Parsonage-Turner Syndrome Associated With Influenza Vaccination: A Case Report With Discussion Of Vaccination Neurologic Complications And Causation

D H Marks

Citation

D H Marks. *Parsonage-Turner Syndrome Associated With Influenza Vaccination: A Case Report With Discussion Of Vaccination Neurologic Complications And Causation*. The Internet Journal of Neurology. 2019 Volume 21 Number 1.

DOI: 10.5580/IJN.54559

Abstract

This case report describes a 61-year-old male who received a vaccination against influenza in August 2010 and again on November 2013. He did not experience a reaction to the first vaccination, but within 6 weeks after the second flu vaccination, he began to experience shoulder and neck pain, with weakness of his left upper extremity. He was diagnosed by a neurologist with Parsonage Turner Syndrome (PTS) / brachial neuritis. Using accepted standard rules for determining causation in the vaccine industry and the FDA, the author has determined that this rare neurologic event adverse (AE) was probably causally related to the influenza vaccination. A review is presented of neurologic AE from vaccines, determination of vaccine AE causation, specific vaccine lot issues, and vaccine molecular mimicry.

INTRODUCTION

Although vaccinations are an important aspect of public health and are generally safe, nevertheless a wide range of AE have been reported via the medical literature and the Vaccine Adverse Event Reporting System VAERS after vaccination. Vaccines are known to induce AE, both predictable and unpredictable, mild and severe (Fenichel 1982; Marks 2011; NRC 2004; Nøkleby 2007). Neurological adverse effects occurring as a consequence of vaccine exposure are known for a wide range of vaccines [Bale 2004], and documented by the vaccine manufacturers in the prescribing information. This includes Guillan-Barre syndrome from influenza vaccine, transverse myelitis caused by duck embryo rabies vaccine, and seizures from pertussis vaccine. Some of these vaccine AE can mimic symptoms from an actual infection with the pathogen which the vaccine is designed to protect from (Marks 2011),

CASE PRESENTATION

This case report describes a 61-year-old male who was vaccinated against influenza in August 2010 and again in November 2013. He did not experience a reaction to the first vaccination, but within 6 weeks after the second flu vaccination he began experiencing dull, aching left shoulder pain, followed by pain in the back of his neck initially characterized as “electrical and shooting, later tightness.” These symptoms were followed by weakness of his left upper extremity, initially involving his left thumb and index finger, then progressing to include the entire hand and proximal left upper extremity. Hand grasp on the left was markedly decreased when compared to the right. An evaluation by a neurologist resulted in a diagnosis of Parsonage-Turner syndrome (PTS). Several years later, his symptoms still persist

DISCUSSION

Neurologic Complications from Vaccination:

A wide range of neurological complications have been reported via the medical literature and the VAERS system after vaccination with a number of vaccines (Marks 2011). For example, in the case of a vaccine consisting of recombinant outer surface protein A (OspA) of Borrelia burgdorferi, 24 patients reporting neurological AE after vaccination, out of a group of 94 patients reporting all adverse events (Marks 2011). These AE reports included five cerebral ischemia, two transient ischemic attacks, five demyelinating events, two optic neuritis, two reports of transverse myelitis, and one non-specific demyelinating condition. The median age was 62 years (the patient in this case report was 61 years old), There were two reports of

optic neuritis, one 131 days after the vaccine, the other an unknown number of days after the vaccine. Two reports of transverse myelitis were given, 10 and 13 days after the vaccine. One non-specific demyelinating condition was diagnosed 208 days after vaccination. The remainder of the neurological events didn't fall into any single diagnostic category.

GBS

Neurological complications of influenza vaccination were first recognized in 1976 following mass immunization, which resulted in a sevenfold increase in the incidence of Guillain-Barre syndrome (GBS) (Poser 1982, Shaikh 2012). GBS is an acute, monophasic, autoimmune neurologic disorder of the peripheral nerves characterized primarily by muscle weakness and loss of reflexes (Poser 1982, Vellozzi 2014).

PTS

In contrast to GBS, The National Organization for Rare Disorders NORD describes PTS as an uncommon neurological disorder characterized by rapid onset of severe pain in the shoulder and arm. NORD states that although the exact cause of PTS is unknown, PTS is believed to be caused by an abnormality of the immune system – an immune-mediated disorder. According to NORD, most cases of PTS can be caused by an immune-mediated inflammatory response to some infection or environmental trigger that damages the nerves of the brachial plexus. The most common 'triggering' factor associated with the development of PTS seems to be a recent viral illness, but can include recent immunization.

The defining clinical characteristic of PTS, painful or non-painful onset notwithstanding, is upper extremity muscular weakness, with or without sensory impairment; deep tendon reflexes are typically diminished. Onset and course of PTS is within days to weeks, occasionally extending over months. Pain is often the first symptom, with aching or dysesthesia about the shoulder, possibly involving nearby structures such as the neck or underarm. Movement about the shoulder girdle or more distally in the upper extremity may exacerbate pain. PTS can be bilateral but most often involves only one upper extremity, as in this case report.

A near total or total paralysis may be seen in the affected muscles of patients with PTS, which distinguishes PTS from the typical radiculopathic patterns, which almost never cause complete paralysis of a muscle. The muscles most often involved in PTS are those about the proximal shoulder and upper arm, particularly the serratus anterior, triceps, biceps, and deltoid, all of which may demonstrate near or complete paralysis. Some reports have more distal involvement where the hand is concomitantly or solely affected.

There is no pathognomic laboratory test for PTS; constitutional and general laboratory findings are usually minimal although white cells in the spinal fluid with increased spinal fluid protein can occur. Electrophysiologic testing may show denervative changes. Phrenic nerve involvement may impair respiratory function.

Although improvement of PTS is described in the literature, complete return of function is unusual. Thus, current treatment involves a combination of steroids, analgesics and physiotherapy. Anecdotal evidence suggests that steroids used early in the disease course may limit the painful phase of illness but do not seem to affect the long-term prognosis. In most cases, there is improvement and recovery of muscle strength over the course of 3–4 months. In one case series, 89% of patients showed complete resolution at 3 years (Tsairis 1972), however, weakness may persist for several years before recovery and some patients unfortunately experience permanent weakness, as in the case reported here.

Determining Causal Relatedness of Complications to Vaccination:

The generally accepted procedures used by FDA, CBER and Vaccine Manufacturers (Marks 2014) to determine whether a causal relationship exists between a drug, biological or vaccine and an adverse event is based upon accepted rules of scientific evidence, often using algorithms, as described by Hill and Riddell 1982. Standard discussions of techniques include the quoted IOM publication 2011. A systematic determination of the following aspects of the adverse event is made, taking into account:

1. New onset or worsening of an adverse condition,

2. Time for onset / temporality / latency,

3. Challenge, re-challenge phenomena,

4. Known pattern of reaction to that or similar vaccines,

5. Known biologic mechanisms of explanation,

6. Absence of reasonable alternative explanation,

A discussion of each of these factors follows :

The **first criterion** for determining causation is met for this case report because the adverse event was a **new onset**. Before vaccination, the vaccine recipient for this case report had not experienced PTS / brachial neuritis.

The **second criterion** for causation was also met because the patient's **neurologic symptoms developed within days to weeks** after flu vaccination, and the neurologic symptoms persisted. This is consistent with the time period described in a number of neurologic non-allergic non-immediate reaction vaccine-related adverse effects, including GBS, explained as follows.

Ojha (2014) reviewed VAERS data to assess whether GBS is reported more frequently following HPV vaccination than for other vaccinations. They defined GBS as any report that listed the MedDRA term "Guillain-Barre syndrome" as an adverse event between 5 and 42 days following vaccination (Stratton 1994). The Institute of Medicine Vaccine Safety Committee used "… data on experimental acute demyelinating encephalomyelitis and post-infectious GBS to establish a time window of 5 days to 6 weeks for the likely occurrence of a vaccine-caused case of GBS, with those cases occurring 7 to 21 days post-vaccination judged as being especially likely to be caused by the vaccine." Poland et al (2016) support this time period.

Evans et al (2009), citing Nachamkin (2008), point out that the risk estimates for GBS attributable to swine flu vaccination in the 6 weeks after immunization ranged from 4.9 to 11.7 cases per 1 million adult vaccine recipients. In the case of PTS presented here, the neurologic symptoms did not pre-exist and they developed within days to weeks after flu vaccination, and persisted. This time to onset is certainly consistent with the time period described in a number of neurologic non-allergic non-immediate reaction vaccine-related adverse effects, including GBS.

The **third criteria** for determining causation involves **challenge and re-challenge**. The prior flu vaccination in this case report may have provided immunologic priming for an adverse reaction, in that there was antigen overlap between the 2011 and 2013 flu vaccinations. As the vaccine manufacturer appears to have been Novartis (Lot #111768P1 Exp Date 02/28/11), it is likely that this patient received Fluvirin, described in the prescribing information as "trivalent, sub-unit (purified surface antigen)" and that "...surface antigens, hemagglutinin and neuraminidase are obtained from the influenza virus particle." Per the CDC, the trivalent 2010-11 vaccine would have included the following three viruses:

A/California/7/2009-like (H1N1)

A/Perth/16/2009-like (H3N2); -

B/Brisbane/60/2008.

The 2013-14 trivalent vaccine (per the CDC) contained the following three viruses: -

A/California/7/2009 (H1N1) pdm09-like virus; -

A(H3N2) virus antigenically like the cell-propagated prototype virus

A/Victoria/361/2011; -

B/Massachusetts/2/2012-like virus.

What appears to be a prior product insert for the 2012-14 vaccine located on a website dedicated to preventing infections: www.uprevent.mckesson.com/2855wp/wp-content/uploads/2013/11/ Fluvirin2013-14-PL.pdf identified different strains that are "like virus" of those recommended by the CDC, to wit: -

45 mcg hemagglutinin (HA) per 0.5 ml dose... –

A/Christchurch/16/2010, NIB-74 (H1N1) (an A/California/7/2009-like virus); -

A/Texas/50/2012, NYMC X-223 (H3N2) (an A/Victoria/361/2011-like virus; -

B/Massachusetts/2/2012.

An overlap of antigens between the 2010 – 2011 and 2012 – 2013 vaccine preparations is the antigen A/California/7/2009-like (H1N1). The fact that the case did not have a reaction to the 2010 influenza vaccination but did have a reaction after the 2013 influenza vaccination most likely indicates that the first exposure to A/California/7/2009-like (H1N1) in 2010 primed for the second exposure in 2013.

Risi et al 2013 report on a study of adults who were randomized 15 months previously to receive an A/Indonesia/5/2005 (H5N1) influenza vaccine administered alone or in combination with an oil-in-water emulsion based Adjuvant System containing tocopherol per dose. The study participants then received one booster dose of A/turkey/Turkey/1/2005 (H5N1) vaccine with or without AS03. An anamnestic antibody response 15 months after priming (the initial flu vaccination) led Risi's team to propose that, "One influenza pandemic preparedness strategy involves priming a population with a pre-pandemic subtype-specific vaccine and boosting the immunological response at the time of the pandemic with a strain-matched vaccine." The Risi study demonstrates the effect of antigen priming on producing a strong immune response on repeat challenge, as occurred in this case presentation.

Hoft et al (2016) studied the impact of priming on T-cell proliferation and cytokine production. Subjects primed with clade 1 H5 antigen, with or without adjuvant, and H5-naive individuals were boosted with clade 2H5antigen. Subjects received 2–3 intramuscular injections 1–6 months apart, containing purified H5 (the priming antigen) prepared by either Sano? (subvirion) or Novartis (puri?ed surface antigen) from a clade 1 A(H5N1) virus (A/H5N1/Vietnam/ 1203/2004), with or without adjuvant. A subset of subjects who completed antigen priming were enrolled into the heterotypic H5 booster trial. (364 received Sano? clade 1 H5 priming, 120 received Novartis clade 1 H5 priming, and 33 received placebo). Subjects in vaccine arms of the priming studies were randomized to receive a single vaccination of H5 antigen derived from the clade 2 A/H5N1/Indonesia/05/05 virus. Hoff et al found that subjects previously vaccinated with clade 1H5 antigen developed signi?cantly enhanced clade 2H5 cross-reactive T-cell responses detectable 6 months after vaccination with clade 2 H5 antigen. The magnitude of CD4+ interferon–? producing T cells correlated with H5 antibody responses. They concluded that H5 heterotypic priming prior to onset of an A(H5N1) pandemic may increase the magnitude and duration of immunity against a newly drifted pandemic H5 virus. The studies of Hoff et al and of Risi et al are just two instances showing that prior flu vaccination can provide immunologic priming for a stronger immune response to antigen re-exposure, such as for this case report when the flu vaccine recipient received antigen overlap A/California/7/2009-like (H1N1) between the 2011 and 2013 flu vaccinations.

The **fourth criterion** of causation is that the adverse reaction follows a **known pattern of reaction** to that (influenza) or similar vaccines. Supporting the fourth criterion, GBS certainly is a recognized potential neurologic adverse event from influenza vaccination. Neurological complications of in?uenza vaccination were first recognized during the H1N1 swine flu outbreak of 1976. Mass immunization resulted in a sevenfold increase in the incidence of Guillain-Barre syndrome (GBS). As pointed out by Nøkleby (2007), from the Norwegian Institute of Public Health, Division of Infectious Disease Control, in Oslo, referencing Schonberger 1979, "… based on the 1976 experience in the USA, we already know that influenza vaccines may be responsible for the development of GBS." Other reported neurological complications from use of flu vaccine include optic neuritis, peripheral polyneuropathy and isolated hypoglossal nerve paralysis.

The official prescribing information for FluVirin lists a wide range of post-marketing neurologic injury reports, which further supports causation (known adverse effect):

"Nervous system disorders: Headache; dizziness; neuralgia; paraesthesia; confusion; febrile convulsions; Guillain-Barré Syndrome; myelitis (including encephalomyelitis and transverse myelitis); neuropathy (including neuritis); paralysis (including Bell's Palsy)"

There are many reports (Ishii 2014; Shaikh 2012) in the medical literature which document neuropathic conditions such as brachial plexus following use of various vaccines (again supporting known causation); vaccines including flu vaccine, and conditions including Bell's palsy, optic neuritis and abducens nerve palsy. Adverse neurological effects of vaccines other than the influenza vaccine include optic neuritis and facial nerve palsy caused by the anthrax vaccine, abducens nerve paralysis in children following measles, mumps, rubella (MMR) and diphtheria, pertussis, tetanus (DPT) vaccination and oculomotor nerve paralysis in response to the MMR vaccine, and neurologic, cardiac and rheumatologic sequella of OspA Lyme vaccine (Marks 2011). Cranial neuropathy can develop as post-vaccination GBS. More specifically to this case, PTS itself and related neurologic conditions have been reported following vaccination with a wide array of vaccines, such as influenza [Shaikh 2012, Shoji 2003, Taras 2014], human papilloma virus [Debeer 2008, Taras 2011], DPT (diphtheria, pertussis, tetanus) [Taras 2011, Hamati-Haddad 1997, Martin 1973], swine flu [Weintraub 1977] and tetanus [Taras 2011,

Stratton 1994].

Shaikh et al (2012) point out that, "Brachial neuritis (PTS) after administration of an in?uenza vaccination has previously been reported in three publications" (Miller 2000; Wells 1971; Hansen 2005). Both PTS and GBS are uncommon neurological disorders which have been temporally and causally related to influenza vaccination, so a discussion of the immunologic and vaccination causation of GBS is therefore relevant and applicable to any similar discussion of PTS.

The **fifth criteria** for supporting a causal relatedness is that the reaction should have a **known biologic mechanism** of explanation. The etiology of brachial neuritis is unclear but is thought to be an immune-mediated inflammatory reaction against brachial plexus nerve fibers involving complement, antiperipheral nerve myelin antibodies and T cells (Shaikh 2012). A list of mechanisms most likely to contribute to the development of adverse events after vaccination include immune-mediated reactions, viral activity, and injection-related reactions.

FluVirin is an inactivated influenza virus vaccine, so it is not able to initiate adverse events from direct viral activity. There was no report in this case reports medical records of a physical traumatic injection-related problem. By exclusion, only an immune-mediated mechanism could apply.

Many vaccines, particularly subunit vaccines (e.g., recombinant hepatitis B and tetanus toxoid), contain adjuvants that help to increase the response rates to vaccines and facilitate the use of fewer and smaller doses (Coffman et al., 2010). Adjuvants may directly activate cells of the innate immune system leading to the release of inflammatory mediators and enhancement of the immune response, as I previously reviewed. Fluvirin does not contain an adjuvant.

OspA can cause induction and secretion of the inflammatory cytokine IL-6 by human glial cells Habicht 1991; Pachner 1997). Production of IL-6 and INF have been associated with neurological damage in Lyme disease. As a basis for use as a vaccine antigen / immunogen, OspA can stimulate a protective immune response against Borrelia b.[Kurtenbach 1997]. OspA, presented in association with HLD-DR4 MHC proteins, can produce DR-4 restricted T cells. These activated T cells are known to produce a Th1 type IR, releasing a number of inflammatory cytokines (IL-1, IL-6, IL-12) [Wooten 1996]. This inflammation attracts a number of leukocytes (neutrophils, monocytes, macrophages), resulting in the release of several inflammatory mediators (NO, Interferon gamma, tumor necrosis factor) which can damage surrounding tissue. As clinical verification, the levels of IL-1 and IL-6 can be elevated in the serum and CSF of LD patients, and levels of IL-6 can parallel disease activity [Weller 1991].

Immune-mediated mechanisms:

Antibodies are antigen-binding proteins produced by terminally differentiated effector B cells – the plasma cells. Neutralization of an antigen or pathogen (such as influenza virus) expressing the target antigen is one effector mechanism attributed to antibodies. Antibodies against influenza virus hemagglutinin neutralize the virus by blocking the interaction of the virus with the receptor on the target cell, thereby preventing infection (Han and Marasco, 2011). In addition, while not preventing influenza infection, antibodies against influenza neuraminidase restrict replication of the virus by preventing release of virus from infected cells (Han and Marasco, 2011). Neutralization of self-antigens by autoantibodies can also contribute to the pathogenesis of some autoimmune diseases, such as autoimmune pulmonary alveolar proteinosis.

Antibodies that bind antigens derived from or similar to the host organism (i.e., self-antigens) are referred to as autoantibodies. Autoantibodies are considered one of the hallmarks of certain autoimmune diseases (Hammoudi 2015), however, the presence of autoantibodies does not correlate perfectly with disease. Autoantibodies have been detected in healthy individuals as well as those with autoimmune diseases (Elkon and Casali, 2008; Zelenay et al., 2007). The mechanisms whereby autoantibodies exert their effects in the disease process are the same used by antibodies against foreign antigens (i.e., non-self-antigens). These include, but are not limited to, opsonization, neutralization, complement activation, augmentation, and engagement of constant region (Fc) receptors. Molecular mimicry (discussed elsewhere in this case report) and bystander activation are reported as possible mechanisms by which vaccines can cause autoimmune reactions (Hammoudi 2015). Idiopathic Thrombocytopenia Purpura, Myopericarditis, Primary Ovarian Failure, Systemic Lupus Erythematosus (SLE) and Acute Disseminated Encephalomyelitis (ADEM) are all autoimmune conditions with reported links to vaccinations.

Autoantibodies use multiple mechanisms during a disease

process. Antigen-bound autoantibodies can both (1) engage Fc receptors and (2) induce activation of the complement system. These processes lead to the activation of inflammatory cells such as neutrophils and macrophages, and to generation of pro-inflammatory mediators that can play pathogenic roles in autoimmune diseases. Several immune-mediated mechanisms have been hypothesized to be involved in the pathogenesis of tissue damage or clinical disease related to natural infection or immunizations. The pathophysiological mechanisms seem to involve an interaction between an underlying genetic predisposition, a mechanical vulnerability, and an autoimmune trigger (Fransz 2014).

Molecular Mimicry:

Some vaccine AE can mimic symptoms from an actual infection with the pathogen which the vaccine is designed to protect from (Marks 2011), In the case of Lyme Disease from a successful infection with Borrelia burgdorferi (Bb), an array of associated neurological manifestations are known to occur, including neuropathy and cognitive dysfunction. It should be anticipated that a vaccine which is composed of an outer surface protein from Borrelia b and is designed to induce a protective immune response against Bb may have associated with its use a range of neurologic AE that are manifestations of the actual infection.

Molecular mimicry is a well-recognized theory providing a biological explanation for how a vaccine can cause autoimmune reactions. Molecular mimicry refers to a defined sequence and/or conformational homology between an exogenous agent (foreign antigen, such as influenza vaccine) and self-antigen leading to the development of tissue damage and clinical disease from antibodies and T cells directed initially against the exogenous agent (influenza antigens) that also react against self-antigen. The concept of co-evolved epitope redundancy (Moise) may provide part of the explanation of how T-cell reactivity can develop. Some experimental evidence (Albert and Inman, 1999; Fujinami et al., 2006; Rose and Mackay, 2000) suggests or implicates molecular mimicry in certain human neurologic autoimmune diseases including (among others):

* Multiple sclerosis and exposure to several different viruses;

* Demyelinating diseases and hepatitis B: (Fujinami and Oldstone, 1985).

* Guillan Barre Syndrome (Kuwabara et al., 2004; Rees et al., 1995).

As noted above, brachial neuritis / PTS is thought to be an immune-mediated inflammatory reaction against brachial plexus nerve fibers involving complement, anti-peripheral nerve myelin antibodies and T cells. The flu vaccine has been linked to GBS (Israeli 2012), ADEM and similar diseases, providing a basis of consistency with the reaction of flu vaccine to PTS. Waisbren (Medical Hypotheses 2008) note that sometimes more than one type of autoimmune disease occurs, and can be explained by the fact that specific autoimmune T-cells have been shown to develop clones that attack multiple human tissues. Autoimmune T-cells that emerge in SLE can loose their autoimmune specificity and have off shoots of “rogue” T-cell clones that attack multiple tissues. Gran and Martin showed that less sequence homology then heretofor was thought necessary for this phenomenon, could be its cause. Molecular mimicry fulfills one of the components for determining causation: known similar action by like agents (other vaccines), thereby supporting a finding that the mechanism operates the same in the case of Fluvirin vaccine and PTS. Thus, in the analysis of whether the flu vaccine (including Fluvirin) can cause PTS, molecular mimicry provides a persuasive biological explanation.

Using vaccine-initiated GBS as an analogy, Evans et al (2009) has stated that: “Some subsets of patients with GBS develop anti-ganglioside antibodies that are implicated in the pathogenesis of the (GBS) disease [Hughes 2005]. Antibodies to a number of different complex gangliosides can be detected in patients with GBS and may arise as a consequence of molecular mimicry with antigens on infecting pathogens. Ganglioside GM1, a monosialylated glycosphingolipid, is one of several gangliosides considered a target antigen in the pathogenesis of GBS [Nachamkin 2008]. C. jejuni expresses ganglioside-like structures that can induce anti-ganglioside antibodies, such as anti-GM1.”

Cusick et al (2012) discuss the potential expression of dual T cell receptors (TCR) on a single T cell. These T cells would have dual reactivity to both foreign (anti-influenza) and self (such as ganglioside) antigens, leaving the host vulnerable to foreign insults (such as vaccination with influenza antigens) capable of triggering an autoimmune (i.e. brachial neuritis) response. Cusick et al point out that there may be at least three different mechanisms, including molecular mimicry, dual TCRs, and chimeric TCRs, by which dual reactivity of

the T cell may play a role in autoimmune (such as GBS and brachial neuritis) diseases.

Nachamkin et al (2008) et al hypothesized that influenza HA may be involved in eliciting anti- antibodies in mice, and that the differential risk of GBS in these vaccinated mice might be explained by viral neuraminidase levels. Under this theory, the 1976 swine flu vaccine might have allowed formation of sialic acid–HA complexes that mimic GM1 ganglioside in susceptible hosts due to low levels of viral neuraminidase in the vaccine preparation. No direct evidence supporting this hypothesis was provided in the report. Two recombinant HA proteins derived from the H5N1 viruses A/HK/156/97 and A/Vietnam/1203/04 also induced anti-GM1 antibodies in mice. Drawing on the analogy between immune-mediated vaccine-induced GBS and immune-mediated vaccine-induced brachial neuritis, which I previously explored, these findings support molecular mimicry as a cause of this case report developing brachial neuritis.

Finally, as I have discussed elsewhere (Marks 2011), vaccines are known to induce a wide range of adverse events (AE), both predictable and unpredictable, mild and severe. Neurological adverse effects (AE, illnesses occurring as a consequence of vaccine exposure) are known for a number of vaccines [Bale 2004], and described by the vaccine manufacturers in the prescribing information. This includes Guillan-Barre syndrome from influenza vaccine, transverse myelitis caused by duck embryo rabies vaccine, and seizures from pertussis vaccine. Some of these vaccine AE can mimic symptoms from an actual infection with the pathogen which the vaccine is designed to protect from. In the case of Lyme Disease from a successful infection with Borrelia burgdorferi Bb, an array of associated neurological manifestations are known to occur, including neuropathy and cognitive dysfunction. It should be anticipated that a vaccine which is composed of an outer surface protein from Bb and is designed to induce a protective immune response against Bb may have associated with its use a range of neurologic AE that are manifestations of the actual infection. These findings support the theory of molecular mimicry, as discussed elsewhere in this paper.

The **sixth factor** in determining a causal relatedness of an adverse effect to a vaccine is whether there is a **reasonable alternative explanation**. Complex regional pain syndrome, frozen shoulder, and syncope are potential adverse events resulting from the direct trauma from the actual injection occurring with various vaccines. These adverse events are not necessarily attributable to the contents of the vaccine. There is no evidence that the patient for this case presentation suffered from mechanical trauma from the vaccination (absence of reasonable alternative explanation).

Degree of Causal Relatedness:

The degree of causal relatedness is typically rated along the scale of:

unrelated / unlikely / possible / probable / definite.

Because of the number of supporting factors including temporality, consistency to other examples of vaccine-induced neurologic injury, and an absence of alternative explanations, the degree of causal relatedness for this case report is Probable, or expressed another way, more likely than not. This reported adverse event had a reasonable temporal relationship to vaccination, could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions and follows a known pattern of response to vaccination.

The author cautions to actively looking for neurologic AE, and to consider causal relatedness even when the incidence rate is too low to raise a calculable difference to natural occurrence. AE that are infrequent, although potentially serious and severe, might not be visible within relatively small size vaccine clinical efficacy studies with a few thousand healthy persons. This illustrates the importance of post-marketing surveillance of vaccine AE, including publications and the VAERS system.

For OspA vaccine administered to prevent Lyme disease, the medical literature as of 2011 indicated 7 cases of neurocognitive complaints. Yet, when the publically available VAERS data were analyzed, these 7 cases did not seem to be in the VAERS reports. One possible explanation is that the neurocognitive AEs were reported after the end of the available VAERS data set period. Another consideration is that AEs are often reported only if they are looked for, and if they are suspected of being causally related to the vaccine. If no one was aware that an OspA vaccine could be causally related to cognitive deficits, for example, then that particular line of data might not be questioned for nor captured in the case report forms for the vaccine clinical studies (Marks 1994 and 1995).

CONCLUSION

Parsonage-Turner Syndrome is a rare neurologic condition that may follow viral illness or vaccination. Confirmation that development of any vaccine associated disease meets the required criteria of causality is vital to the continued success of these important public health interventions. Evaluation of such supportive information was presented. Patients should be informed that vaccines can be associated with a wide spectrum of neurologic adverse events. Care must be taken when considering the patient's past medical history, risk factors, adequate informed consent and clinical presentation of adverse events after vaccination.

References

1. FluVirin Prescribing Information https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm123694.pdf
2. Alfen & Baziel. The clinical spectrum of neuralgic amyotrophy in 246 cases. Brain - 2006 pgs 438-450.
3. Bale JF. Neurologic complications of immunization, J Child Neurol 19(6) (June 2004), 405–412.
4. Cusick MF, Libbey JE, Fujinami RS, PhD Molecular Mimicry as a Mechanism of Autoimmune Disease. Clin Rev Allergy Immunol. 2012 February ; 42(1): 102–111.
5. Debeer P, De Munter P, Bruyninckx F, Devlieger R. Brachial plexus neuritis following HPV vaccination. Vaccine. 2008 Aug 18;26(35):4417-9.
6. Elkon K1, Casali P. Nature and functions of autoantibodies. Nat Clin Pract Rheumatol. 2008 Sep;4(9):491-8.
7. Evans D, Cauchemez S, and Hayden FG. Pre-pandemic Immunization for Novel Influenza Viruses, “Swine Flu” Vaccine, Guillain-Barré Syndrome, and the Detection of Rare evere Adverse Events J Infect Dis. 2009 Aug 1; 200(3): 321–328.
8. Fenichel GM. Neurological complications of immunization. Ann Neurol. 1982 Aug;12(2):119-28.
9. Fransz DP, Schönhuth CP, Postma TJ, van Royen BJ Parsonage-Turner syndrome following post-exposure prophylaxis. BMC Musculoskelet Disord. 2014 Aug 7;15:265.
10. Haber P, Sejvar J, Mikaeloff Y, DeStefano F. Vaccines and Guillain-Barré syndrome. Drug Saf. 2009; 32: 309-323.
11. Hamati-Haddad A, Fenichel GM. Brachial neuritis following routine childhood immunization for diphtheria, tetanus, and pertussis (DTP): report of two cases and review of the literature.
12. Pediatrics. 1997 Apr;99(4):602-3.
13. Hammoudi D, Sanyaolu AO, Orish VN et al.. Induction of Autoimmune Diseases Following Vaccinations: A Review. SM Vaccine Vaccin. 2015;1(3):1011.
14. Han T, Marasco WA. Structural basis of influenza virus neutralization. Annals of the New York Academy of Sciences. 2011;1217:178–190.
15. Habicht GS, Katona LI, Benach JL, Cytokines and the pathogenesis of neuroborreliosis: Borrelia burgdorferi induces glioma cells to secrete interleukin-6, J Infect Dis 164(3), Sep 1991, 568–574.
16. Pachner AR, Amemiya K, Delaney E et al. Interleukin-6 is expressed at high levels in the CNS in Lyme neuroborreliosis, Neurology 49, 1997, 147–152.
17. Hansen O. Acute brachial neuropathy following in?uenza vaccination. Ugeskr Laeger 2005;167:1297–8.
18. Hasselbacher. Neuropathy after Influenza Vaccination. Lancet Volume 1-1977; pages 551-552:
19. Hoft DF, Lottenbach K, Goll JB et al. Priming Vaccination With In?uenza Virus H5 Hemagglutinin Antigen Signi?cantly Increases the Duration of T cell Responses Induced by a Heterologous H5 Booster Vaccination. The Journal of Infectious Diseases 2016;214:1020–9.
20. Hughes 2005 RA, Cornblath DR. Guillain-Barre syndrome. Lancet. 2005;366:1653–66].
21. Institute of Medicine IOM. Immune Response to Vaccine Antigens, Vaccine Safety Forum : Summaries of two workshops in 1997. Washington, DC. The National Academies Press.
22. Ishii K et al. Glossopharyngeal Nerve and Vagus Nerve Palsies Associated with Influenza Vaccination. Intern Med 53: 259-261, 2014.
23. Israeli E, Agmon-Levin N, Blank M, Chapman J, Shoenfeld Y. Guillain-Barré syndrome--a classical autoimmune disease triggered by infection or vaccination. Clin Rev Allergy Immunol. 2012 Apr;42(2):121-30.
24. Kurtenbach K, Dizij A, Voet P et al. Vaccination of natural reservoir hosts with recombinant lipidated OspA induces a transmission-blocking immunity against Lyme disease spirochaetes associated with high levels of LA-2 equivalent antibodies, Vaccine 15(15) (Oct 1997), 1670–1674.
25. Larner AJ, Farmer SF. Myelopathy following influenza vaccination in inflammatory CNS disorder treated with chronic immunosuppression. : Eur J Neurol. 2000 Nov;7(6):731-3
26. Marks DH, Hosbach P, Koster F et al. Clinical studies in humans of outer surface protein A vaccine for LD. Abstract of presentation at VI International Conference on Lyme Borreliosis, Bologna, Italy, June 19, 1994.
27. Marks DH, Hosbach P, Meschievitz CK, Design issues for clinical trials of vaccine for Lyme disease, Presented at Symposium on the Therapy and Prophylaxis for Lyme Borreliosis, Portoroz, Slovenia, 13–16 May 95.
28. Marks DH. Evaluation of Medical Causation, in Drug Injury. 3rd and 4th Editions, O’Donnell JT editor. L&J Publications, 2012 and 2016.
29. Marks DH. Neurologic Complications of Vaccination with Outer Surface Protein A (OspA). The International Journal of Risk and Safety in Medicine, 2011 Jan 1;23(2):89-96.
30. Mikaeloff Y, Caridade G, Suissa S, Tardieu M. Hepatitis B vaccine and the risk of CNS inflammatory demyelination in childhood. Neurology. 2009; 72: 873-880
31. Miller JD, Pruitt S, MacDonald TJ. Acute brachial plexus neuritis: an uncommon cause of shoulder pain. Am Fam Physician 2000;62:2067–72.
32. Moise L, Beseme S, Tassone R et al. T cell epitope redundancy: cross-conservation of the TCR face between pathogens and self and its implications for vaccines and autoimmunity. Expert Rev Vaccines. 2016 May;15(5):607-17.
33. Nakamura N, Nokura K, Zettsu T et al. Neurologic complications associated with influenza vaccination: two adult cases. Intern Med. 2003 Feb;42(2):191-4. Comment in: Intern Med. 2003 Feb;42(2):139.
34. Nachamkin I, Shadomy SV, Moran AP, et al. Anti-ganglioside antibody induction by swine (A/NJ/1976/H1N1) and other influenza vaccines: insights into vaccine-associated Guillain-Barre syndrome. J Infect Dis.

2008;198:226–33.
35. National Research Council NRC. Immunization safety review: influenza vaccines and neurological complications. The National Academies Press, Washington, DC; 2004: 44.
36. Nøkleby N. Neurological Adverse Events of Immunization: Experience With an Aluminum Adjuvanted Meningococcal B Outer Membrane Vesicle Vaccine. Expert Rev Vaccines. 2007;6(5):863-869.
37. Ojha RP, Jackson BE, Tota JE et al. Guillain–Barre syndrome following quadrivalent human papillomavirus vaccination among vaccine-eligible individuals in the United States. Human Vaccines & Immunotherapeutics 10:1, 232–237; January 2014.
38. Poland G, Whitaker J, Poland CM, Kennedy RB. Vaccinology in the third millennium: Scientific and social challenges. April 2016 Current Opinion in Virology 17:116-125.
39. Poser CM, Behan PO. Late onset of Guillain-Barré syndrome. J Neuroimmunol. 1982; 3: 27-41.
40. Poser CM. Neurological complications of swine in?uenza vaccination. Acta Neurol Scand 1982;66:413–31.
41. Reutens DC, Dunne JW, Leather H. Neuralgic amyotrophy following recombinant DNA hepatitis B vaccination. Muscle Nerve. 1990 May;13(5):461.
42. Riddell RH., ed. Pathology of Drug-Induced and Toxic Diseases. Churchill Livingstone, New York, 1982 (3-9)
43. Risi G, Frenette L, Langley JM et al. Corrigendum to "Immunological priming induced by a two-dose series of H5N1 influenza antigen, administered alone or in combination with two different formulations of AS03 adjuvant in adults: Results of a randomised single heterologous booster dose study at 15 months" [Vaccine 29 (2011) 6408–6418]. Vaccine, Volume 31, Issue 2, 2 January 2013, Pages 436-437
44. Adverse Effects of Vaccines. Evidence and Causality. Committee to Review Adverse Effects of Vaccines; Institute of Medicine IOM. Washington (DC): National Academies Press (US); 2011 Aug 25.
45. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ et al. Guillain–Barré syndrome following vaccination in the National Influenza Immunization Programme, United States, 1976–1977. Am. J. Epidemiol.110, 105–123 (1979).
46. Sejvar JJ Kohl KS Gidudu J et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011; 29: 599-612.
47. Shaikh MF, Baqai TJ, Tahir H. Acute brachial neuritis following influenza vaccination. BMJ Case Rep. 2012 Nov 28;2012.
48. Shaw FE Jr, Graham DJ, Guess HA et al. Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination. Experience of the first three years.
49. Am J Epidemiol. 1988 Feb;127(2):337-52..
50. Shoji H, Kaji M. The influenza vaccination and neurological complications. Intern Med. 2003 Feb;42(2):139. Comment on: Intern Med. 2003 Feb;42(2):191-4.
51. Sonneville R, Klein IF, Wolff M Update on investigation and management of post-infectious encephalitis. Curr Opin Neurol. 2010; 23: 300-304.
52. Hi
53. Stratton KR, Howe CJ, Johnson RB. Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality. Washington DC: National Academy Press, 1994.
54. Tsairis P, MD; Dyck PJ; Mulder DW. Natural History of Brachial Plexus Neuropathy. Report on 99 Patients. Arch Neurology 1972. Vol 27: 109-117.
55. Taras JS, Donohue KW. Radial nerve motor palsy following seasonal influenza vaccination: a case report. J Surg Orthop Adv. 2014 Spring;23(1):42-4.
56. Tomljenovic L Shoenfeld Y. Association between vaccination and Guillain-Barré syndrome. Lancet Infect Dis. 2013; 13: 730-731
57. Vellozzi C et al. Cumulative Risk of Guillain–Barre Syndrome Among Vaccinated and Unvaccinated Populations During the 2009 H1N1 In?uenza Pandemic. American Journal of Public Health. April 2014, Vol 104 4).
58. Wells CEC. A neurological note on vaccination against in?uenza. BMJ 1971;3:755–6.
59. Waisbren BA. Acquired autoimmunity after viral vaccination is caused by molecular mimicry and antigen complimentarity in the presence of an immunologic adjuvant and specific HLA patterns. Medical Hypotheses (2008) 70, 346–348.
60. Weintraub MI, Chia DT. Paralytic brachial neuritis after swine flu vaccination.
61. Arch Neurol. 1977 Aug;34(8):518.
62. Weller M, Stevens A, Sommer N et al. Cerebrospinal fluid interleukins, immunoglobulins and fibronectin in neuroborreliosis, Arch Neurol 48 (1991), 837–841.
63. Wooten RM, Modur VR, McIntyre et al. Borrelia burgdorferi outer membrane protein A induces nuclear translocation of nuclear factor-kappa B and inflammatory activation in human endothelial cells, J Immunol 157(10) (15 Nov 1996), 4584–4590
64. Zelenay S, Moraes Fontes MF et al. Physiopathology of natural auto-antibodies: the case for regulation. J Autoimmun. 2007 Dec;29(4):229-35

Author Information

Donald H. Marks, M.D., Ph.D.
Trinitas Medical Center
Elizabeth, New Jersey