Guillain–Barré Syndrome—A Classical Autoimmune Disease Triggered by Infection or Vaccination

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Abstract Guillain–Barré syndrome (GBS) is a rare autoimmune disorder, the incidence of which is estimated to be 0.6–4/100,000 person/year worldwide. Often, GBS occurs a few days or weeks after the patient has had symptoms of a respiratory or gastrointestinal microbial infection. The disorder is sub-acute developing over the course of hours or days up to 3 to 4 weeks. About a third of all cases of Guillain–Barré syndrome are preceded by *Campylobacter jejuni* infection. *C. jejuni* strains isolated from GBS patients have a lipooligosaccharide (LOS) with a GM1-like structure. Molecular mimicry between LOS and the peripheral nerves as a cause of GBS was demonstrated in animal models of human GBS. Following the “swine flu” virus vaccine program in the USA in 1976, an increase in incidence of GBS was observed and the calculated relative risk was 6.2. Later studies have found that influenza

vaccines contained structures that can induce anti-GM1 (ganglioside) antibodies after inoculation into mice. More recent information has suggested that the occurrence of GBS after currently used influenza and other vaccines is rare. GBS involves genetic and environmental factors, may be triggered by infections or vaccinations, and predisposition can be predicted by analyzing some of these factors.

Keywords Guillain–Barré syndrome · Infections · Autoimmunity · Vaccines · *C. jejuni* · Influenza

Definition

Guillain–Barré syndrome is a disorder in which the immune system attacks gangliosides on the peripheral nervous system. The first symptoms of this disorder include varying degrees of weakness or tingling sensations in the legs. In many instances, the weakness and abnormal sensations spread to the arms and upper body [1]. These symptoms can increase in intensity until the muscles fail completely and the patient is almost totally paralyzed or there is severe dysfunction of the autonomic nervous system. In these cases, the disease is life-threatening and is considered a medical emergency. Most patients, however, recover from even the most severe cases of Guillain–Barré syndrome, although some continue to have some degree of weakness. Guillain–Barré syndrome is rare, incidence worldwide is estimated to be 0.6–4/100,000 person/year [1]. Often (in around one third of cases), Guillain–Barré occurs a few days or weeks after the patient has had symptoms of a respiratory or gastrointestinal microbial infection. Occasionally, surgery or vaccinations will trigger the syndrome. The disorder can develop over the course of hours, days, or it may take up to 3 to 4 weeks, and reflexes are usually lost.

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Due to slow down of signals travelling along the nerve, nerve conduction velocity test can aid the diagnosis. The cerebrospinal fluid contains more protein than usual, but normal cell count, so a spinal tap is important for the diagnosis.

Clinical Variants

Although ascending paralysis is the most common form of spread in GBS, other variants also exist. Miller Fisher Syndrome is a rare variant of GBS, proceeding in the reverse order of the more common form of GBS. It usually affects the ocular movements first and presents as ophthalmoplegia, ataxia, and areflexia. Anti-GQ1b (a ganglioside, see “Possible Mechanism that can Trigger GBS” in the “Discussion” section) antibodies are present in 90% of cases but not anti-GD3 antibodies [2]. Acute motor axonal neuropathy (AMAN) [3] also termed Chinese paralytic syndrome is prevalent in China and Mexico. The disease may be seasonal and recovery can be rapid. Anti-GD1a antibodies [4] are present. Anti-GD3 antibodies are found more frequently in AMAN. Acute motor sensory axonal neuropathy is similar to AMAN but also affects sensory nerves with severe axonal damage. Recovery is slow and often incomplete [5].

GBS as an Autoimmune Disease

To establish that a disease has an autoimmune etiology, Witebsky–Rose postulates that an autoimmune response be recognized in the form of an autoantibody or cell-mediated immunity, that the corresponding antigen be identified, and that an analogous autoimmune response be induced in experimental animals. Finally, the immunized animals must develop a similar disease [6].

How does GBS match the criteria for an autoimmune disease? Shoenfeld et al. [7] addressed this question and concluded that four major Witebsky–Rose criteria [6] are fulfilled in GBS. (1) Autoantigens (i.e., myelin constituents) evoking an autoantibody response could be demonstrated; (2) the presence of autoantibodies has been confirmed and several pathogenic mechanisms by which they may exert their influence have similarly demonstrated in vitro; (3) active immunization with myelin constituents has been shown to cause an autoimmune phenomena resembling human GBS; (4) an adoptive transfer of autoantibodies and or autoreactive T cells results in nerve demyelination, clinical signs, and laboratory findings of GBS [8]. Additionally, GBS is commonly seen in association with other autoimmune diseases, changes in T cells subclasses, and change in cytokine profile [7].

Willison [9] studied the motor nerve terminal as a model site of injury, and through combined active and passive immunization paradigms, have developed murine neuropathy phenotypes mediated by anti-ganglioside antibodies. This has been achieved through use of glycosyltransferase and complement regulator knock-out mice, both for cloning anti-ganglioside antibodies and inducing disease. Through such studies, Willison and his group have proven “a neuropathogenic role for murine anti-ganglioside antibodies and human GBS-associated antisera and identified several determinants that influence disease expression including (a) the level of immunological tolerance to microbial glycans that mimic self-gangliosides; (b) the ganglioside density in target tissue; (c) the level of complement activation and the neuroprotective effects of endogenous complement regulators; and (d) the role of calcium influx in mediating axonal injury”.

Environmental Factors Involved in GBS—Infection and Vaccination

Infections and GBS

An infection can induce or trigger autoimmune disease via two mechanisms—antigen-specific or antigen non-specific—which can operate either independently or together. An autoimmune disease will only arise, however, if the individual is genetically predisposed to that particular condition. A common explanation for how infectious agents stimulate autoimmunity in an antigen-specific way is via molecular mimicry. Antigenic determinants of microorganisms can thus be recognized by the host immune system as being similar to antigenic determinants of the host itself. Molecular mimicry among sugar structures is common and leads to numerous manifestations of infection-associated and antibody-mediated neuropathies. About a third of all cases of Guillain–Barré syndrome are preceded by *Campylobacter jejuni* infection [10]. This bacterium expresses a lipooligosaccharide molecule that mimics various gangliosides present in high concentrations in peripheral nerves. Numerous viruses also collect gangliosides as they incorporate plasma membrane from the host cell. As a result, viral infections (i.e., influenza, parainfluenza, polio, herpes) are often associated with Guillain–Barré syndrome, and both bacterial and viral vaccines have been linked with induction of the condition [11].

Numerous epidemiological studies and anecdotal cases have established an association between infections and Guillain–Barré syndrome (Table 1).

Kinnunen et al. [12] performed a retrospective analysis of the incidence of Guillain–Barré syndrome (GBS) in Finland in 1981–1986. Monthly rates showed an increased

Table 1 Infectious agents associated with GBS

Infectious agent	Year	Incidence per 10 ⁶	Time post infection	Reference
Chikungunya virus	2009	Up 22% from baseline (3.3)	2–3 weeks	[16]
Influenza	1990–2005	7.3 16.6 RI	90 days 30 days	[15]
Coxsackieviruses; <i>Chlamydia</i> CMV; <i>M. pneumoniae</i> ; <i>C. jejuni</i>	Prospective	?	6 weeks	[14]
Echo/Coxsackie; varicella; mumps; rubella; influenza; HIV; <i>Borrelia</i> ; <i>M. pneumoniae</i> ; <i>C. jejuni</i>	90'	?	Weeks	[7]
<i>C. jejuni</i>	2003	9.5 OR	?	[13]
Polio (circulating type 3)	1981–1986	Increase from (8.2) baseline	Weeks	[12]
Hepatitis E	2009	1 case	Weeks	[17]

incidence from baseline of GBS (8.2 per million) in March 1985, following by a few weeks of the onset of the nationwide oral poliovirus vaccine campaign and partly overlapping it. Analysis of the time series in depth suggested, however, that a change point in the occurrence of GBS had already taken place before the oral poliovirus vaccine campaign. Widespread circulation of wild-type 3 poliovirus in the population immediately preceded the oral poliovirus vaccine campaign and the peak occurrence of GBS. These results demonstrate a temporal association between poliovirus infections, caused by either wild virus or live attenuated vaccine, and an episode of increased occurrence of GBS.

Shoenfeld et al. [7], in a comprehensive review about GBS as an autoimmune disease, cite numerous bacterial and viral infections associated with the disease. Among the viruses, echo, coxsackie, varicella, mumps, rubella, influenza, and HIV are documented as infections preceding episodes of GBS. Bacterial infections preceding GBS included *Borrelia*, *Mycoplasma pneumoniae*, and *C. jejuni*.

A strong association between *C. jejuni* infection and GBS, with an OR of 9.5, was also demonstrated in another study, confirming a causal association [13].

Microbiological studies carried out on 84 patients resulted in a probable diagnosis of infectious diseases etiology in 46 (55%). Coxsackieviruses (15%), *Chlamydia pneumoniae* (8%), cytomegalovirus (7%), and *M. pneumoniae* (7%) were the most frequently involved agents. Serological evidence of a *C. jejuni* infection was found in six patients (7%). The authors conclude that the etiology of antecedent diseases is distributed over a wide spectrum of pediatric infectious diseases. Most of the children who had been vaccinated showed concomitant infectious diseases, thus obscuring the causative role for GBS [14].

Another strong association between GBS and influenza infections was documented by Stowe et al. [15]. The

authors used the self-controlled case series method to investigate the relation of Guillain–Barré syndrome with influenza vaccine and influenza-like illness using cases recorded in the General Practice Research Database from 1990 to 2005 in the United Kingdom. The relative incidence of Guillain–Barré syndrome within 90 days of vaccination was 0.76 (95% confidence interval, 0.41–1.40). In contrast, the relative incidence of Guillain–Barré syndrome within 90 days of an influenza-like illness was 7.35 (95% confidence interval, 4.36–12.38), with the greatest relative incidence (16.64, 95% confidence interval, 9.37–29.54) within 30 days. The relative incidence was similar (0.89, 95% confidence interval, 0.42–1.89) when the analysis was restricted to a subset of validated cases. The authors found no evidence of an increased risk of Guillain–Barré syndrome after seasonal influenza vaccine.

The finding of a greatly increased risk after influenza-like illness is consistent with anecdotal reports of a preceding respiratory illness in Guillain–Barré syndrome and has important implications for the risk/benefit assessment that would be carried out, should pandemic vaccines be deployed in the future.

Two recent reports (2009) document association of GBS and relatively rare viral infections: Lebrun et al. [16] report two cases of GBS after Chikungunya virus infection in Réunion Island, which correlated with epidemiological data conferring the association between the two. Chikungunya virus is an RNA alphavirus (group A arbovirus) in the family Togaviridae. *Aedes aegypti* and *Aedes albopictus* are the known mosquito vectors. Anti-Chikungunya IgM was found in serum and CSF, although genomic products in serum and CSF were negative, which was not surprising, given the brief period (4–5 days) of viremia. These findings strongly supported a disseminated acute Chikungunya infection and support the conclusion that Chikungunya virus was probably responsible for the GBS. In 2006,

Chikungunya virus was found on Réunion Island; seroprevalence on the island was estimated to be 38.2% among 785,000 inhabitants (95% confidence interval 35.9%–40.6%).

Epidemiologic data also support a causal relationship between Chikungunya infection and GBS: The incidence rate of GBS increased 22% in 2006 (26/787,000, persons) over the rate in 2005 (21/775,000 or 2.7/10,000 persons) and then declined to a rate closer to baseline in 2007 (23/800,000 or 2.87/100,000 persons).

Loly et al. [17] report a case of Guillain–Barré syndrome in a patient sporadically contaminated in a Western country. This is the third report of GBS in a patient with hepatitis E, and the first occurring in a patient sporadically contaminated in a Western country. The authors believe it is the first description of the presence of anti-ganglioside GM2 antibodies in GBS associated with a hepatotropic virus, suggesting possible molecular mimicry involving gangliosides.

In all the above reports, the time between the infection disease and the onset of GBS was a few weeks, ranging from 2 to 3 weeks to 3 months. This time period is in agreement with a temporal association between an environmental trigger and the onset of an autoimmune disease. Adding the high odds ratio of association calculated for some of these infections, (OR=9.5 for *C. jejuni*) and augmentation of the relative incidence following infection, (RI=7.3–16.6 for influenza), the conclusion is quite obvious, that these bacterial and viral infections, as well as others are strong environmental agents involved with the onset of GBS.

Most infectious agents, such as viruses, bacteria and parasites, can induce autoimmunity via a number of mechanisms. In many cases, it is not a single infection but rather the “burden of infections” from childhood that is responsible for the induction of autoimmunity in adulthood, many years after the original infection [18].

Vaccinations and GBS

There are anecdotal reports of GBS occurring in a time frame after immunizations that can indicate a temporal association between the two events. The period between vaccination and first symptoms of GBS, range from as short as 3–5 days, to 6–10 weeks, and up to a few months and even years (Table 2). The temporal association and lack of infections in those individual cases can indicate a causal association [19–23]. However, in the epidemiological studies cited, no significant causal association was found. Incidence observed for GBS following the vaccinations was either “small”, “in the expected range”, same as “background”, “extremely rare”, or lower than “baseline”. Only two studies with polio vaccination found an increase

incidence from a background of $8.2:10^6$ and an OR of 7.27 (10, 11).

Influenza Vaccination

Following the “swine flu”) influenza A/New Jersey) virus vaccine program in the USA in 1976, an increase in incidence of GBS was observed [24] (Table 3). The National Influenza Immunization Program was suspended on December 16, 1976 and nationwide surveillance for GBS was begun. This surveillance uncovered a total of 1,098 patients with onset of GBS from October 1, 1976, to January 31, 1977, from all 50 states. A total of 532 patients had received an A/New Jersey influenza vaccination prior to their onset of GBS (vaccinated cases), and 15 patients received a vaccination after their onset of GBS. Epidemiologic evidence indicated that many cases of GBS were related to vaccination. When compared to the unvaccinated population, the vaccinated population had a significantly elevated attack rate in every adult age group. The estimated attributable risk of vaccine-related GBS in the adult population was just under one case per 100,000 vaccinations. The period of increased risk was concentrated primarily within the 5-week period after vaccination, although it lasted for approximately 9 or 10 weeks. The mean interval from vaccination to onset was 3.9 weeks. The incidence rose from $2.6:10^6$ for nonrecipients to $13.3:10^6$ for vaccine recipients (corrected later by Breman and Hayner [25] to be $11.7:10^6$), and the calculated relative risk was 6.2. More recent information suggested that the occurrence of GBS after currently used influenza and other vaccines is extremely rare [26]. Case control studies have shown no evidence of a significant increase in risk of having received an immunization preceding GBS (i.e., measles, mumps, rubella) compared with contemporary controls [27–29].

Retrospective examination of the incidence of GBS for the seasons of the 1992–3 and 1993–4 influenza vaccination programs in the USA suggested that influenza vaccination only caused 1–2 extra cases of GBS per million vaccines [30]. The calculated relative risk in different studies from 1978 to 2005 produced RR values ranging from 0.4 to 1.7. Only one study documenting the years 1991–1999 came up with higher RR values (4.3–8.5), which may establish a significant causal association between the influenza vaccination program and incidence of GBS. Despite this evidence, GBS is an autoimmune condition and the knowledge that immunizations are designed to activate the immune system give rise to continued unease about immunization following the disease [31, 32]. This unease is enhanced by a report of two cases of GBS recurring following swine influenza vaccine [33]. In addition, recurrent attacks of chronic inflammatory

Table 2 Correlation between vaccinations and GBS

Vaccine	Year	Incidence	Time post vaccination	Reference
Hepatitis B	2004	1 case	10 weeks	[73]
HBV	1983–2002	19 cases	3 days–9 months	[73]
Measles; rubella	2003	Under baseline	6–10 weeks	[74]
Live measles and rubella	1976	2 cases	1 week	[75]
Meningococcal MCV4	2005–2006	Small	6 weeks	[76]
Smallpox	2002–2004	Expected range	12 days	[77]
Hepatitis A	2004	1 case	5 days	[78]
Polio	2003	7.27 OR	?	[13]
	1981–1986	Increase from baseline	10 weeks	[12]
Sabine strain	1996	38 cases	Sabine strain isolated days–weeks of onset	[79]
MMR	1982–1986	Background	80 days–years	[80]
Tetanus	90'	Extremely rare	6 weeks	[81]
Tetanus-diphtheria	1997	1 case	4 days	[19]
H influenza type B	1993	1 case (+4)	10 days	[20]
Rabies (Semple vaccine)	90'	5 cases	?	[82]
(Diploid human cells)	1980	1 case	14 days	[83]

demyelinating polyradiculoneuropathy have followed tetanus toxoid immunization [31, 34]. However, many patients have received immunizations after the acute phase of their disease, sometimes repeatedly [35], without suffering a relapse. The number of such patients has, however, not been monitored and the actual risk is not known. In the absence of adequate evidence and the difficulty of conducting an adequately powered randomized trial, it would be appropriate to audit a recovered GBS patient population to discover the proportion receiving immunizations and the corresponding outcome. Although the experiment has never been done in GBS, patients with multiple sclerosis have been randomized to receive or not receive influenza vaccine, and no evidence emerged to suggest that immunization stimulated relapse [36, 37]. There are structural differences between nodes in the central nervous system (CNS) and peripheral one (PNS) that might explain the susceptibility of the PNS in GBS

[38]. In the PNS, specialized microvilli project from the outer collar of Schwann cells and come very close to nodal axolemma of large fibers. The projections of the Schwann cells are perpendicular to the node and are radiating from the central axons. However, in the CNS, one or more of the astrocytic processes come in close vicinity of the nodes. These processes may stem from multi-functional astrocytes, as opposed to from a population of astrocytes dedicated to contacting the node. On the other hand, in the PNS, the basal lamina that surrounds the Schwann cells is continuous across the node.

Discussion

An etiology for the 1976 increase in incidence of GBS following the influenza vaccination program was suggested by Nachamkin et al. [39]. The authors hypothesized that the

Table 3 Causal correlation between influenza vaccination and GBS

Vaccination years/country	Relative risk	Significance	Reference
1976/USA	6.2	Yes	[84]
1978–1979 USA	1.4	No	[85]
1980–1981 USA	1.4	No	[86]
1976–1977 USA	Attrib. risk 1:100,000	Yes	[24]
1992–1994 England/Wales	1.7	No	[29, 31]
1991–1999 USA	4.3–8.5	Yes	[87]
1993–1994	1.7	No	[88]
2002–2003 USA	0.4		
1992–2004 Canada	1.45	Small	[89]
1990–2005/UK	0.76	No	[15]

swine flu vaccine contained contaminating moieties (such as *C. jejuni* antigens that mimic human gangliosides or other vaccine components) that elicited an anti-GM1 antibody response in susceptible recipients. Surviving samples of monovalent and bivalent 1976 vaccine, comprising those from 3 manufacturers and 11 lot numbers, along with several contemporary vaccines were tested for hemagglutinin (HA) activity, the presence of *Campylobacter* DNA, and the ability to induce anti-*Campylobacter* and anti-GM1 antibodies after inoculation into C3H/HeN mice. The researchers found that, although *C. jejuni* was not detected in 1976 swine flu vaccines, these vaccines induced anti-GM1 antibodies in mice, as did vaccines from 1991 to 1992 and from 2004 to 2005. Preliminary studies suggest that the influenza HA induces anti-GM1 antibodies. The authors concluded that influenza vaccines contain structures that can induce anti-GM1 antibodies after inoculation into mice.

Possible Mechanism that can Trigger GBS

Molecular mimicry is one mechanism by which infectious agents may trigger an immune response against autoantigens. Although several examples of molecular mimicry between microbial and self-components are known [40], in most cases, the epidemiological relationship between autoimmune disease and microbial infection has not been established. In other cases, moreover, no replicas of human autoimmune disease have been obtained by immunizing with the mimic of an infectious agent. Replicas associated with definite, epidemiological evidence of microbial infection are required to test the molecular mimicry theory of the development of autoimmune diseases. Guillain–Barre’ syndrome, the prototype of postinfectious autoimmune diseases, ranks as the most frequent cause of acute flaccid paralysis, and *C. jejuni* is the most frequent antecedent pathogen. Epidemiological studies, which established the relationship between GBS and antecedent *C. jejuni* infection, showed that one fourth to one third of GBS patients develop the syndrome after being infected. GBS was considered a demyelinating disease of the peripheral nerves, but the existence of primary “axonal GBS” has been confirmed and is now widely recognized. Ganglioside GM1 is an autoantigen for IgG Abs in patients with axonal GBS subsequent to *C. jejuni* enteritis. *C. jejuni* strains isolated from such patients have a lipooligosaccharide (LOS) with a GM1-like structure. To verify that molecular mimicry between an environmental agent and the peripheral nerves causes GBS, Yuki et al. [41] sensitized animals with *C. jejuni* LOS and produced a model of human GBS, generated anti-GM1 mAb by immunization with the LOS, and determined the distribution of GM1 in human spinal nerve roots. As further proof that an autoimmune reaction

causes neuromuscular disease, the authors also showed that anti-GM1 monoclonal antibody (mAb) blocked muscle action potentials in a muscle–spinal cord co-culture. “On sensitization with *C. jejuni* lipooligosaccharide, rabbits developed anti-GM1 IgG antibody and flaccid limb weakness. Paralyzed rabbits had pathological changes in their peripheral nerves identical with those present in Guillain–Barre’ syndrome. Immunization of mice with the lipooligosaccharide produced mouse antibodies, from which mAb were produced, that reacted with GM1 and bound to human peripheral nerves. The mouse mAb and anti-GM1 IgG from patients with Guillain–Barre’ syndrome did not induce paralysis but blocked muscle action potentials in a muscle–spinal cord co-culture, indicating that anti-GM1 antibody can cause muscle weakness” [41].

New tests were developed recently, for better detection of antiganglioside-specific antibodies and antiganglioside complexes [42]. The antibody specifically recognizes a new conformational epitope formed by two gangliosides (ganglioside complex) in the acute-phase sera of some GBS patients. In particular, the antibodies against GD1a/GD1b and/or GD1b/GT1b complexes are associated with severe GBS requiring artificial ventilation. Some patients with Miller Fisher syndrome also have antibodies against ganglioside complexes including GQ1b; such as GQ1b/GM1 and GQ1b/GD1a. The antibodies against ganglioside complexes may therefore directly cause nerve conduction failure and severe disability in GBS.

C. jejuni infection also often precedes acute motor axonal neuropathy (AMAN), a variant of GBS. Anti-GM1, anti-GM1b, anti-GD1a, and anti-GalNAc-GD1a IgG antibodies are associated with AMAN. Carbohydrate mimicry (Galbeta1–3GalNAcbeta1–4(NeuAcalpha2–3)Gal-beta1) was seen between the lipooligosaccharide of *C. jejuni* isolated from an AMAN patient and human GM1 ganglioside. Sensitization with the lipooligosaccharide of *C. jejuni* induces AMAN in rabbits as does sensitization with GM1 ganglioside. Paralyzed rabbits have pathological changes in their peripheral nerves identical to changes seen in human GBS. *C. jejuni* infection may induce anti-ganglioside antibodies by molecular mimicry, eliciting AMAN. This is a verification of the causative mechanism of molecular mimicry in an autoimmune disease. To express ganglioside mimics, *C. jejuni* requires specific gene combinations that function in sialic acid biosynthesis or transfer. The knock-out mutants of these landmark genes of GBS show reduced reactivity with GBS patients’ sera, and fail to induce an anti-ganglioside antibody response in mice. These genes are crucial for the induction of neuro-pathogenic cross-reactive antibodies [43].

Koga et al. [44] performed a comprehensive analysis of bacterial risk factors for the development of GBS after *C. jejuni* enteritis. *C. jejuni* strains carry a sialyltransferase

gene (cst-II), which is essential for the biosynthesis of ganglioside-like lipooligosaccharides (LOSs). Strains of *C. jejuni* from patients with GBS had LOS biosynthesis locus class A more frequently (72/106; 68%) than did strains from patients with enteritis (17/103; 17%). Class A strains predominantly were serotype HS:19 and had the *cstII* (Thr51) genotype; the latter is responsible for biosynthesis of GM1-like and GD1a-like LOSs. Both anti-GM1 and anti-GD1a monoclonal antibodies regularly bound to class A LOSs, whereas no or either antibody bound to other LOS locus classes. Mass-spectrometric analysis showed that a class A strain carried GD1a-like LOS as well as GM1-like LOS. Logistic regression analysis showed that serotype HS:19 and the class A locus were predictive of the development of GBS. The high frequency of the class A locus in GBS-associated strains, which was recently reported in Europe, provided the first GBS-related *C. jejuni* characteristic that is common to strains from Asia and Europe. The class A locus and serotype HS:19 seem to be linked to *cstII* polymorphism, resulting in promotion of both GM1-like and GD1a-like structure synthesis on LOS and, consequently, an increase in the risk of producing antiganglioside autoantibodies and developing GBS. The sialyltransferase gene polymorphism may also direct the clinical features of GBS.

The *C. jejuni* sialyltransferase (cst-II) consists of 291 amino acids, and the 51st determines its enzymatic activity. Strains with cst-II (Thr51) expressed GM1-like and GD1a-like LOS, whereas strains with cst-II (Asn51) expressed GT1a-like and GD1c-like LOS. Patients infected with the cst-II (Thr51) strains had anti-GM1 or anti-GD1a IgG antibodies, and showed limb weakness. Patients infected with the cst-II (Asn51) strains had anti-GQ1b IgG antibodies and showed ophthalmoplegia and ataxia. The cst-II gene is responsible for the development of Guillain–Barré and Fisher syndromes, and the polymorphism (Thr/Asn51) determines which syndrome develops after *C. jejuni* enteritis [45].

The Role of the Nodes of Ranvier

Vucic et al. [1] reviewed the role of sodium channels in the pathology of GBS. Specifically, the rapid improvement in clinical deficits following immunomodulatory treatment (such as IVIG) [46], often within hours, cannot be explained by axonal remyelination, but possibly by removal of antibodies or other circulating factors that may interfere with Na⁺ channel function. Inactivation of Na⁺ channels results in a conduction block and slowing of conduction velocity. In GBS patients, Na⁺ channel blocking factors have been demonstrated in the CSF. GM1 gangliosides, immunological targets in GBS, are localized to the nodes of Ranvier where sodium and other targets are clustered. By

using binding assay of cholera and tetanus toxins, respectively, it was established [47] that GM1 and G1b-series gangliosides are predominantly localized to axonal and glial structures of the nodes of Ranvier and to paranodal/internodal axolemma, while polysialogangliosides not of the G1b-series are present on the internodal Schwann cell surface. Shavit and colleagues [48] have demonstrated also a conduction block using protease-activated receptor 1 (PAR-1) on the nodes of Ranvier, implicating this structure and PAR-1 activation in the pathogenesis of conduction block in inflammatory and thrombotic nerve diseases. An immune response to this structure may induce conduction block which is one of the electrophysiological hallmarks of GBS.

As mentioned above, antecedent infections, particularly infections with *C. jejuni*, are associated with production of IgG antibodies against gangliosides, especially GQ1b. GQ1b gangliosides are abundantly expressed in the paranodal myelin sheets of extraoculomotor nerves, the neuromuscular junction, and dorsal root ganglia. Anti-GQ1b IgG antibodies are strongly associated with Fisher syndrome and correlate with clinical features of ophthalmoplegia and ataxia. The neurological effects of anti-GQ1b antibodies are induced by complement-mediated destruction of both perisynaptic Schwann cells and axonal terminals, resulting in neuromuscular junction blockade. Patch clamp techniques have shown that anti-GQ1b antibodies inhibit presynaptic Ca²⁺ inflow and interact with proteins of the exocytotic apparatus, thereby interfering with neurotransmitter release, which prevents activation of postsynaptic neurons and ultimately results in muscle weakness.

Conclusion

Judging by the evidence presented here, the etiology of GBS can be multifactorial, as in other autoimmune diseases. It involves genetic and environmental factors, may be triggered by infections or vaccinations, and predisposition can be predicted by analyzing some of these factors. Shoenfeld et al., in a series of three enlightening reviews, depict the Mosaic of Autoimmunity. The authors present the multifactorial character of autoimmune diseases, including GBS, and concentrate on genetic factors, hormonal and environmental ones, and focus also on prediction and therapy of these disorders [49–51]. GBS is unique in the aspect that it can be triggered both by infection (*C. jejuni*) or vaccination (influenza, polio), and in this respect, it can serve as a model for the linkage between exposure to environmental agents and autoimmune diseases. Many other autoimmune diseases may be triggered by infections and/or vaccinations, the pathologic mechanism may involve molecular mimicry, and they can be treated by IVIG [52–

71]. However, GBS is still a classical example of an autoimmune disease triggered by either infection or vaccination.

The Global Advisory Committee on Vaccine safety considers that investigation of a possible causal relationship could best be achieved by large-scale studies of the incidence of GBS before and after an immunization program. All incident cases would need to be carefully ascertained and documented to ensure as accurate a diagnosis as possible and to identify the form of GBS (principally AIDP or AMAN). Improved understanding of the pathogenesis of all forms of GBS will assist the investigation of possible associations between GBS and immunization. In this context, the collection of serum samples from incident cases of GBS would contribute to the identification of the different forms of the disease and of understanding their possible relationship with vaccines. Such studies would be particularly helpful in investigating neurological adverse events following immunization that occur in association with pandemic or pre-pandemic influenza vaccines [72]. On August 31, 2009, the Centers for Disease Control and Prevention (CDC) and the American Academy of Neurology (AAN) started a campaign, requesting neurologists to report any possible new cases of Guillain-Barré syndrome (GBS) following 2009 H1N1 flu vaccination using the CDC and U. S. Food and Drug Administration Vaccine Adverse Event Reporting System. Although they do not anticipate that the 2009 H1N1 vaccine will have an increased risk of GBS, out of an abundance of caution, and given that GBS may be of greater concern with any pandemic vaccine because of the association of GBS with the 1976 swine flu vaccine, the CDC and AAN asked neurologists to report any potential new cases of GBS after-vaccination as part of the CDC's national vaccine safety monitoring campaign (<http://www.aan.com/press/?fuseaction=release.view&release=757>). This campaign is now in progress.

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