Guillain-Barre’ Syndrome and Campylobacter jejuni Infection: A Review

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Abstract

Guillain-Barre’ syndrome (GBS), a neurologic disease that produces ascending paralysis, affects people all over the world. Acute infectious illness precedes 50%-75% of the GBS cases. Although many infectious agents have been associated with GBS, the strongest documented association is with Campylobacter infection. The first line of evidence supporting Campylobacter infection as a trigger of GBS is anecdotal reports. The second line of evidence is serological surveys, which have demonstrated that sera from GBS patients contain anti Campylobacter jejuni antibodies, consistent with recent infection. Finally, culture studies have proven that a high proportion of GBS patients have C. jejuni in their stools at the time of onset of neurological symptoms. One of every 1058 Campylobacter infections results in GBS. Sialic acid containing lipooligosaccharides (LOS) biosynthesis gene locus are associated with GBS and the expression of ganglioside mimicking structures. GM₁₄ was the most prevalent ganglioside mimic in GBS associated strains. Molecular mimicry between C. jejuni LOS and gangliosides in human peripheral nerves, and cross-reactive serum antibody precipitate the majority of GBS cases in Bangladesh, like worldwide.

Keywords: Campylobacter jejuni; Guillain-Barre’ syndrome; molecular mimicry; ganglioside.
following the enteric infection with *C. jejuni*. It is difficult to positively associate *C. jejuni* with GBS because the bacteria are usually eliminated from the body within 16 days of infection and before the onset of neurological symptoms, which normally begin 10 days to 3 weeks after the onset of diarrhea. Although *Campylobacter* is prevalent in most parts of the world, it is not routinely diagnosed in rural health clinics. For this reason, many *Campylobacter* associated GBS cases may go unrecognized because by the time the person presents with GBS, *Campylobacter* is no longer present.

*C. jejuni* probably triggers the GBS through molecular mimicry between lipooligosaccharides (LOS) in the bacterial cell wall and gangliosides in human peripheral nerve tissue. Various ganglioside mimicking structures have been identified in the LOS fraction of *C. jejuni* cell wall. The mechanisms by which *C. jejuni* infections cause neuropathy is probably a consequence of immunological cross reactions of antibodies stimulated against bacterial cell surface carbohydrates with human gangliosides.

In this review we aimed to explore the association between *C. jejuni* infection with GBS, its molecular aspect, different molecular association worldwide and situation of GBS followed by *C. jejuni* infections in Bangladesh.

**Materials and method**

We performed a PubMed search of studies published from July 1997 to August 2012 that investigated the relationship between infection due to *Campylobacter* and GBS. We searched using combinations of the following Medical Subjects Headings (MeSH): ‘Guillain-Barré Syndrome’ and ‘Campylobacter’.

Studies were included if serum and stool samples were collected during the acute phase of GBS, within 24 to 48 hours of patient’s admission to hospital and no longer than four weeks after admission. Studies were excluded if they relied on a complement fixation assay (CFA) for the diagnosis of *Campylobacter*. Definitions of GBS in the studies were based on currently accepted criteria for diagnosing GBS (i.e. a progressive, symmetric ascending paralysis with a relative sensory sparing in more than one extremity with hypo or areflexia). Studies were included if these used appropriate microbiological methods (serological assays and stool cultures) for detecting *Campylobacter* species.

**GBS and preceding infections**

It has long been recognized that frequently GBS is preceded by an acute infectious illness. In 1892, Sir William Osler, a renowned late nineteenth and early twentieth century physician, called the syndrome “acute post infectious polyneuritis”. Investigators all over the world have confirmed that gastrointestinal infections, including diarrheal illness, precede GBS in 10%–30% of the cases. A study describes an outbreak of *C. jejuni* enteritis involving three family members of whom one developed GBS. The patient’s serum reacted strongly with several gangliosides and with LOS fractions from *C. jejuni* strains from its family members. Serum and stool samples were collected from a number of patients with GBS in Curaceo, Netherlands, where 8 out of 10 serums showed recent infection with *C. jejuni*. In another study, Pulsed Field Gel Electrophoresis (PFGE) analysis of 83 *C. jejuni* isolates from stool cultures of patients with GBS revealed a strong reaction of patient’s serum with LOS of strain GB 5.1 and presence of co infection with two different strains in one patient (8%).

**Incidence of GBS following *C. jejuni* infection**

Evidence of recent or ongoing *C. jejuni* infection has been found in approximately one out of every four cases of GBS. The most recently published estimate was 1 in 1,058. Noel and Johan found the annual incidence of GBS from Swedish inpatient register, about 1.45 to 2.30 per 100,000 per year between 1986-1993. This is found to be similar to occur in European population.

They considered the follow up period for detection of GBS after the *C. jejuni* report date was 6 months for most of the cases. Their study estimates the incidence of GBS following symptomatic *C. jejuni* infection by an unknown serotype to be 30.4 per 100,000. On the basis of the current study and other published work, the excess risk of GBS appears to be confined to the 2 month period following *C. jejuni* infection, approximately 100 times higher.
Association of C. jejuni infection with GBS

The evidence that C. jejuni is the most important trigger of GBS comes from 3 sources—anecdotal reports, serological studies, and culture data. As with many new medical discoveries, the association between GBS and C. jejuni was first described in clinical anecdotes. In 1982, Rhodes and Tattersfield9 were the first to report on a patient who developed GBS 10 days after C. jejuni infection. Almost immediately, several similar responses from other physicians came.27-31 In these early reports, it was frequently noted that GBS following C. jejuni infection was severe, with extensive axonal damage.

The mean excretion time of C. jejuni in stools is only 16 days,32 whereas antibodies to C. jejuni may remain elevated for several weeks after acute infection;33 therefore, serological assays have been done to assess the frequency of preceding C. jejuni infection in GBS patients. Several studies have documented a high prevalence of antibodies to C. jejuni in the serum of patients with GBS.34-39 Gruenwald et al.36 found that 3 (18%) out of 17 patients with GBS had elevated titers in two or more immunoglobulin classes by immune dot assays. Similarly, Winer et al.35 found that 14 (14%) out of 99 patients with GBS had positive C. jejuni in serological tests. In a Japanese study of GBS patients, 36% were sero positive.38

Though the reference standard for determining C. jejuni infection is not serology but culture of the organism, but 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 their stools by the time 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 neurological symptoms. Campylobacter is not a part of normal stool flora, and detection of the organism would not be expected in the absence of recent infection. Thus, the serological and cultural studies demonstrate that at least 30%-40% of GBS patients have been infected with Campylobacter in the 10 days to 2 weeks prior to the onset of their neurological symptoms.4

The crucial role of C. jejuni genes in anti-ganglioside antibody induction in GBS

Five classes of lipooligosaccharides (LOS) locus (A-E) were isolated from a collection of patients with neuropathy and C. jejuni enteritis. Only 3 out of 5 identified classes of LOS locus, i.e, classes A, B and C contain genes that are involved in biosynthesis and transfer of sialic acid, an essential component of gangliosides. Of these 3, class A locus is found specifically associated with GBS and presence of a GM1 like structure. The presence of anti-GM1 antibodies has been found to be associated with a preceding Campylobacter infection.40 Therefore class A strains expressing GM1 like LOS structures are more likely to induce GBS. An important feature in ganglioside mimicry is the presence of sialic acid (N-acetylneuraminic acid) in both LOS and gangliosides.41 Mass spectrometry analysis revealed that genes involved in sialylation of LOS induce formation of anti ganglioside auto antibodies that lead to GBS.42 All these results indicate that genes unique to class A and B loci and genes involved in sialic acid biosynthesis or transfer may appear crucial for induction of neuropathogenic cross reactive antibodies, which is considered as GBS marker genes.

Structural characterization of C. jejuni lipooligosaccharides outer core associated with GBS

Since the first report in 1993, several studies have demonstrated ganglioside like structures in the LOS outer core of C. jejuni strains isolated from GBS patients.43 Mass spectrometry and nuclear magnetic resonance analyses of individual strains have revealed the presence of GM1a, GD3, GD1a and GT1a mimics in GBS associated strains.44-48 Sixteen of 22 (73%) GBS associated isolates expressed LOS with ganglioside mimics including GM1a, GM1b, GM2, GD1a, GD1c, GD2, among which GM1a was the most prevalent ganglioside mimic in GBS associated strains, present in 10 out of 22 strains (45%). GM1a also predominantly present in combination with GD1a mimics (36% of all GBS strains), only in strains with class A LOS locus which was found previously associated with GBS.49-51 The high prevalence of GM1a/GD1a mixture in GBS associated strains suggests that a cluster or complex of these two ganglioside mimics may be the target antigens in GBS than single ganglioside mimics. Serological studies of larger collections of isolates have confirmed and extended these findings.52,53 The presence of polymorphism within the cstII gene has
been associated with expression of ganglioside mimics and with clinical features of GBS.54, 55

Molecular association between C. jejuni and patients with GBS

GBS related C. jejuni strains have been reported to be associated with specific Penner serotypes O:19 and O:41, and these appeared to be clonally related.56-59 The risk of developing GBS may be higher after infections with serotype O:19.58 Endtz et al.57 found O:2 serotype in two GBS related strains and in two strains from family members of a GBS patient and also reported two new C. jejuni O serotypes, C. jejuni O:35 and O:13/65 in association with GBS. C. jejuni O:2 is the prevailing serotype from patients with enteritis in his study and, according to Oosterom et al.58 accounts for 25% of the enteritis strains in Netherlands. However, C. jejuni serotype O:19 appears to be over represented among strains isolated from patients with GBS from United States and Japan.57,61 In a Japanese study,57 serotype O:19 comprised 12 out of 16 (75%) of the GBS related C. jejuni isolates, while in a U.S. based study,61 2 out of 7 (29%) were of serotype O:19. In South Africa, 9 out of 9 (100%) C. jejuni isolates from GBS patients were of serotype O:41.57 PCR-RFLP analysis demonstrated considerable variation in gene content and overall sequence heterogeneity in C. jejuni LOS biosynthesis locus.59 Sequence typing confirms that a particular variant of the short variable region (SVR) of the flagellum encoding gene, flaA is the marker for C. jejuni strains to cause GBS.60

The results of sero typing and genotyping of C. jejuni enteritis followed by GBS demonstrate a clonal relationship of the strains and, therefore, suggest the importance of host factors in the pathogenesis of GBS.61

Guillain-Barré Syndrome (GBS) followed by C. jejuni enteritis in Bangladesh

GBS in Bangladesh is frequently preceded by an enteric infection caused by Campylobacter jejuni.62 A study in Bangladesh showed that 69% GBS patients had clinical evidence of a preceding infection where the most frequent symptom was diarrhea (36%).63 Frequent exposure to enteric pathogens at an early age may increase the incidence of GBS. The crude incidence rates of GBS among children <15 years of age varied from 1.5 to 1.7 per 100,000 per year in Bangladesh. This crude incidence rate of GBS appeared to be 2.5 to 4 times higher than the other parts of the world. Incidence rates were high (>5.0/100,000) in southern Bangladesh. A seasonal fluctuation was found in the frequency of patients with GBS; the most cases occurred in May and the lowest in February.64

Unusually high frequency of acute motor axonal neuropathy (AMAN) variant of GBS in Bangladesh has been reported recently which is associated with preceding C. jejuni infections and the presence of serum antibodies against GD1a and GM1,63 the most prevalent ganglioside mimic in GBS associated C. jejuni strains, and it was predominantly found in LOS class A strains.62 In a study it was found that (1) the serum IgG response to C. jejuni LOS and to gangliosides are closely associated in patients with GBS, (2) patient serum anti-ganglioside IgG antibodies cross-react to C. jejuni LOS and, (3) the C. jejuni isolates from Bangladeshi GBS patients have a LOS biosynthesis class A associated with ganglioside mimicry.62 All these supported the hypothesis that C. jejuni infections induce GBS in these patients by molecular mimicry and induction of a cross reactive immune response to nerve gangliosides.

A comparative genotyping of 49 C. jejuni strains, isolated from GBS and enteritis patients in Bangladesh were done. All strains were serotyped and analyzed by LOS genotyping, amplified fragment length polymorphism (AFLP), multi locus sequence typing (MLST) and pulsed field gel electrophoresis (PFGE). It was found that the LOS class A was significantly over represented in GBS associated strains. MLST demonstrated that C. jejuni HS:23 was a predominant serotype among GBS patients (50%),65 all were clonal and belonged to ST-403 complex.66 Particularly, the presence of a clonal and putative neuropathogenic C. jejuni HS:23 serotype may contribute to the high prevalence of C. jejuni related GBS in Bangladesh.

Discussion

C. jejuni is the most significant bacterial cause of human gastroenteritis.67 GBS is an acute post-infectious immune mediated peripheral neuropathy with a marked variation in pathology.
clinical presentation and prognosis. The association between GBS and C. jejuni infection has been demonstrated by case reports and case series, many of which have been described in this article. A biological mechanism involving molecular mimicry and consequent cross reaction of the immune response formed against C. jejuni antigens with gangliosides (GM₁) present in nerves have been suggested and is supported by laboratory studies.

The development of these autoimmune neuropathies after C. jejuni infection is primarily related to sialylated lipooligosaccharides (LOS) on the cell surface of C. jejuni. These exhibit significant molecular mimicry with gangliosides on human peripheral nerves. Most patients who develop GBS after C. jejuni enteritis have IgG autoantibodies that react with gangliosides (such as GM₁, GD₁a). Comparison of the LOS loci of various C. jejuni strains has demonstrated that only the class A, B and C LOS loci contain the genes that are necessary for the biosynthesis of ganglioside mimics. It was described previously that the GBS patient serum contains anti-asialo GM₂ antibodies that are cross-reactive with GBS LOS, which suggests that GBS was induced by molecular mimicry with C. jejuni LOS without ganglioside mimics.

Serology is the preferred mechanism of detection because, Campylobacter specific antibodies can be detected in serum of the patient for an indefinite length of time compared to Campylobacter antigens in stool samples, which are cleared, on an average, 16 days after infection. Though it has been suggested that the Penner HS:19 serotype is associated with a C. jejuni clone which has a higher probability of association with neuropathy, but LOS genotyping, MLST, AFLP and PFGE helped to identify the HS:23 strains from GBS or enteritis patients as clonal in Bangladesh. The most common Bangladeshi lineage was the ST-403 complex which is also different from other studies. In patients with preceding C. jejuni infections, the specificity of these cross reactive antibodies is determined by the carbohydrate outer core of the C. jejuni LOS, which is controlled by genetic polymorphisms.

We would like to conclude that the majority of C. jejuni strains isolated from GBS patients express single or multiple ganglioside mimics in their LOS. Outcome of Campylobacter associated GBS is more severe and causes more irreversible neurological damage. Although understanding of the relation between C. jejuni infection and GBS has improved rapidly, the overall risk of GBS following the diagnosis of C. jejuni infection has not been measured. This method relies on assumptions only, because of the lag time between C. jejuni infection and onset of neurological symptoms, these numbers likely to underestimate the association between C. jejuni infection and GBS. Further research is necessary to elucidate the mechanism by which C. jejuni determines the fine specificity of the anti-ganglioside antibodies and their rapid diagnostic methods.

References


