Review Article

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Influenza vaccination and Guillain–Barré syndrome: Reality or fear

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ABSTRACT

Guillain–Barré syndrome (GBS) is an inflammatory disorder and an acute immune-mediated demyelinating neuropathy that causes reduced signal transmissions, progressive muscle weakness, and paralysis. The etiology of the syndrome still remains controversial and uncertain. GBS can be initiated and triggered by respiratory tract infections such as influenza, and intestinal infections such as *Campylobacter jejuni*. In addition, there is considerable evidence suggesting links between influenza vaccination and GBS. As reported previously, the incidence of GBS in individuals receiving swine flu vaccine was about one to two cases per million. Despite the influenza vaccine efficacy, its association with an immune-mediated demyelinating process can be challenging as millions of people get vaccinated every year. In this review we will discuss the association between influenza infection and vaccination with GBS by focusing on the possible immunopathological mechanisms.

Key words: influenza, flu vaccination, Guillain–Barré syndrome

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INTRODUCTION

Guillain–Barré syndrome (GBS) is a rare immune disorder in which the immune system invades Schwann cells of the peripheral nervous system (PNS).[1-3] The etiology of GBS is still unclear. Recent investigations demonstrated that GBS can be triggered by several respiratory tract and intestinal infections. A significant number of GBS cases were also inflicted by Zika virus infection. After a large-scale vaccination campaign in 1976 against swine influenza, an increase in the incidence of GBS was noticed and thus raising the doubts on the safety of influenza vaccination.[4] Subsequently, many studies were performed to evaluate the association of infections and in particular influenza as well as influenza vaccination with an incidence of GBS.

GUILLAIN–BARRÉ SYNDROME: SYMPTOMS AND CAUSES

Since the eradication of polio, GBS has become the most common cause of acute flaccid paralysis. GBS is an autoimmune disorder affecting the Schwann cells of the PNS. This immune-mediated demyelinating neuropathy can rapidly evolve over a period of few days or more and can lead to paralysis or even death.[5-7] The initial symptoms of GBS include muscle weakness that starts from distal limbs which subsequently progresses to proximal limbs.[8] GBS may lead to respiratory failure requiring mechanical ventilation over 15% of cases.[9] In some cases, GBS can affect the heart rate and changes the blood pressure by disrupting the autonomic nervous system.[10] The disease can be self-limiting, with muscle

strength reaching a lowest point in few days, followed by a partial or full recovery over weeks to months. Diagnosis of this syndrome is based on the clinical signs and symptoms and through rule out of other differential diagnoses as shown in Table 1. The treatment includes administration of intravenous immunoglobulins or plasmapheresis, and supportive therapies. Although most people have an uneventful recovery, up to one-third of the cases are left with severe neurological deficits.[11, 12] The mortality rate of the disease is approximately 8% in developing world, but much lower in developed countries.[13] The incidence of GBS increases with age, and people older than 50 years are at greatest risk for developing GBS. The estimated risk of developing GBS in the world is one to two cases per 100,000 people per year.[14] Severe autoimmune responses resulted from infections by external infectious agents are considered as major initiating factors of the syndrome.[15, 16] Infection by *Campylobacter jejuni* is identified as the most common inciting event although other agents such as herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), Zika virus (ZIKV), *Mycoplasma pneumoniae, Haemophilus influenza*, and influenza have been reported.[7, 17-22] Vaccination to influenza has been implicated in GBS, although the evidence for this link is controversial.[23]

IMMUNOPATHOLOGY OF GUILLAIN–BARRÉ SYNDROME

Access to the PNS by the immune system requires crossing of the blood–nerve barrier. The blood–nerve barrier is not as tight as the blood–brain barrier, so that small amounts of circulating proteins and immunoglobulin G (IgG) can leak into PNS making it vulnerable to the immune attacks. The blood–nerve barrier is particularly leaky within the dorsal root ganglia and is altogether absent at nerve terminals, making these areas especially vulnerable to immune-mediated attacks. As previously mentioned, GBS begins with infectious agents such as influenza virus. Antigen-presenting cells (APCs) including dendritic cells (DCs), macrophages, and B lymphocytes are in the frontline dealing with the influenza infections.[24, 25] Epitopes displayed by the virus interact with pattern recognition receptors (PRRs) on APCs, especially DCs. Stimulation of APCs results in T cell activation and differentiation into either a Th1 (T helper cell type 1) or Th2 phenotype. Each phenotype has its specific cytokine signature and function. Once inside the PNS, the Th1 phenotype of differentiated Th cell recruits and activates macrophages. Macrophages initiate damage to PNS by producing and secreting matrix metalloproteinases (MMPs) and nitric oxide.[26] Humoral responses are initiated through activation of B cells by Th2 lymphocytes or by the epitopes of the virus cross-linking the B cell receptors. Both these pathways can result in class switching of activated B cells to IgG-producing plasma cells. The secreted IgG binds to viral surface epitopes and cross-reacts with similar epitopes in the peripheral nervous tissues. These antigen–antibody interactions can activate the complement system, resulting in membrane attack complex (MAC) formation [27] leading to nerve cell membrane damage and destruction.[28]

INFLUENZA AND ITS COMPLICATIONS

Influenza is a highly contagious respiratory infection that is common in cold seasons.[29] Annually, influenza epidemics cause 3–5 million severe cases of hospitalization and 300,000–600,000 deaths.[30, 31]

Typical symptoms of influenza infection include fever with shaking chills, myalgia, fatigue, anorexia, and diarrhea. The severity of these symptoms and their sudden occurrence can help differentiate influenza from other respiratory viral infections.[29,32,33] Symptoms such as cough and sore throat are prevalent in influenza; however symptoms such as coryza are more due to common cold infections than influenza infection.[34] Influenza viruses are divided into influenza A, B, and C types. Influenza A and B viruses circulate in the community in the winter every year and are found to be responsible for seasonal epidemics.[35] Influenza C viruses usually have no symptoms or show mild symptoms and do not cause epidemics.[36] Mutations in the influenza viral genomes leading to antigen changes (shift or drift), as well as the existence of animal reservoirs, can make the influenza treatment challenging as public immunity from previous immunizations may not be enough for protection.[37] In some instances the changes to the viral genomes are so intense that the existing vaccines may no longer be effective leading to pandemics, such as a late

Table 1: Some diagnostic criteria in Guillain–Barré syndrome.

Criteria for diagnosis of Guillain–Barré syndrome	
Required	Weakness within 4 weeks from onset of syndrome (starting muscle weakness in lower limbs)
	Hyporeflexia
Supportive	Lack of fever in the patient
	Infections of the respiratory and gastrointestinal system during the past few weeks
	Increased protein concentration in cerebrospinal fluid (CSF) with moderate increase in the cell

winter outbreak of swine flu (pH1N1) in 1976 and flu pandemic or swine flu in 2009 (caused by influenza A virus type pH1N1).[38] The complications of influenza infection can be either mild or very severe. Sinusitis and otitis are examples of moderate complications of influenza.[39] Serious complications include viral pneumonitis, secondary bacterial pneumonia (*Staphylococcus aureus* pneumonia or *Streptococcus pneumoniae*),[39, 40] myocarditis, encephalitis, myositis or rhabdomyolysis, GBS, and multiple organ failures.[41-43]

INFLUENZA VACCINES AND ADVERSE EFFECTS

Influenza vaccines are commonly available for seasonal influenza and new versions of the vaccines are developed every year as the virus rapidly changes. Pandemic influenza vaccines are produced against certain strains of the influenza virus, such as the 2009 pH1N1 virus for rapid distribution during an influenza pandemic.[44] Flu vaccines are available either as injectable inactivated vaccines or nasal spray flu vaccines (live attenuated influenza vaccine).[45, 46] Some resources report that injectable trivalent and quadrivalent inactivated influenza vaccines are frequently used globally. Serious side effects to the flu vaccination are not very common. The most common adverse effects include pain at the injection site, muscle aches, fever, and malaise.[47, 48] Allergic reactions have also been rarely reported.[49] GBS after influenza vaccination was first reported in 1976, which has become the origin of numerous studies on the association between this neurological disease and the vaccine.[50, 51] Before that, GBS was only associated with infectious diseases, but since 1976 an increase in the incidence of GBS after influenza vaccination has been noted with the same antigenic similarity in the role of vaccines, especially the influenza vaccine.

INFLUENZA VACCINE AND GUILLAIN–BARRÉ SYNDROME

Incidence of GBS after influenza vaccination was first reported in 1976 during a national vaccination program against pandemic swine flu in the United States.[50, 51] About 40 million people were vaccinated with the influenza A vaccine (influenza A vaccine in New Jersey) during the pandemic, and subsequently an eight-times increase in GBS incidence was observed (especially at 2–3 weeks or even more after vaccination).[52] Since then, many researches evaluated the risk of GBS after receiving the seasonal and pandemic inactivated influenza vaccine. An overview conducted on 39 studies reported that the relative risk of GBS after pandemic influenza vaccination was higher than that after seasonal influenza vaccination, with an overall relative risk for the incidence of GBS after influenza vaccination was 1.4 (95% CI: 1.2–1.7).[4] Other studies investigating the association between GBS and seasonal influenza vaccines after 1976 indicated the risk as very minimal with less than one case per million.[53] Risk of GBS is maximum in the first 2–3 weeks post vaccination, but in most cases the estimated risk was one to two cases per million vaccinations.[54, 55] Furthermore, the biologic mechanism for GBS following influenza vaccine may involve the synergistic effects of endotoxins and vaccine induced autoimmunity. Following the H1N1 influenza pandemic in 2009 and the administration of the pH1N1 monovalent vaccine due to its similarity to the H1N1 monovalent vaccine in 1976, there were concerns about the probability of GBS. However, the studies that investigated this issue estimated the attributable risk to be about one to five per million doses of vaccination. In a meta-analysis conducted following the 2009 H1N1 monovalent influenza vaccination program (the largest nationwide vaccination program in the United States), the incidence of GBS was reported as 1.6 cases per million vaccinated people, which is approximately equal to the attributable risk reported for the seasonal influenza vaccination. Therefore, there is currently no consensus on the prohibition of the administration of the influenza vaccine. Nonetheless, it was recommended that caution should be taken in the revaccination of persons who have developed GBS within 6 weeks after receiving the influenza vaccine.

INFLUENZA AND GUILLAIN–BARRÉ SYNDROME

Even before the term "Guillain–Barré syndrome" was used in the clinical medicine, cases of infectious polyneuritis have been reported during influenza pandemic in the early twentieth century. About two-thirds of the influenza-infected patients initially present respiratory or gastrointestinal tract infections. Two studies in England (2007 and 2009) reported a strong association between influenza infection and GBS, with GBS occurring within 3 months after the influenza-like illness (ILI).[23] In further strengthening the association of influenza infection to GBS, another study conducted on GBS patients confirmed a prior influenza infection.[56] The relative incidence of GBS after influenza was highest in the first week after infection and decreased during the next 6 weeks. The estimated risk of GBS after influenza was reported as 17.2 cases per 1 million patients hospitalized with influenza.[57] A study in Norway during the 2009 pandemic (H1N1) influenza showed a much higher GBS in influenza patients with a relative risk of 4.89 (95% CI: 1.7–20.36). The risk of incidence of GBS post influenza infection was also higher

than the relative risk of 1.1 (95% CI: 0.51–2.43) reported for pH1N1 vaccination.[58]

GUILLAIN–BARRÉ SYNDROME, INFLUENZA VIRUS INFECTION, AND INFLUENZA VACCINE

According to several studies, there has been no proven association between the incidence of GBS and influenza vaccination with the exception of 1976 H1N1 influenza vaccination campaign in New Jersey.[59] In fact 1976 H1N1 influenza vaccine in New Jersey is the only proven association of GBS and influenza vaccination. A study that analyzed few cases of GBS or Miller Fisher syndrome reported that the increase in the incidence of GBS syndrome was unlikely to occur over 40 days after vaccination.[60] These studies suggest that the proven association between influenza vaccines and GBS is very little, and most often occurs in the case of pandemic vaccines. It seems that no prohibition can be considered for administration of influenza vaccine, except in persons who have had a history of GBS within 6 weeks after vaccination. On the other hand, some studies have noted seasonal winter patterns for GBS incidence.[61] A study that examined the seasonal pattern of GBS for the year 2009 reported that an increase in vaccination coverage from 19.7% to 35.5% resulted in no similar increase in GBS cases.[62] Some other studies revealed that influenza cases increased during 2004–2005 exactly overlapping with the wave of hospitalization due to GBS during the same period.[63] These findings suggest a significant association between hospitalization due to GBS and influenza cases, but the coverage of influenza vaccine did not significantly affect the pattern of GBS incidence in the general population.

CONCLUSION

Given the very strong association between influenza infection and the incidence of GBS, and considering the requirement of vaccination in the prevention of influenza, we should not deprive the general population from getting vaccinated on the grounds of risk for GBS due to vaccination. It is to be noted that preventing the complications of influenza is one of the important benefits of the influenza vaccine. In fact, the complication of GBS due to vaccination is a rare event and thus poses very minimal risk. Therefore educational programs are required to erase this fear from the general public opinion.

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Conflict of Interest

There are no conflicts of interest.

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