Review Article

Campylobacter infections and Guillain Barré syndrome

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ABSTRACT

Guillain Barré syndrome (GBS) is a serious disorder of the peripheral nerves preceded by a recognized acute infectious illness. *Campylobacter jejuni* has been recognized as an important pathogen precipitating GBS and the structure of *C. jejuni* lipooligosaccharide (LOS) might have a role in the outcome of infection. The development of GBS and Miller Fisher syndrome has been reported to be due to expression of a GM1 like LOS in class A strains and GQ1b like LOS in class B strains of *C. jejuni* respectively. Virulence of *C. jejuni*, subtle differences in the interaction between different strains with the host T lymphocyte receptor and MHC class II and host susceptibility may have a role to play in the development of GBS. A humoral immunopathogenic mechanism for GBS has been envisaged as the disease develops 1 to 3 weeks after *C. jejuni* infection. Antibodies to *C. jejuni* may remain elevated for several weeks after acute infection. Host susceptibility factors are also important in the pathogenesis of GBS as this disease occurs within families. Association between the occurrence of GBS and a particular HLA type has been envisaged, but studies to prove it are inconclusive. Despite our increasing understanding of the pathophysiology of GBS, the triggering event leading to the disease is still indeed a great puzzle. This review describes the in-depth association of *Campylobacter* infections with GBS.

Keywords: *Campylobacter*, GBS , lipooligosaccharide

INTRODUCTION

Guillain Barré syndrome (GBS) is a serious disorder of the peripheral nerves and is characterized by ascending paralysis. Since the decline of polio cases, GBS is considered as the most common cause of acute neuromuscular paralysis. GBS is preceded by a recognized acute infectious illness of the lungs or the gastrointestinal system in 50-70% of cases after an interval of 1 to 6 weeks.[1] For the past three decades, *Campylobacter jejuni* has been recognized as the single most common pathogen precipitating GBS as documented by anecdotal reports, serological studies and culture data.[1-2] Even though the strongest documented association of GBS is with *Campylobacter* infections, from time to time a few other infectious agents like *Mycoplasma pneumoniae*, Hepatitis B virus, Cytomegalovirus, Varicella Zoster virus, Epstein Barr virus, Rubeola and human immunodeficiency virus have also been reported to be associated with GBS.[3-5]

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C. jejuni was found to be the most common pathogen in infections preceding GBS as reported from United States[6-7] United Kingdom,[1] Netherlands[8] and Japan[9] by stool cultures and serological investigations. Over 2.5 million cases of *C. jejuni* infections occur each year in the United States.[10] Out of an estimated 2,628 to 9,575 patients diagnosed with GBS in the United States annually, 526 to 3,830 (20-40%) are triggered by *Campylobacter* infection.[11] GBS is more common among males than among females and occurs in a ratio of 3:1.[6] This review shall describe the in-depth association of *Campylobacter* infections with GBS.

Epidemiology

The association of *C. jejuni* infection as a possible

etiological agent of GBS was first reported in a 45-year-old man who developed severe GBS 19 days after *C. jejuni* infection.[12] This triggered investigations worldwide to corroborate the association between the two and soon a flurry of report accumulated documenting the occurrence of GBS following *C. jejuni* infection.[13-15] Prior to 1982, as routine culture of stools for *Campylobacter* was not being done, *C. jejuni* was not being associated with GBS until then.[12] Earlier studies from India involving GBS patients were related to electrophysiological tests alone.[16] Serological studies that could determine the association of *C. jejuni* and GBS are negligible. Serological investigations conducted by various otherworkers estimated the occurrence of *C. jejuni* enteritis in 13-72% of GBS patients.[17] Thus it is the most frequently implicated pathogen followed by Cytomegalovirus infection in 10-20% for GBS cases.[18]

A study from Lucknow showed *C. jejuni* to be present in 26% cases of GBS patients.[19] A statistically significant association of both *C. jejuni* and *M. pneumonia* infections in GBS has also been reported from New Delhi.[20] In a study from Kerala, investigation of serum samples for *C. jejuni* in a group of 43 cases of GBS, 32 non-GBS neurology patients and 35 healthy controls found 26% of samples from GBS with high antibody levels. Of 8 stool samples of new GBS cases examined by culture, 38% were positive for *C. jejuni* or *C. coli*, suggesting that at least a quarter of GBS cases studied were associated with *Campylobacter* infections.[21] Sharma *et al*[22] studied the relationship between preceding *C. jejuni* infection and its correlation to the various subtypes of GBS by electrophysiological and serological testing. They found that preceding *C. jejuni* infection is common among GBS patients and is often associated with the axonal variety, which is generally present in a younger age group as compared to patients with AIDP (*acute inflammatory demyelinating polyneuropathy).* Vaishnavi *et al*[23,24] reported a case-control study for the estimation of anti-ganglioside antibodies in GBS patients (n=59) and their neurological (n=58) and non-neurological controls (n=60) by both subjective and automatic estimation of IgG and IgM antibodies to seven gangliosides using EUROLineScan software. They observed that anti-ganglioside antibodies were present in highly significant levels in the GBS group, though they were also present in the non-paralytic neurological control patients compared to the non-neurological control group.

C. jejuni infection in GBS patients has been reported in a range of 13-72% from different geographic regions. In northern China, up to 66% association with GBS has been reported whereas as low as 15% prevalence has been found in Europe.[25] In United Kingdom, the Netherlands, USA and Japan, evidence of a recent *C. jejuni* infection by culture or serological methods ranged from 23-45% in GBS patients.[26-28] Some studies carried out in China and Japan have shown that *C. jejuni* infection appears to be closely associated with the axonal forms of GBS.[29] However in western countries the percentage of AMAN *(acute motor axonal neuropathy)* with antecedent *C. jejuni* infection is less than 10% and therefore this association is inconsistent, though no reason for this inconsistency is identified.[28]

C. jejuni strains associated with GBS

There is an increasing body of evidence indicating that the structure of *C. jejuni* lipooligosaccharide (LOS) might have a role in the outcome of infection.[30] *C. jejuni* has 7 classes (A-G) of LOS locus based on the organization of the 37 distinct genes found in the LOS biosynthesis loci of 20 strains of *C. jejuni*.[31] The development of GBS and Miller Fisher syndrome (MFS) has been reported to be due to expression of a GM1 like LOS in class A strains and GQ1b like LOS in class B strains respectively.[32] However this does not shed light on which genetic difference leads to the presence of these diverse ganglioside mimics despite the almost identical gene profile in class A and class B loci. A study from Japan on *C. jejuni* serotypes, genotype and ganglioside mimics on LOS revealed a high frequency of class A locus reported in Europe which gave the first GBS related *C. jejuni* characteristics frequent to strains in Europe and Asia.[33] The class A locus and serotype 0:19 is probably associated with sialytransferase gene (*cst II*) polymorphism ensuing in the promotion of both GM1-like and GDA-like structure synthesis on LOS. This may lead to a risk of producing anti-ganglioside antibodies and resultant GBS.[33,34] The locus typing of LOS would be useful in the identification of the gene content responsible for GBS development. Reports from The Netherlands and Belgium indicate that class A locus was overrepresented in GBS associated strains of *C. jejuni* (53%) as compared to enteritis associated strains (14%) as all MFS strains had class B locus. Parker *et al*[35] have

confirmed the high frequency of class A locus in GBS-associated strains of of *C. jejuni.*

Virulence of *C. jejuni*, subtle differences in the interaction between different strains with the host T lymphocyte receptor and MHC class II and host susceptibility may have a role to play in the development of GBS.[33] Huizinga *et al*[36] investigated intrinsic dendritic cell responsiveness to *C. jejuni* LOS first in 20 healthy controls at three time points with a 3-month interval, and second in patients, who previously developed GBS after a *C. jejuni* infection (n = 27) and controls (n = 26) and concluded that a strong response to TLR4 stimulation is a critical host condition for the development of GBS after an infection with *C. jejuni.*

Geographical distribution of *C. jejuni* strains associated with GBS is varied and Penner serotypes O:19 and O:41 with O:2 and O:4 complexes are the dominant serotypes in MFS.[37] In Japan 52–77% of patients with *C. jejuni*-associated GBS had serotype Penner O:19,[38] in Germany 93% had Lior 11[39] and in South Africa 53% had the Penner O:41 strains.[40] In Japan of 12 *C. jejuni* isolates from GBS patients, 10 belonged to serotype O:19, but this serotype represents <2% of *C. jejuni* isolates from patients with uncomplicated enteritis.[33,37,41]

Pathogenesis of GBS

A humoral immunopathogenic mechanism for GBS has been envisaged as the disease develops 1 to 3 weeks after *C. jejuni* infection. As per an earlier study one of every 1058 *Campylobacter* infections results in GBS, and 1 of 158 *Campylobacter* type O:19 infections results in GBS.[42] Later on, it was estimated that one of every 3285 *Campylobacter* infections results in GBS.[27] Amongst other infections, *Campylobacter* associated GBS has been found to be more severe resulting in extensive irreversible neurologic damage. Antibodies to *C. jejuni* may remain elevated for several weeks after acute infection. Thus serologic assays help to assess the frequency of preceding *C. jejuni* infection in GBS patients.[1]

C. jejuni antibodies can precipitate GBS by different methods. Suggested methods are (i) Immunological cross reaction between *C. jejuni* and neural tissue (ii) Molecular mimicry and (iii) Toxic neural damage.

(i) Immunological cross reaction

The nervous system has a variety of gangliosides like GM1, GD1a, GD1b, and GT1b. The IgG class of antibodies is most frequently stimulated, with GM1 being the most commonly implicated ganglioside. However IgM and IgA antibodies to GM1 have been detected in 10-20% of GBS patients in most studies with a few normal controls also showing the same.[43] An immune response to gangliosides may be directly pathogenic in some cases of axonal GBS.[17,44-46]

In a large epidemiological survey, therapeutic injection of gangliosides for various conditions such as stroke and sciatica was seen to be associated with an increased risk of developing GBS. Seven of the GBS patients with subgroup AMAN studied in detail, had IgG antibodies to gangliosides, particularly to GM1, whereas these antibodies were absent in any of the eight subjects who received gangliosides without developing GBS.[47] Antibodies to definite gangliosides have been linked to different GBS subtypes and vary in the degree to which they cross react with more than one ganglioside. For example, antibodies to GM1 were found to be linked to patients with motor nerve involvement. Similarly GQ1b antibodies were found to be related to MFS in 90% of the cases with sensory axons.[48]

(ii) Molecular mimicry

The theory of molecular mimicry came into picture when *C. jejuni* (Penner serotype O:19) infection in Japanese patients with GBS[49] produced a humoral immune response that cross reacted with neural antigens leading to the pathogenesis of GBS. The pathogenesis of GBS in *C. jejuni* infection may involve molecular mimicry where dissimilar genes produce molecules that bind to similar structures.[17] Many strains of *C. jejuni* have sialyated carbohydrate residues identical to human gangliosides GM1, GD1a or GT1a in the LOS of their cell wall. It is established that sialylated LOS of *C. jejuni* are a crucial virulence factor in GBS development as *C. jejuni* with sialylated LOS are frequently detected in stools derived from patients with uncomplicated enteritis. Heikema *et al*[50] in order to assess whether the polysaccharide capsule is a marker for GBS, determined the capsular genotypes of two geographically distinct GBS-associated *C. jejuni* strain

collections and an uncomplicated enteritis control collection from The Netherlands and Bangladesh. Multilocus sequence typing revealed restricted genetic diversity for strain populations with the capsular types HS2, HS19 and HS41. The authors concluded that capsular types HS1/44c, HS2, HS4c, HS19, HS23/36c and HS41 are markers for GBS and that besides a crucial role for sialylated LOS of *C. jejuni* in GBS pathogenesis, the identified capsules may contribute to GBS susceptibility.

Anti-ganglioside GM1 activity of IgG from Dutch patients with GBS was found to be inhibited by absorption with whole *C. jejuni* of serotypes O:4, O:22 and O:41, and different strains inhibited different sera[51] giving rise to the hypothesis of antibody cross reactivity. Cross reactivity has also been observed in MFS patients of whose serum IgG antibodies to GQ1b bound to surface antigenic molecules on their own *C. jejuni* isolates.[51] However the molecular mimicry hypothesis has some limitations due to over simplifi-cation and does not clarify many observations.[17] In fact many GBS patients with anti-GM1 antibodies are found not to be exposed to a *C. jejuni* infection. Additionally, *C. jejuni* with GM1 epitopes have sometimes been isolated from GBS patients who did not produce serum antibodies to GM1. It may also be mentioned that sialylated LOS occur in a few other bacterial species such as *Neisseria* and *Haemophilus*, which have never been found to be linked to GBS. Thus the theory of mimicry may not be fully acceptable, and some host susceptibility factors may be involved.

(iii) *Toxic neural damage*

Some workers believe that *C. jejuni* might have a role in binding to neural tissues by production of enterotoxin similar to that by cholera toxin which binds avidly to gangliosides.[52]

GBS and HLA

Host susceptibility factors are also important in the pathogenesis of GBS as this disease occurs within families. Association between the occurrence of GBS and a particular HLA type has been envisaged, but studies to prove it are inconclusive. Another study from England investigating HLA type class II alleles showed that HLA DQB1*03 (corresponding to HLA DQw3 antigen) was present in 83% of the 30 *C. jejuni* related GBS patients.[53] But no significant difference in HLA type was seen in a series of 81 Japanese patients with GBS when compared to 87 healthy controls.[38] Thus more studies are needed to elucidate the relation of GBS with HLA types.[28,54]

Association of severe GBS with *C. jejuni*

Some investigators have reported that there is an association of severe GBS with *C. jejuni* infection and this may be a more irreversible neurologic damage than that precipitated by other likely infections. Vriesendorp *et al*[55] reported 10 of 58 GBS patients to have serologic evidence of recent *C. jejuni* infection among whom 30% had severe GBS defined as fulminating disease with quadriplegia and ventilator dependence within 24-48 hours of onset. On the other hand none of the 48 patients without recent *C. jejuni* infection had severe GBS. In another study from Britain, of 101 GBS patients, 23% who had Campylobacter associated GBS were not able to walk without assistance one year after the onset of symptoms in contrast to only 9% of uninfected GBS patients.[56] In a study from The Netherlands 14 of 24 *C. jejuni* infected GBS patients treated with plasma exchange were unable to walk unassisted 6 months after the onset of their symptoms in comparison to only 12% of similarly treated GBS patients who had no indication of preceding *Campylobacter* infection.[57]

Serological identification of *C. jejuni*

Campylobacters are excreted in stools of infected persons for a median duration of only 16 days with a lag time between infection and GBS onset being 1-3 weeks. Thus stool cultures in many of the GBS patients with preceding *Campylobacter* infection might be falsely negative.[58] Serological studies help to define the pathogenesis of infection, particularly the role of antibodies in host response.[58] Thus when stool cultures are negative, serological assays can retrospectively determine whether or not a patient was infected with *C. jejuni*. Serological assays like ELISA has high sensitivity and specificity and can be used for the detection of antibody response to *C. jejuni* infection.[58]

In *Campylobacter* infection the IgG and IgM levels in serum rise and remain elevated for 3-4 weeks before declining to normal levels, similar to other infectious diseases. Serum IgA levels however appear during the first few weeks of infection and then fall rapidly. These

antibodies can also be detected in the feces and urine of some patients with *C. jejuni* infection only during the first week after acute infection. Demonstration of a significant increase or decrease in immunoglobulin levels in paired sera are useful for confirming a recent infection.[57]

Humoral immune factors are responsible for neural damage and demyelination seen in GBS. In a retrospective study by Kaldor & Speed[44] evidence of *C. jejuni* was found in 21% of 56 Australian GBS patients with those having serological evidence of a preceding *C. jejuni* infection manifesting significantly the more severe form of the disease. A study from North China (1991-1992) in GBS patients investigating for IgG, IgM and IgA antibodies specific to *C. jejuni* showed 66% of 38 GBS patients and 16% of controls had evidence of recent *C. jejuni* infection.[7] *C. jejuni* was more frequent among AMAN (76%) than AIDP (42%) group indicating that prominent axonal involvement is more common among *C. jejuni* associated GBS.[7] Mishu *et al*[59] in a large, blinded case control study in the United States, evaluated 118 GBS patients and 113 controls. They found that 36% of the GBS patients were seropositive for *C. jejuni* and were >5 times likelier to have serologic evidence of recent *C. jejuni* infections than the controls.

In a study from Japan 36% of the GBS patients were seropositive for *C. jejuni*.[9] Other studies from Netherlands (32%) and United Kingdom (26%)[8] also showed high incidence of *C. jejuni* infection. However in reports from UK[3,56] and Massachusetts[60] relatively low frequencies of *C. jejuni* infection associated with GBS were observed being 14% and 18% respectively. This possibly reflected the difference in the methods used for detection of *C. jejuni* infection as also the sociodemographic variation among the study population.

CONCLUSION

Despite our increasing understanding of the pathophysiology of GBS, the triggering event leading to the disease is still indeed a great puzzle. A range of causal agents have been implicated, though in a significant proportion this remains unclear. *C. jejuni* has been found to be most commonly associated with GBS, yet no global consensus exists in its reported frequency. Very few studies are available in the world, inclusive of India, regarding the standardization of serological technique and controlled clinical trials with adequate sample size, making meaningful interpretation of available data difficult. However based on serologic and culture evidence, the involvement of *Campylobacter* with the development of GBS has now been established.

CONFLICT OF INTEREST

Nil

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