.2% of a healthy control population had *C. jejuni* isolated from stool samples. Of 12 isolates studied by heat-stabile (HS) serotyping (Penner system), 10 isolates were serotype HS:19. This particular serotype was an infrequent serotype in patients with gastroenteritis, occurring in 1.7% of 1150 strains from patients in the region. Further studies in Japan by Yuki et al. [8] showed that HS:19 occurred in 52% of 31 isolates from patients with GBS compared with 5% of control isolates. In another study from Japan, Saida et al. [9] found HS:19 isolates in 12 of 16 culture-positive patients. Studies in northern China [10] and Mexico City [11] have also suggested that HS:19 is a unique serotype among patients with *Campylobacter*-induced GBS.

Another serotype, HS:41, has emerged as a unique pathogenic strain in the patients with GBS in Cape Town, South Africa [12]. Nine of 14 children with GBS had positive stool cultures for *C. jejuni* and two-thirds of the isolates were serotype HS:41. This was a very uncommon serotype in patients with enteritis, being detected in 0.1% of strains in 19 years. We recently isolated an HS:41 strain from a patient with GBS in Mexico City [11], thus it does not appear that this serotype is restricted to South Africa.

Other serotypes have been isolated in patients with GBS including HS:1, HS:2, HS:4, HS:5, HS:10, HS:16, HS:23, HS:37, HS:44 and HS:64 [6]. However, the over-representation of HS:19 or HS:41 serotype has not been observed in other studies, particularly by the European GBS study groups [13,14]. Application of molecular techniques such as flagellin restriction fragment length polymorphism, randomly amplified polymorphic DNA and amplified fragment length polymorphism analysis suggests that HS:19 and HS:41 strains are a clonal population [15–17]. In an analysis of HS:19 strains by multilocus enzyme electrophoresis, we recently found that HS:19 strains comprise a clonal, but not a monomorphic population distinct from non-HS:19 strains [18]. While the majority of HS:19 strains were contained within a single clone, ET4, a unique clone associated with GBS was not identified.

The molecular basis for Penner serotyping has now been elucidated. Until recently, this serotyping system was thought to detect determinants in lipooligosaccharide (LOS). However, Karlyshev and colleagues have demonstrated that a capsular polysaccharide, not LOS, is the likely determinant in this serotyping scheme [19].



Reference: [50].

Fig. 1. Human ganglioside structures of particular interest in *Campylobacter* biology.

4. Molecular mimicry in *Campylobacter*

Patients with GBS frequently develop serum anti-ganglioside antibodies [3]. Gangliosides are glycosphingolipids characterized by the presence of sialic acid (*N*-acylneuraminic acid) linked to the oligosaccharide core [20]. They are classified commonly by letters referring to the number of sialic acid moieties, i.e. M (-mono), D (-di), T (-tri), Q (-quad) (Fig. 1). Certain gangliosides, such as GM1, are localized in peripheral nerve tissue [21] and these sites may be the target of an immune-mediated attack by pathogenic antibodies [3].

Several studies have linked certain anti-ganglioside antibodies with different forms of GBS. For example, anti-GD1a antibodies have been found to be primarily restricted in patients with acute motor axonal neuropathy (AMAN), the predominantly motor form of GBS [22–24]. Miller Fisher syndrome, considered in the clinical spectrum of GBS, is highly associated with the presence of anti-GQ1b antibodies [20].

The role of anti-ganglioside antibodies in the pathogenesis of GBS is not entirely clear, but complement-mediated antibody damage to peripheral nerve myelin and axons has been demonstrated in elegant pathologic studies by Hafer-Macko et al. [25,26]. More recent studies by Goodyear et al.

[27] showed that antibodies reactive with GQ1b, GT1a and GD3 caused neurotransmission block in an ex vivo muscle–nerve model.

How do these antibodies develop following *Campylobacter* infection? Moran et al. [28] first described the presence of sialic acid in LOS of *C. jejuni*. Subsequently, Yuki et al. [29] and Aspinall et al. [30] provided structural analysis of the LOS core region in serotype HS:19 and found ganglioside mimicry of relevance to GBS. This was followed by a series of biochemical and immunological studies on the core LOSs in a variety of *Campylobacter* serotypes (reviewed in reference [6]). Ganglioside mimicry was found in serotypes HS:1 (GM2), HS:4 (GD1a, GM1), HS:10 (GD3), HS:19 (GM1, GD1a, GD3, GT1a), and HS:23 (GM2). Ganglioside mimicry has not been found in type strain of HS:2 or HS:3.

Many structures within the peripheral nervous system are potential targets for damage by anti-ganglioside antibodies. To show that anti-*Campylobacter* antibodies with specificity for ganglioside epitopes were pathogenic, Goodyear et al. [27] raised monoclonal antibodies against *Campylobacter* LOS that expressed GT1a/GD3-like mimicry. These antibodies were tested for binding to peripheral nerve and the ability to block neurotransmission. Antibodies bound to motor nerve terminals as well as causing neurotransmission block in a muscle–nerve ex vivo model. These recent studies provide a very strong case for the pathogenicity of anti-ganglioside antibodies produced in response to *C. jejuni.*

Could other epitopes aside from ganglioside-like moieties be involved in molecular mimicry? Localization studies by Sheikh et al. [21] showed that axolemma surface of mature myelinated fibers and the Schwann cell surface contain Gal(β1-3)GalNAc binding sites and could be the target of cross-reactive antibodies from a response to other, yet to be identified, components of *Campylobacter*. *Campylobacter* flagellin (i.e. the subunit protein of the flagellar filament) has been shown to be glycosylated and involves, in part, the addition of a terminal sialic acid moiety [31–33]. Further, the genes involved in glycosylation of flagellin appear to be involved in glycosylation of other proteins as well [33]. Whether these structures are involved in mimicry with peripheral nerve targets is not known.

The molecular basis for ganglioside expression in *Campylobacter* is now coming to light. Gilbert et al. [34] recently identified several genes named *cst* (Campylobacter sialyltransferase) and *cgt* (Campylobacter galactosyltransferase), involved in the ganglioside mimicry with GT1a. They proposed that the role of *cst-I*, an α2,3-sialyltransferase, is to add the first sialic acid residue to a Gal-β-1,4-Glu backbone followed by the addition of a β-1,4-linked GalNAc by *cgt*A, a β-1,4-*N*-acetylgalactosaminlytransferase, to produce a GM2 type mimicry. The GM2 moiety is then elongated by *cgtB*, a β-1,3-galactosyltransferase, to give a GM1a type mimicry, and this serves as a substrate for either *cst-I* or *cst-II*, a bifunctional α-2,3/α-2,8 sialyltransferase to add additional sialic acid residues.

In addition to the above genes, Linton et al. [35] recently identified a sialic acid synthetase gene, *neu*B1, involved in sialyation of *Campylobacter* LOS. They suggest that *neuB1* is involved in the sialyation of LOS containing only a single sialic residue, as seen with GM1. Another gene, *wlaN*, a β-1,3-galactosyltransferase, with close similarity to *cgtB*, was also recently described and is involved in GM1 mimicry [36]. This enzyme is able to convert a GM2-like structure to a GM1-like structure by the addition of a terminal Gal to the core structure.

Linton et al. [36] also found that the phase variable expression of *wlaN* results in alternative expression of GM1 or GM2 type mimicry. Colony blots of *C. jejuni* NCTC11168 with cholera toxin (GM1 is the receptor for CT), showed primarily positive colonies, but a few CT negative binding colonies were observed. The *wlaN* gene contains a homopolymeric tract of either eight or nine G residues in length. When a tract of eight residues is present, a full-length gene product is produced (303 aa). However, with nine residues, there is a frameshift and truncated product (133 aa) and results in the loss of GM1 mimicry. Thus, a GM1 type LOS is produced in one phase, and a GM2 type LOS is produced in an alternate phase. Elucidation of this important finding was hastened by completion of the *Campylobacter* genome sequence, recently published by Parkhill et al. [37]. However, the biological implications of phase variation in these ganglioside mimics has yet to be determined.

5. Host factors are important in the development of GBS

Ganglioside mimicry in *Campylobacter* is an important factor in the pathogenesis of post-infectious GBS; however, it is not the entire story. Although there are certain serotypes particularly linked to GBS, not all patients with *Campylobacter* enteritis infected with these types develop GBS. Further, strains from a variety of serotypes isolated from enteritis patients clearly demonstrate ganglioside mimicry [38]. Thus, additional bacterial virulence factors are likely involved, but host factors that regulate the immune responses to these gangliosides are also important in the development of GBS.

Only a few thousand cases of GBS develop in the US each year and the worldwide incidence is 0.4–4 per 100,000 [5]. The risk of developing GBS following *Campylobacter* infection is approximately 1 per 1000 infections and about 1 per 200 HS:19 infections [39]. GBS is primarily a sporadic disease and multiple, epidemiologic linked cases have rarely been described [40,41]. The fact that many individuals are exposed to strains exhibiting ganglioside mimicry, yet only few develop GBS strongly supports a role for host factors as a determinant of disease outcome. The

major histocompatibility system is critical in controlling host immune responses. A number of studies have reported on either HLA class I or class II associations with GBS; however, many of these studies have involved small numbers of patients and were not well controlled (reviewed in reference [6]). In a particularly well-controlled study by Rees et al. [42], GBS patients with evidence of *Campylobacter* infection were more likely to have HLA DQβ1*03 than *C. jejuni*-negative patients (83 vs. 49%, $P = 0.05$). This association was not confirmed, however, by Yuki et al. [8]. It is, therefore, not surprising that strong HLA associations have not yet been described and are likely a function of the number of patients studied, the degree to which the disease is characterized (i.e. AIDP, AMAN, etc.), HLA typing methods used, and suitability of control populations used for comparisons.

6. Animal models reproducing the disease are lacking

Animal models for enteric *Campylobacter* infection have been very difficult to develop and have been used primarily to study colonization and immune responses following infection with the organism. A recent review of *Campylobacter* animal models was published by Young et al. [43]. Despite the limitations of enteric disease models, significant progress in using experimental models to study *Campylobacter*-induced GBS is being made.

The traditional animal model for studying GBS is the Lewis rat model and is a model for T-cell-mediated damage following sensitization with myelin proteins [44]. This model, however, appears to be unresponsive to challenge with *Campylobacter* [45,46]. Li and colleagues reported that infection of chickens with *C. jejuni* resulted in motor weakness with characteristic nerve pathology, similar to that seen in the AMAN form of GBS [47]. Reports substantiating these observations have not been forthcoming and we have been unable to reproduce this model (Nachamkin et al., unpublished results). Rabbits have also been reported to develop a sensory neuropathy following immunization with GD1a [48].

A number of other experimental models, such as passive transfer of antibodies to animal nerves and ex vivo mouse hemi-diaphragm preparations, are being used to study the pathologic and physiologic effect of anti-ganglioside antibodies in the pathogenesis of GBS [20]. Studies by Goodyear et al. [27] using the mouse hemi-diaphragm model confirm that antibodies raised in response to *Campylobacter* cause immune-mediated damage to peripheral nerve and this model will be exceptionally useful for studying the fine specificity of antibodies involved in the pathologic process. Finally, Lunn et al. [49] have used ganglioside knockout mice to produce high-affinity antibodies to GD1a, and the use of these mice may be useful to generate *Campylobacter*-specific anti-ganglioside antibodies for further studies on pathogenesis.

7. Future directions

Insights into the pathogenesis of GBS following *Campylobacter* infection are gaining considerable momentum. Completion of the *Campylobacter* genome sequence has already paid dividends in advancing the molecular pathogenesis of ganglioside mimicry in *C. jejuni*; however, many questions are yet to be answered. For continued advancement in this field, individuals with a variety of interests including microbiology, immunology, molecular biology, and neuroscience will need to work in a collaborative effort to dissect the mechanisms of molecular mimicry and immune-mediated nerve damage.

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