Guillain-Barre´ Syndrome and *Campylobacter jejuni* Infection: A Review

Nurun Nahar Mawla[1], Shahin Sultana[2], Nayareen Akhter[3]

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. GM_{1a} 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.*

Delta Med Col J. Jan 2014;2(1):28-35

1. Assistant Professor, Department of Microbiology, Delta Medical College, Dhaka, Bangladesh.
2. Associate Professor & Head, Department of Microbiology, Delta Medical College, Dhaka, Bangladesh.
3. Assistant Professor (c.c) Department of Microbiology, Delta Medical College, Dhaka, Bangladesh.

Correspondence: Dr. Nurun Nahar Mawla. e-mail: drnnmawla@gmail.com

Introduction

Guillain-Barré syndrome (GBS) is a nervous system disorder, usually triggered by an acute respiratory (22-53%) or gastrointestinal (6-26%) infections.[1,2] GBS is an autoimmune disease, results from nerve damage frequently becomes severe with a mortality of 2-7% and different morbidity. Two to three weeks after a viral or bacterial infection, some people may have trouble walking. GBS causes muscle weakness, loss of reflexes and numbness or tingling in arms, legs, face, and other parts of the body that may rapidly progress to complete paralysis. A variety of infections have been associated with GBS, of which *Campylobacter jejuni (C. jejuni),* a bacterial infection frequently causing diarrhea is among the most commonly linked.[3]

GBS, the most common cause of acute neuromuscular paralysis is clinically defined by Asbury and Cornblath, as a progressive motor weakness of more than one limb with low or absence of reflexes and no other identifiable causes.[4,5] The global incidence of GBS ranges from 0.4 to 4.0 (median 1.3) cases per 100,000 people annually, occurring more often in adolescents and young adults than in children.[5,6] Guillain-Barré syndrome is the most frequent cause of non polio acute flaccid paralysis (AFP) in Bangladesh which has an incidence rate of 3.25 cases per 100,000 children of <15 years of age.[7]

C. jejuni was first associated with GBS in 1982 when Rhodes and Tattersfield reported a case of GBS

following the enteric infection with *C. jejuni*.[8,9] 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.[4,6] 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.[10,11]

C. jejuni probably triggers the GBS through molecular mimicry between lipooligosaccharides (LOS) in the bacterial cell wall and gangliosides in human peripheral nerve tissue.[12] Various ganglioside mimicking structures have been identified in the LOS fraction of *C. jejuni* cell wall.[13] 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.[10,14]

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).[5,15] Studies were included if these used appropriate microbiological methods (serological assays and stool cultures) for detecting *Campylobacter* species.[8]

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''.[16] Investigators all over the world have confirmed that gastrointestinal infections, including diarrheal illness, precede GBS in 10%–30% of the cases.[17] 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.[18] 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.*[19] 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%).[20]

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.[21,22] The most recently published estimate was 1 in 1,058.[4] 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.[23,24] 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,[25,26] 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 Tattersfield[9] 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 GM_1 like structure. The presence of anti-GM_1 antibodies has been found to be associated with a preceding *Campylobacter* infection.[40] Therefore class A strains expressing GM_1 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 GM_{1a}, GD_3, GD_{1a} and GT_{1a} mimics in GBS associated strains.[44-48] Sixteen of 22 (73%) GBS associated isolates expressed LOS with ganglioside mimics including GM_{1a}, GM_{1b}, GM_2, GD_{1a}, GD_{1c}, GD_2, among which GM_{1a} was the most prevalent ganglioside mimic in GBS associated strains, present in 10 out of 22 strains (45%). GM_{1a} also predominantly present in combination with GD_{1a} 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 GM_{1a}/GD_{1a} 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 GD_{1a} and GM_1,[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 ganglisoides.

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.[68] 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 (GM_1) present in nerves have been suggested and is supported by laboratory studies.[42,69]

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.[48,70,71] Most patients who develop GBS after *C. jejuni* enteritis have IgG autoantibodies that react with gangliosides (such as GM_1, GD_{1a}).[72] 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.[73] It was described previously that the GBS patient serum contains anti-asialo GM_2 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,[55] 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.[74]

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

1. McGrogan A, Madle GC, Seaman HE, de Vries CS. The Epidemiology of Guillain-Barré Syndrome Worldwide. A Systematic Lliterature Rreview. Neuroepidemiology. 2009;32:150-63.
2. Jacobs BC, Van Belkum A, Endtz HP. Guillain-Barré Syndrome and Campylobacter Infection. American Society for Microbiology;1998. p245-61.
3. Hubert PE. Paralysis after Diarrhoea? Guillain-Barré Syndrome in Bangladesh. 2008 [Internet].[cited 2013 Dec 8]. Available from: http://www.icddrb.org/ media-centre/news/2021.
4. Allos BM. Association between Campylobacter Infection and Guillain-Barré Syndrome. J Infect Dis. 1997; 176 (Suppl):S125-28.
5. Asbury AK, Cornblath DR. Assessment of Current Diagnostic Criteria for Guillain-Barré Syndrome. Ann Neurol. 1990;27 (Suppl):S21-4.
6. Hadden RD, Gregson NA. Guillain-Barré Syndrome and Campylobacter jejuni Infection. Symp Ser Soc Appl Microbiol. 2001;30 (Suppl):S145-54.
7. World Health Organization [Internet]. EPI Surveillance Bulletin. 2008 [cited 2010 Dec 1];11(6). Available from: http://www.searo.who.int/vaccine.
8. Prendergast MM, Moran AP. Lipopolysaccharides in the Development of the Guillain-Barré Syndrome and Miller Fisher Syndrome Forms of Acute Inflammatory Peripheral Neuropathies. J Endotoxin Res. 2000;6:341-59.
9. Rhodes KM, Tattersfield AE. Guillain-Barré Syndrome Associated with Campylobacter Infection. Br Med J (Clin Res Ed). 1982;285:173-74.

10. Hughes RA, Hadden RD, Gregson NA, Smith KJ. Pathogenesis of Guillain-Barré Syndrome. J Neuroimmunol. 1999;100:74-97.

11. McCarthy N, Giesecke J. Incidence of Guillain-Barré Syndrome Following Infection with Campylobacter jejuni. Am J Epidemiol. 2000;153:610-14.

12. Ang CW, Jacobs BC, Laman JD. The Guillain-Barré Syndrome: A True Case of Molecular Mimicry. Trends Immunol. 2004;25:61-6.

13. Moran AP. Structure and Conserved Characteristics of Campylobacter jejuni Lipopolysaccharides. J Infect Dis. 1997;176 (Suppl):S115-21.

14. Willison HJ, O'Hanlon GM. The Immunopathogenesis of Miller Fisher Syndrome. J Neuroimmunol. 1999;100:3-12.

15. Criteria for Diagnosis of Guillain-Barré Syndrome. Ann Neurol. 1978;3:565-66.

16. Osler W. The Principles and Practice of Medicine. 1st ed. New York: Appleton; 1982.

17. Kennedy RH, Danielson MA, Mulder DW, Kurland LT. Guillain-Barre´Syndrome. A 42-year Epidemiologic and Clinical Study. Mayo Clin Proc. 1978;53:93-9.

18. Ang CW, van Doorn PA,. Endtz HP, Merkies ISJ, Jacobs BC, de Klerk MA, van Koningsveld R, van der Meche´ FGA. A Case of Guillain-Barre´ Syndrome Following a Family Outbreak of Campylobacter jejuni Enteritis. J Neuroimmunol. 2000;111:229-33.

19. van Koningsveld R, Gerstenbluth RR, Schmitz PI, Ang CW, Merkies S, Jacobes BC, Halabi Y, Endtz HP, van der Meche FGA, van Doorn PA. Gastroenteritis Associated Gullain- Barre´ Syndrome on the Caribbean Island Curacao. Neurology. 2001;56(11):1467-72.

20. Godschalk PC, Gilbert M, Jacobs BC, Kramers T, Tio-Gillen AP, Ang CW, van den Braak N, Li J, Verbrugh HA, van Belkum A, Endtz HP. Co-Infection with Two Different Campylobacter jejuni Strains in a Patient with the Guillain-Barre´ Syndrome. Microbes Infect. 2006;8:248-53.

21. Tauxe RV. Epidemiology of Campylobacter jejuni Infections in the United States and Other Industrialized Nations. In: Nachamkin I, Blaser MJ, Tompkins LS, editors. Campylobacter jejuni-Current Strategy and Future Trends. Washington DC: American Society for Microbiology; 1992. p.9-19.

22. Chalker RB, Blaser MJ. A Review of Human Salmonellosis. III. Magnitude of Salmonella Infection in the United States. Rev Infect Dis. 1988;10:111-24.

23. Jiang GX. Guillain-Barré Syndrome in Sweden (Doctoral thesis). Stockholm, Sweden: Karolinska Institute; 1996.

24. Jiang GX, Cheng Q, Link H, de Pedro-Cuesta J. Epidemiological Features of Guillain-Barré Syndrome in Sweden, 1978-93. J Neurol Neurosurg Psychiatry. 1997;62:447-53.

25. Mishu B, Blaser MJ. Role of Infection Due to Campylobacter jejuni in the Initiation of Guillain-Barré Syndrome. Clin Infect Dis. 1993;17:104-8.

26. Ho TW, Mishu B, Li CY, Gao CY, Cornblath DR, Griffin JW, Asbury AK, Blaser MJ, McKhann GM. Guillain-Barré Syndrome in Northern China: Relationship to Campylobacter jejuni Infection and Anti-Glycolipid Antibodies. Brain. 1995;118:597-605.

27. Molnar CK, Mertsola J, Erkko M. Guillain-Barre´ Syndrome Associated with Campylobacter Infection [letter]. Br Med J. 1982;285:652.

28. Constant OC, Bentley CC, Denman AM, Lehane JR, Larson HE. The Guillain-Barre´ Syndrome Following Campylobacter Enteritis with Recovery after Plasmapheresis. J Infect. 1983;6:89-91.

29. Pryor WM, Freiman JS, Gillies MA, Tuck RR. Guillain-Barre´ Syndrome Associated with Campylobacter Infection. Aust NZ J Med. 1984;14:687-88.

30. Speed B, Kaldor J, Cavanagh P. Guillain-Barre´ Syndrome Associated with Campylobacter jejuni Enteritis. J Infect. 1984;8:85-6.

31. Wroe SJ, Blumhardt LD. Polyneuritis with Cranial Nerve Involvement Following Campylobacter jejuni Infection [letter]. J Neurol Neurosurg Psychiatry. 1985;48:593.

32. Svedhem A, Kaijser B. Campylobacter Fetus Subspecies jejuni: A Common Cause of Diarrhea in Sweden. J Infect Dis. 1980;142:353-59.

33. Blaser MJ, Duncan DJ. Human Serum Antibody Response to Campylobacter jejuni Iinfection as Measured by Enzyme-linked Immunosorbent Assay. Infect Immun. 1984;44:292-98.

34. Ropper AH. Campylobacter diarrhea and Guillain-Barre´ Syndrome. Arch Neurol. 1988;45:655-56.

35. Winer JB, Hughes RAC, Anderson MJ, Jones DM, Kangro H, Watkins RPF. A Prospective Study of Acute Idiopathic Neuropathy II. Antecedent events. J Neurol Neurosurg Psychiatry. 1988;51:613-18.

36. Gruenwald R, Ropper AH, Lior H, Chan J, Lee R, Molinaro VS. Serologic Evidence of Campylobacter jejuni coli Enteritis in Patients with Guillain-Barre´ Syndrome. Arch Neurol. 1991;48:1080-82.

37. Kaldor J, Speed BR. Guillain-Barre´ Syndrome and Campylobacter jejuni. Br Med J. 1984;288:1867-70.

38. Speed BR, Kaldor J, Watson J, Newton-John H, Tee W, Noonan D, Dwyer BW. Campylobacter jejuni/Campylobacter coli Associated Guillain Barre´ Syndrome: Immunoblot Confirmation of the Serologic Response. Med J Aust. 1987;147:13-6.

39. Kuroki S, Saida T, Nukina M, Haruta T, Yoshioka M, Kobayashi Y, et al. Campylobacter jejuni Strains from Patients with Guillain-Barre´ Syndrome Belong Mostly to Penner Serogroup 19 and Contain b-N-acetylglucosamine. Ann Neurol. 1993;22:243-47.

40. Yuki N. Infectious Origins of, and Molecular Mimicry in, Guillain-Barré and Fisher Syndromes. Lancet Infect Dis. 2001;1:29-37.

41. Chiu CP, Watts AG, Lairson LL, Gilbert M, Lim D, Wakarchuk WW, Withers SG, Strynadka NC. Structural Analysis of the sialyl transferase CstII from Campylobacter jejuni in Complex with a Substrate Analog. Nat Struct Mol Biol. 2004;11:163-70.

42. Yuki N, Taki T, Inagaki F, Kasama T, Takahashi M, Saito K, Handa S, Miyatake T. A Bacterium Lipopolysaccharide That Elicits Guillain-Barré Syndrome Has a GM1 Ganglioside Like Structure. J Exp Med. 1993;178:1771-75.

43. Aspinall GO, Fujimoto S, McDonald AG, Pang H, Kurjanczyk LA, Penner JL. Lipopolysaccharides from Campylobacter jejuni Associated with Guillain-Barré Syndrome Patients Mimic Human Gangliosides in Structure. Infect Immun. 1994;62:2122-25.

44. Aspinall GO, McDonald AG, Pang H, Kurjanczyk LA, Penner JL. Lipopolysaccharides of Campylobacter jejuni serotype O:19: Structures of Core Oligosaccharide Regions from the Serostrain and Two Bacterial Isolates from Patients with the Guillain-Barré Syndrome. Biochemistry. 1994;33:241-49.

45. Prendergast MM, Lastovica AJ, Moran AP. Lipopolysaccharides from Campylobacter jejuni O:41 Strains Associated with Guillain-Barré Syndrome Exhibit Mimicry of GM1 Ganglioside. Infect Immun. 1998; 66:3649-55.

46. Salloway S, Mermel LA, Seamans M, Aspinall GO, Shin JEN, Kurjanczyk LA, Penner JL. Miller-Fisher Syndrome Associated with Campylobacter Jejuni Bearing Lipopolysaccharide Molecules that Mimic Human Ganglioside GD3. Infect Immun. 1996;64:2945-49.

47. Yuki N, Taki T, Takahashi M, Saito K, Tai T, Miyatake T, Handa S. Penner's Serotype 4 of Campylobacter Jejuni Has a Lipopolysaccharide That Bears a GM1 Ganglioside Epitope as Well as one That Bears a GD1a Epitope. Infect Immun. 1994;62:2101-3.

48. Godschalk PCR, Heikema AP, Gilbert M, Komagamine T, Ang CW, Glerum J, Brochu D, Li J, Yuki N, Jacobs BC, van Belkum A, Endtz HP. The Crucial Role of Campylobacter Jejuni Genes in Anti-Ganglioside Antibody Induction in Guillain-Barré Syndrome. J Clin Investig. 2004;114:1659-65.

49. Koga M, Gilbert M, Takahashi M, Li J, Koike S, Hirata K, Yuki N. Comprehensive Analysis of Bacterial Risk Factors for the Development of Guillain-Barré Syndrome after Campylobacter Jejuni Enteritis. J Infect Dis. 2006;193:547-55.

50. Ang CW, Laman JD, Willison HJ, Wagner ER, Endtz HP, de Klerk MA, Tio-Gillen AP, van den Braak N, Jacobs BC, van Doorn PA. Structure of Campylobacter jejuni Lipopolysaccharides Determines Antiganglioside Specificity and Clinical Features of Guillain-Barré and Miller Fisher Patients. Infect Immun. 2002;70:1202-8.

51. Nachamkin I, Liu J, Li M, Ung H, Moran AP, Prendergast MM, Sheikh K. Campylobacter jejuni from Patients with Guillain-Barré Syndrome Preferentially Expresses a GD_{1a}-Like Epitope. Infect Immun. 2002;70:5299-303.

52. Koga M, Takahashi M, Masuda M, Hirata K, Yuki N. Campylobacter Gene Polymorphism as a Determinant of Clinical Features of Guillain-Barré Syndrome. Neurology. 2005; 65:1376-81.

53. van Belkum A, van den Braak N, Godschalk P, Ang CW, Jacobs BC, Gilbert M, Wakarchuk W, Verbrugh H, Endtz HP. A Campylobacter Jejuni Gene Associated with Immune-Mediated Neuropathy. Nat Med. 2001;7:752-53.

54. Fujimoto S, Mishu AB, Misawa N, Patton C, Blaser MJ. Restriction Fragment Length Polymorphism Analysis and Random Amplified Polymorphic DNA Analysis of Campylobacter jejuni Strains Isolated from Patients with Guillain-Barré Syndrome. J Infect Dis. 1997;176 (Suppl 2):S1105-8.

55. Lastovica AJ, Goddard EA, Argent AC. Guillain-Barré Syndrome in South Africa Associated with Campylobacter jejuni O:41 strains. J Infect Dis. 1997;176 (Suppl. 2):S139-43.

56. Saida T, Kuroki S, Hao Q, Nishimura M, Nukina M, Obayashi H. Campylobacter jejuni isolates from Japanese Patients with Guillain-Barré Syndrome. J Infect Dis. 1997;176 (Suppl 2):S129-34.

57. Endtz HP, Ang CW, van Den Braak N, Duim B, Rigter A, Price LJ, Woodward DL, Rodgers FG, Johnson WM, Wagenaar JA, Jacobs BC, Verbrugh HA, van Belkum A. Molecular Characterization of Campylobacter jejuni from Patients with Guillain-Barré and Miller Fisher Syndromes. J Clin Microbiol. 2000;38:2297-301.

58. Oosterom J, Bänffer JRJ, Lauwers S, Busschbach AE. Determination of Serotype and Hippurate Hydrolysis for Campylobacter jejuni Isolates from Human Patients, Poultry and Pigs in the Netherlands. Antonie leeuwenhoek J Microbiol. 1995;51:65-70.

59. Penner JL, Hennessy JN, Congi RV. Serotyping Of Campylobacter jejuni and Campylobacter coli on the Basis of Thermo Stable Antigens. Eur J Clin Microbiol Infect Dis. 1983;2:378-83.

60. Dingle KE, van den Braak N, Colles FM, Price LJ, Woodward DL, Rodgers FG, Endtz HP, van Belkum A, Maiden MCJ. Sequence Typing Confirms That Campylobacter jejuni Strains Associated with Guillain-Barré and Miller Fisher Syndromes are of Diverse Genetic Lineage, Serotype and Flagella Type. J Clin Microbiol. 2001;39:3346-49.

61. Godschalk PC, van Belkum A, van den Braak N, van Netten D, Ang CW, Jacobs BC, et al. PCR-Restriction Fragment Length Polymorphism Analysis of Campylobacter jejuni Genes Involved in Lipooligosaccharide Biosynthesis Identifies Putative Molecular Markers for Guillain-Barre´ syndrome. J Clin Microbiol. 2007;45:2316-20.

62. Ang CW, van Doorn PA, Endtz HP, Martina ISJ, Jacobs BC, van Koningsveld R, van der Meché FGA. A Single Case of Guillain-Barré Syndrome in a Family with Campylobacter jejuni Enteritis. J Neurol. 1998;245:417.

63. Islam Z, Jacobs BC, van Belkum A, Mohammad QD, Islam MB, Herbrink P, et al. Axonal Variant of Guillain-Barré Syndrome Frequently Associated with Campylobacter Infections in Bangladesh. Neurology. 2010;74:581-87.

64. Islam Z, Jacobs BC, Islam MB, Mohammad QD, Diorditsa S, Endtz HP. High Incidence of Guillain-Barre´ Syndrome in Children, Bangladesh. Emerg Infect Dis. 2011;17:1317-18.

65. Islam Z, van Belkum A, Cody A J, Tabor H, Jacobs BC, Talukder KA, Endtz HP. A Campylobacter jejuni HS:23 Serotype and New Multi Locus Sequence Type Frequently Associated with Guillain-Barre´ Syndrome in Bangladesh. Emerg Infect Dis. 2009;15:1316-18.

66. Islam Z, Gilbert M, Mohammad QD, Klaij K, Li J, van Rijs W, Tio-Gillen AP, Talukder KA, Willison JH, van Belkum A, Endtz HP, Jacobs BC. Guillain-Barre´ Syndrome Related Campylobacter jejuni in Bangladesh: Ganglioside Mimicry and Cross Reactive Antibodies. PLoS ONE [Internet]. 2012 [cited 2013 Dec 10];7(8): e43976.

67. Allos BM. Campylobacter Jejuni Infections: Update on Emerging Issues and Trends. Clin Infect Dis. 2001;32:1201-6.

68. Hughes RA, Cornblath DR. Guillain-Barre´ syndrome. Lancet. 2005;366:1653-66.

69. Oomes PG, Jacobs BC, Hazenberg MP, Bänffer JR, van der Meché FG. Anti-GM1 IgG Antibodies and Campylobacter Bacteria in Guillain-Barré Syndrome: Evidence of Molecular Mimicry. Ann Neurol. 1995;38:170-75.

70. Godschalk PC, Kuijf ML, Li J, St Michael F, Ang CW, Jacobs BC, et al. Structural Characterization of Campylobacter Jejuni Lipooligosaccharide Outer Cores Associated with Guillain-Barre and Miller Fisher Syndromes. Infect Immun. 2007;75:1245-54.

71. Karlyshev AV, Linton D, Gregson NA, Lastovica AJ, Wren BW. Genetic and Biochemical Evidence of a Campylobacter Jejuni Capsular Polysaccharide That Accounts for Penner Serotype Specificity. Mol Microbiol. 2000;35:529-41.

73. Willison HJ, Yuki N. Peripheral Neuropathies and Anti-Glycolipid Antibodies. Brain. 2002;125:2591-625.

74. Parker CT, Horn ST, Gilbert M, Miller WG, Woodward DL, Mandrell RE. Comparison of Campylobacter Jejuni Lipooligosaccharide Biosynthesis Loci from a Variety of Sources. J Clin Microbiol. 2005;43:2771-81.