



## Guillain-Barre Syndrome Following PCV Vaccine

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### Abstract

Guillain-Barre syndrome (GBS) is a rapid-onset muscle weakness caused by the immune system attacking the peripheral nervous system. Although the causes still remain elusive, many studies in the past have linked GBS to vaccinations, such as influenza, but pneumococcal vaccine remains to be studied. This case report highlights a woman who developed bilateral lower extremity weakness from Guillain-Barre a month after administration of the PCV vaccine and subsequent respiratory failure. Possible etiology could be linked to the T-dependent stimulation response of GBS to the G1-specific B cells found in the peripheral blood. Full recovery is often rare in the syndrome, but rapid administration of IV Ig and extensive therapy has proved to show a good long-term outcome.

**Keywords:** Guillain-Barre syndrome; PCV vaccine; Peripheral nervous system

### Introduction

Guillain-Barre Syndrome (GBS) is a neurological disorder causing acute flaccid paralysis and characterized by varying degrees of weakness, sensory abnormalities and autonomic dysfunction. At present, GBS occurs worldwide with an incidence of 1 to 2 per 100,000 per year [1,2] and continues to be a life threatening disorder. Mortality rates in Europe and North America vary between 3% and 7% [3-6] mainly from an acute progressive stage of ventilator insufficiency, respiratory failure or autonomic dysfunction including arrhythmias. Although the cause of GBS remains to be clearly understood, previous literature indicated an association between vaccinations and GBS. Most notably, the evidence for a causal association is strongest for the swine influenza vaccine that was used in 1976-1977 [7-11] but subsequent evidence found little or no association [12]. The association of GBS following pneumococcal vaccine remains to be one of the vaccinations with sparse previous literature. Here, we have a case of a woman with a diagnosis of Guillain-Barre followed by paralysis after the administration of PCV vaccine.

### Case Presentation

A 66-year old female with a past medical history of hypertension, hyperlipidemia, gastroesophageal reflux disease presented to her local clinic on January 2015 for an annual exam. She was on the cusp of retirement and was told by her physician to receive all the immunizations. She received the first dose of PCV13 in January 2015 and then the second dose of PPSV23 in August 2015. The Advisory Committee on Immunization Practices (ACIP) recommends that pneumococcal vaccine-naïve people age 65 years and older should receive PCV13 first, followed by PPSV23 one year later [13]. The study indicated in this article showed that shorter intervals between PCV-PPSV23 sequence may be associated with increased local reactogenicity when compared with longer intervals, and 2) longer intervals (e.g.,  $\geq 1$  year) may lead to an improved immune response against serotypes in both vaccines compared with a single dose of PCV13 or PPSV23. These studies may thus serve as an explanation for the adverse effects endured by the patient. In September 2015, the patient began to feel weakness in the knees but dismissed it thinking it was mild arthritis. Few days later (approximately 41 days), she was unable to move her legs at all. She went to the ER in October 2015 due to her immobility and was admitted because of severe hyponatremia on admission. After being stabilized and discharged from the hospital, she was given rehabilitation for what they assumed to be an idiopathic cause of immobility. Three days later, she came to the hospital from home on November 11, 2015 for worsening bilateral lower extremity weakness. The neurological examination at the time revealed grossly decreased bilateral muscle strength (<1+) with abated or absent tendon reflexes of the lower limbs; muscle strength, reflexes and muscle tension remained normal in the upper limbs. The patient experienced loss of temperature sensation in distal extremities and symmetrical glove-and stocking-type pinprick sensations, but had normal proprioception and vibration senses. She also had prefrontal and bilateral facial pain with loss of touch and heat sensation; negative bilateral Babinski and Hoffman reflex; regular discriminative

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**Table 1:** CSF Analysis of neurological conditions.

Condition	Average range of CSF protein: mg/dL (g/L)	CSF Biomarkers	CSF Range of monocytes
Guillain Barre Syndrome	400 mg/dL	Anti-C-Dps IgG(C. Jejuni DNA-Binding $\text{mm}^3$ Protein from Starved Cells), Fc R/ FcRL gene polymorphism, Creatine kinase heparin sulfate glycosaminoglycans + others.	< 10 monocytes per
Bacterial Meningitis	21 - 2220	High lactate levels	$\geq$ 1000 per $\text{mm}^3$
Multiple Sclerosis	13-133	Presence of CSF OCB (oligoclonal bands) IgG and/ or KFLC (kappa free light chains), MRZ (mumps, rubella, zoster)-specific OCB	0-20 per $\text{mm}^3$
Neurosyphilis	15-4200	Presence of CXCL13, CXCL10, CXCL8	> 0-221 per $\text{mm}^3$
Amyotrophic Lateral Sclerosis	75-152	Decreased insulin, growth hormone and EPO	

touch.

Lumbar puncture for cerebrospinal fluid (CSF) studies during the acute phase showed albuminocytologic dissociation, with CSF protein of 0.58 g/L and normal white blood cell count that was conducted 7 days post-onset of weakness on September 2015. According to one study based on the Brighton Criteria determining level of diagnostic certainty, the timing of the lumbar puncture determines the severity of CSF protein elevation with a 79% increase in 6-7 days following onset of weakness [14]. Elevated CSF protein is seen in many infections, intracranial hemorrhages, multiple sclerosis, malignancies and a variety of inflammatory conditions. The range of CSF protein, cell differential and microscopic examination helps differentiate these conditions (Table 1).

Electromyography (EMG), nerve conduction velocity (NCV) on November 18, 2015 showed evidence of mixed axonal and demyelinating sensorimotor polyradiculopathy which has the poorest recovery of all GBS variants [15]. The EMG and nerve conduction velocity in four control individuals as indicated by their charts showed no electrical activity when the muscle is at rest and a smooth, wavy line on the recording with each muscle contraction. The nerve conduction velocity controls showed conduction velocity to be approximately 50 to 60 meters per second which is conducive to a functioning muscle.

She thus received 2 rounds of intravenous immunoglobulin therapy (IV Ig) with a standard single IV Ig dose = 0.4 g/kg bodyweight for 5 days from November 19-23<sup>rd</sup>, 2015.

On November 26, 2015, patient had respiratory failure and required intubation. She presented to the hospital for ventilator management due to chronic respiratory failure that developed with presumed Guillain-Barre syndrome. By January 2016, patient became verbally unresponsive, unable to raise/move her forearms and legs but opened eyes when called and shrugged shoulder briefly to commands. She was given consultations for range of motion (ROM) exercises by physical therapy and speech therapy. After continued occupational therapy, physical and speech therapy, patient reported progressive improvement in motor function of upper extremities starting January 24, 2016. By July 2016, patient's respiratory stabilized and was capped around the clock tolerating well on room air. The quadriplegia began improving with Pregalbin 50 mg and daily physical therapy. By November 3, 2016, patient was able to sit up on a chair and

respiratory failure completely resolved. Patient continues to improve on her muscular weakness but did express moving forward, she could tolerate more aggressive physical therapy.

## Discussion

Guillain Barre is an immune disorder resulting from autoimmune antibodies that cross-react with epitopes on peripheral nerves, leading to limb weakness. Early initiation of intravenous immunoglobulins (IV Ig) or plasma exchange is of proven benefit especially in those with rapidly progressive weakness [16]. Recently, IV Ig has replaced plasma exchange in many treatment centers due to its convenience and availability. Hence, IV Ig was administered over plasma exchange in this case.

GBS is commonly linked to different infections, particularly *Campylobacter Jejuni* enteritis, however unwanted autoimmunity does not arise in most individuals (>99%) exposed to *C. Jejuni* [17]. The major mechanism resulting in the autoimmunity by adjuvant vaccinations has been proposed to be due to the epitopes of a vaccine that initiates the development of antibodies and/or T cells that could cross-react with epitopes on myelin or axonal glycoproteins [18]. This was the same mechanism that was seen in the remnant sample of the 1976 swine flu sample where antibodies to the ganglioside GM1 was not detected in subjects infected with or vaccinated against the H1N1 virus [19], but they were detected in a patient who developed GBS associated with the pandemic influenza vaccine [20]. There were far fewer cases reported with GBS development after administration of the pneumococcal vaccine however.

*Streptococcus pneumoniae* cause invasive pneumococcal diseases (IPD), such as bacteremia and meningitis, non-invasive infections, such as acute otitis media, sinusitis and mastoiditis, and pneumonia, which can be either invasive (bacteraemic pneumonia) or non-invasive (non-bacteraemic pneumonia). They are polysaccharide-encapsulated, gram positive, lancet shaped organisms and pneumococcal vaccines rely on these capsules to induce a serotype specific immune response. There are two types of pneumococcal vaccines, plain and conjugated, that have different mechanisms. The plain polysaccharide vaccines are T-cell independent antigens that cross-link B-cell receptors inducing immediate differentiation to plasma cells then antibodies. In contrast, conjugated vaccines elicit a T-cell dependent response. The polysaccharide conjugated to a carrier protein uses MHC class-II dependent response to present the carrier protein to carrier-peptide-specific helper T cells. This leads to enhancement of the B-cell immune response, so that the antibody response is of greater specificity and functionality [21]. One paper indicated that the GM1-specific B cells pre-exist in peripheral blood and respond to T cell-dependent stimulation in Guillain-Barré syndrome and multifocal motor neuropathy [22]. Thus, it can be inferred that the conjugated vaccine produces the enhanced B-cell immune response leading to autoimmune reaction to the peripheral nerves.

Despite the adverse event highlighted in this case, overall incidence of serious adverse events ranged from 1.2% to 5.8% among persons vaccinated with PCV13, and 2.4% to 5.5% among persons vaccinated with PPSV23 1-6 months from initial dose. Common adverse reactions reported with the vaccines were pain, redness, fatigue, headache, chills, generalized muscle pain, and joint pain [23]. The low numbers of reported GBS cases that were temporally associated with vaccinations, including PCV, indicates the benefits

far greater than the risk. The PCV vaccine had significant efficacy in preventing vaccine-type pneumococcal, bacteremic, and non-bacteremic community-acquired pneumonia and vaccine type invasive pneumococcal disease [24,25].

Though randomized controlled studies have shown that plasma exchange and IV Ig lead to quick recovery of GBS patients, concomitant use with other treatments such as ventilation, prevention of deep vein thrombosis and physical rehabilitation have been recommended and effective [26-30]. Lower hospital mortality and improvement in survival have been documented for GBS patients receiving physiotherapy and high-intensity rehabilitation in the acute and sub-acute setting [31].

Although treatment is progressed to mechanic ventilation was likely to occur in patients with rapid disease progression, bulbar dysfunction and respiratory failure, Netto et al indicated 12.1% mortality. Factors determining the mortality rate include elder age group ( $P=0.03$ ), autonomic dysfunction ( $P=0.03$ ), pulmonary complications ( $P=0.001$ ), hypokalemia ( $P=0.001$ ) and bleeding ( $P=0.001$ ).

Although there have been major strides in the management and treatment of Guillain-Barre syndrome, this isolated incident proves there are still many unresolved issues surrounding pathogenesis. All reported cases of GBS are thus crucial in the determination of the causes of GBS and achieving a good, long-term outcome.

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