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SPECIAL ARTICLE

Transverse myelitis and vaccines: a multi-analysis

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Transverse myelitis is a rare clinical syndrome in which an immune-mediated process causes neural injury to the spinal cord. The pathogenesis of transverse myelitis is mostly of an autoimmune nature, triggered by various environmental factors, including vaccination. Our aim here was to search for and analyze reported cases of transverse myelitis following vaccination. A systematic review of PubMed, EMBASE and DynaMed for all English-laguage journals published between 1970 and 2009 was preformed, utilizing the key words transverse myelitis, myelitis, vaccines, post-vaccination, vaccination and autoimmunity. We have disclosed 37 reported cases of transverse myelitis associated with different vaccines including those against hepatitis B virus, measles–mumps–rubella, diphtheria–tetanus–pertussis and others, given to infants, children and adults. In most of these reported cases the temporal association was between several days and 3 months, although a longer time frame of up to several years was also suggested. Although vaccines harbor a major contribution to public health in the modern era, in rare cases they may be associated with autoimmune phenomena such as transverse myelitis. The associations of different vaccines with a single autoimmune phenomenon allude to the idea that a common denominator of these vaccines, such as an adjuvant, might trigger this syndrome. *Lupus* (2009) **18,** 1198–1204.

Key words: transverse myelitis; vaccines; post-vaccination; autoimmunity; adjuvant

Introduction

Transverse myelitis (TM) is a rare clinical syndrome in which an immune-mediated process causes neural injury to the spinal cord, resulting in varying degrees of weakness, sensory alterations and autonomic dysfunction. In 2002, the Transverse Myelitis Consortium Working Group proposed diagnostic criteria for idiopathic TM which includes bilateral sensory, motor, or autonomic dysfunction attributable to the spinal cord, a clearly defined sensory level and peaking of symptoms within 4 hours and 21 days. In addition, evidence of an inflamed spinal cord (e.g. cerebrospinal fluid (CSF) pleocytosis, elevated IgG index or gadolinium enhancement by magnetic resonance imaging) and exclusion of extra-axial compressive etiology by neuroimaging should be observed.[1] The incidence of TM is estimated to be up to five cases per million people a year.[1] It may present in several clinical setups such as a multi-focal central nervous system (CNS) disease (e.g. multiple sclerosis), a result of direct injury to the spinal cord (e.g. radiation, spinal cord infarct), a part of a systemic (e.g. malignancy) or autoimmune disease (i.e. systemic lupus erythematosus), or as an isolated entity.[2]

The pathogenesis of TM is probably of an autoimmune nature, whether TM presents as an isolated disorder or as part of a systemic disease. Several autoimmune diseases such as systemic lupus erythematosus, antiphospholipid syndrome, Sjogren's syndrome, neurosarcoidosis or Behçet's disease have been associated with TM.[3,4] TM involves blood–brain barrier breakdown and CSF pleocytosis within a focal area of the spinal cord.[5] Inflammatory markers such as interleukin-6 (IL-6) and other signaling proteins are elevated and correlate with disease severity,[6] and the presence of anti-SSA/Ro antibodies predict a relapsing course of the disease.[7] Furthermore, TM was found to be associated with serological markers such as collapsing-response-mediator protein-5-IgG and

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amphiphysin-IgG, especially when present as a paraneoplastic syndrome.[6] The autoimmune nature of TM can be exemplified through the syndrome of neuromyelitis optica (Devic's). This is a rare autoimmune syndrome that combines TM and demyelination of the optic nerve, and is characterized by the presence of highly specific anti-NMO (neuromyelitis optica), and anti-aquaporin-4 antibodies.[8] In addition, 50% of NMO-IgG seropositive patients harbor at least one other serum autoantibody,[9,10] thus supporting the role of humoral autoimmunity in this syndrome.

The etiology of most autoimmune processes is of a multi-factorial nature, combining genetic, immunological, hormonal and environmental factors that form the 'mosaic of autoimmunity'.[11–13] Infectious antigens play a key role in this interplay,[14] and up to 40% of TM cases are associated with a preceding infectious illness, mostly within a month of TM onset.[1] In one study of 33 TM patients (ages 18 months–82 years), 46% had a preceding infection of which 73% were respiratory, 13% were gastrointestinal and 13% had flu-like symptoms[15]. Different infectious agents have been implicated in the pathogenesis of TM as influenza, measles, varicella, rubella, mumps, mycoplasma, hepatitis C, polio, cytomegalovirus and the Epstein–Barr virus.[16,17] In most cases symptoms of TM begin after the patient had recovered from the infectious disease, and infectious agents have not been isolated from the nervous system. Thus, TM appears not to be a direct infectious process, but rather an autoimmune response triggered by the infectious antigens. Nonetheless, some reports proposed schistosoma mansoni to be a direct cause of myelopathy occurring in areas where schistosomiasis is endemic.[18] Several cases of TM were reported following vaccination.[19–21] In a center-based analysis of 47 patients, up to 30% of all cases of TM in children had a history of vaccination mostly within 1 month of symptom onset.[19] In the current study our aim was to examine and describe reported cases of TM following vaccination.

Methods

A literature search was performed using various bibliographic tools at the Sheba Medical Center library. All publications were identified through PubMed, EMBASE or DynaMed for all English-language only journals published during the period between 1970 and 2009. The search strategies employed the following key words: transverse myelitis; myelitis; vaccines; post-vaccination; vaccination. We also conducted further searches of article bibliographies to ensure that no studies or reports were missed.

Results

Forty three cases of post-vaccination TM were found in our initial search. Among them, six cases were excluded due to insufficient demographic and clinical data (two cases of influenza vaccine,[22,23] one case each of tetanus,[24] rabies,[25] typhoid[26] and anti-cholera vaccines[27]). The remaining 37 cases are shown in Table 1. Most (73%) cases of TM reported occurred during the first month post-vaccination. The age of the patients varied from several months to 50 years old (18 children (0–18) and 19 adults (18 +)), with an average age of 24.5 ± 17.8 years. There were 13 reported cases of TM following anti-HBV (hepatitis-B virus) vaccination, six after measles–mumps–rubella (MMR) or rubella vaccine, four after diphtheria–tetanus–pertussis (DTP) or diphtheria–tetanus (DT), four after rabies vaccine, three after oral polio virus (OPV), two after influenza vaccine, one after typhoid vaccine, one after pertussis, one after Japanese B encephalitis and two cases were after multiple vaccine regimens.

Discussion

Vaccines are used world wide to eradicate lethal infections and decrease infectious morbidity. However, post-vaccination complications, especially neurological ones, although rare, are well described and include conditions such as seizures, Guillain–Barré syndrome (GBS), peripheral neuropathy, cranial nerve palsy, encephalopathy and TM.[28] Neurologic complications can occur due to a reversion of a mutant vaccine-virus (such as in vaccine-associated paralytic poliomyelitis), but most are immune-mediated. However, it should be emphasized that the contribution of vaccines to individual and global health outweighs by any measure the risk of most neurological adverse events. In the current study we have identified several vaccines to be rarely associated with TM.

HBV vaccine is a genetically engineered recombinant vaccine. HBV vaccine is an efficient and relatively safe vaccine used worldwide for the last 27 years. Nonetheless it has been associated with many

Table 1 Cases of transverse myelitis following vaccination

First author	*Year of publication*	*Vaccine*	*Age (years)*	*Time from vaccination*
Bir[49]	2007	Rabies	25	2 months
Das[67]	2007	Typhoid	19	5 days
Kelly[36]	2006	OPV + DT + Hib	0.5	7 days
Riel-Romero[43]	2006	DTP	0.7	17 days
Lim[68]	2004	Measles or Rubella	9	16 days
Kulkarni[51]	2004	Rabies	45	14 days
Fonseca[33]	2003	HBV	3	10 days
Nakamura[48]	2003	Influenza	70	7 days
Zanoni[69]	2002	MMR	1.25	21 days
Matsui[70]	2002	Japanese B encephalitis	4	14 days
Karaali-Savrun[34]	2001	HBV	42	2 months
		HBV	33	4 weeks
		HBV	40	3 weeks
		HBV	42	3 months
Larner[47]	2000	Influenza	42	Days9
Iñiguez[30]	2000	HBV	15	1 week
Renard[31]	1999	HBV	16	1 week
Tartaglino[28]	1995	HBV	40	2 weeks
Friedrich[38]	1995	OPV	12	6 years
		OPV	8	4 years
		OPV	13	9 years
Joyce[71]	1995	MMR	20	2 weeks
Abdul-Ghaffar[41]	1994	DT	13	3 days
Trevisani[72]	1993	HBV	11	3 weeks
Read[42]	1992	DTP	50	2weeks
D'Costa[37]	1990	Cholera, typhoid, OPV	24	2 days
Shaw[32]	1988	HBV	41.5	2 weeks
		HBV	*	12 weeks
		HBV	*	20 weeks
		HBV	*	27 weeks
Label[52]	1982	Rabies	50	2 days1
Clark[73]	1977	Rubella	16	13 days
Whittle[44]	1977	DTP	0.6	6 days
Holt[74]	1976	Rubella	17	2 weeks
	1976	Rubella	13	4 days
Kulenkampff[75]	1974	Pertussis	6	17 days
Harrington[50]	1971	Rabies	41	14 days

*41.5, average of all four cases presented by Shaw *et al.*[32]

adverse events, and is the second most common vaccine reported to the USA Vaccine Adverse Events Report System.[29] The risk of demyelination disorders following HBV vaccination was brought to public attention two decades ago, but remains a debated issue today.[30,31] In 1982, the Centers for Disease Control, the Food and Drug Administration, and the manufacturer created a surveillance system to monitor adverse events occurring after immunization with HBV vaccine. In the 3 years between 1982 and 1985, an estimated 850,000 persons received the vaccine. During that period, a total of 41 neurologic adverse events were reported (including four TM cases), half of them occurred after the first of three required vaccine doses.[32] We have listed 13 reported cases of TM following HBV vaccination since 1982, which make it the most common vaccine associated with TM. In these post-HBV cases, symptoms rose within days to 3 months following inoculation.[28,30–34] In other reports some of the neurological adverse event appeared in the early days post-vaccination whereas others appeared months and even years thereafter.[35]

The OPV vaccine is a live attenuated vaccine which has significantly decreased the prevalence of polio disease worldwide, but in rare cases can cause polio disease. Poliovirus infection is one of the most prevalent causes of TM and can present as TM in between 1 : 125 and 1 : 800 cases. Therefore, there is a biological plausibility in suggesting a causal relationship between OPV and TM. In 1993 the Institute of Medicine of the National Academies of the United States declared a causal

relationship between OPV and TM using theoretical criteria, clinical history and laboratory results.[36] Therefore, in most developed countries a safer vaccine, the inactivated poliovirus vaccine (IPV), has replaced the OPV, which remains in use mainly in developing countries and in areas endemic for polio. In this review we have listed five cases of TM following OPV given as a single vaccine or in a combination[36–38] (Table 1). In the study of Friedrich *et al.*[38] three cases of TM were associated with OPV administrated years before onset of disease. In these three cases, vaccine-specific strains of the virus were isolated from patients' stool within days of TM onset, suggesting post-vaccination persistent infection or a transmission of the vaccine strain from another subject via the fecal–oral root. Thus, alluding to a much wider time frame or herd-immunization effect in the pathogenesis of vaccine-associated TM. Prolonged periods between vaccination and the appearance of autoimmune phenomena have been reported before.[39]

DTP vaccine is a combination vaccine which encompasses two toxoids (diphtheria and tetanus) and pertussis antigens, previously derived from a whole-cell pertussis vaccine. Infants and children with underlying neurological disorders present a unique problem concerning vaccination with DTP. It was suggested that those children are at an increased risk for the appearance of convulsions, encephalitis and other neurological complications within 2–3 days after vaccination. This association has not been replicated or proven by large case–control studies, but a safer acellular pertussis vaccine (DTaP) was introduced in the US in 1991.[40] Nevertheless, four cases of TM following DT and DTP as single vaccines or in various combinations have been reported since then[41–44] (Table 1).

The influenza vaccine is an inactivated or killed viral vaccine. Unlike other vaccines, the influenza vaccine must be administered every year and its antigenic profile differs yearly. A casual relationship between this vaccine and neurological complications was noted in the outbreak of GBS in 1976 which followed the 'swine flu' vaccine and held a relative risk of 4.0–7.6.[45] This high prevalence of post-vaccination adverse events decreased after the introduction of the HA, (gene from the human lineage of the influenza virus), type of the vaccine. Nevertheless, 70 cases of neurological complications including TM were reported up to 1996,[46] and in recent years two other cases were documented post-influenza vaccination.[47,48] The rarity of post-influenza-vaccination neurological complications reported in recent years makes it impossible to establish a definite causal relation.

The rabies vaccine is a live attenuated vaccine given only on an as-needed basis. The traditional rabies vaccine contains neural elements and withholds the risk of morbid neurological complications, as well as TM.[49–52] A new cell culture rabies vaccine has replaced the traditional one, nevertheless the latter is still in use in some countries as it is less expensive.[51]

Other vaccines such as measles, mumps, rubella, typhoid, Japanese encephalitis and anti-cholera have also been administered prior to TM onset (Table 1).

The mechanisms by which vaccines may induce TM

The immune system's ability to distinguish self from non-self (i.e. immune tolerance) is essential for self-defense as well as for protection from autoimmune destruction. The breakdown of self-tolerance to highly conserved auto-antigens, is essential for the development of autoimmunity, and is strongly associated with exposure to environmental stimulus such as infectious antigens.[13] The host's response to a vaccine, originally generated to produce protective immunity, is similar to its response to an infectious invasion. Therefore, it is reasonable to assume that as infectious agents can induce autoimmunity, so can the recombinant or live attenuated antigens used for vaccination.[53] Several mechanisms by which an infectious antigen may induce autoimmunity have been defined.

- *Molecular mimicry* between infectious antigens and self antigens[54] is the most common mechanism.
- *Epitope spreading*, whereby invading antigens accelerate an ongoing autoimmune process by local activation of antigen presenting cells and over processing of antigens[55] is another mechanism.
- Infectious agents, may induce autoimmunity via *polyclonal activation* of B lymphocytes[56] or *bystander activation* which enhances cytokine production and further induce the expansion of auto reactive T-cells.[57] The latter mechanism may be associated with post-infectious TM as IL-6 levels were found to be markedly elevated in the CSF of TM patients.[6]

In addition to the infectious antigen, vaccines contain several ingredients, such as adjuvants and preservatives.[58] Adjuvants have been called the 'the immunologists dirty little trick', as they are simultaneously administered with vaccines in order to induce a more vigorous immune response to the vaccinated antigens.[59] The mechanisms of

adjuvancy are not fully elucidated, however it seems that adjuvants mimic specific sets of conserved molecules such as bacterial lipopolysaccharides, endocytosed nucleic acids and unmethylated CpG-DNA that activate the innate immune response. Furthermore, adjuvants protect the infectious antigen and may induce an adaptive immune response.[60,61] An unrelated adjuvant or an adjuvant from one vaccine can augment an immune response to another vaccine. In mice vaccinated with a combination of pertussis and anthrax vaccine, the pertussis vaccine acted as an adjuvant to the anthrax vaccine.[62] The administration of multiple or a combination of vaccines although effective and safe for most individuals may have a greater chance of triggering autoimmunity. Such a notorious effect of multiple vaccines has been suggested in the Gulf War syndrome, which might have been related to chronic Th-2 biased immune response and possibly an adjuvant effect following multiple vaccinations.[63–65] One of the most commonly used adjuvants in human vaccines is aluminium salt, currently used in DTP and DTaP, HBV, HiB, rabies and other vaccines. In the last decade it was revealed that aluminum adjuvant, at levels comparable to those administered to Gulf War veterans, can cause motor neuron death.[65] Moreover, adjuvants were found to be independently associated in animal models and in humans with symptoms such as weakness, autoimmune manifestations (i.e. myalgia, arthralgia and the presence of autoantibodies) and neurological manifestations (i.e. memory loss and loss of myelinated nerve fibers).[66] Thus, although adjuvants were originally expected to be only generalized stimulators of the immune system, they were found to induce by themselves the 'adjuvant disease'. The association of TM with so many different vaccines alludes to the idea that a common denominator might be responsible, such as a common adjuvant.

Conclusion

In recent years the intimate interaction between infectious and autoimmune diseases has been clearly defined. At the same time, the association between vaccines and autoimmune diseases remains an issue of debate for most vaccines. As not all individuals who suffered from an infection will eventually develop an autoimmune phenomenon, it was suggested that autoimmune diseases develop in those who are genetically susceptible.[12] Avoiding a triggering stimulus may allow these genetically susceptible individuals to remain asymptomatic throughout their life. In this review we have listed 37 cases of TM which were associated with different vaccines given to infants, children and adults. In most of these cases the temporal association was between several days and 3 months, although a longer time frame of several years was suggested. A pathogenic proof of causality was accepted only in the case of post-OPV TM, however the temporal association between other vaccines and TM, and the possible mechanism associating these phenomena cannot be ignored. The rarity of TM makes it a difficult disease to study. In order to assess the risk of this disease following vaccination and the mechanism involved in this process further studies utilizing animal models of TM are needed. Meanwhile, physicians should be aware of this possible association. Reporting those cases to various local vaccines adverse events registrations as well as the medical literature will enable better assessment of the true prevalence of post-vaccination TM, while examining the susceptibility and safety of different vaccines.

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