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Neurological complications of vaccination with outer surface protein A (OspA)

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Abstract. A wide range of neurological complications have been reported via the medical literature and the VAERS system after vaccination with recombinant outer surface protein A (OspA) of Borrelia. To explore this issue, 24 patients reporting neurological adverse events (AE) after vaccination with Lymerix, out of a group of 94 patients reporting adverse events after Lymerix vaccination, were examined for causation. Five reports of cerebral ischemia, two transient Ischemic attacks, five demyelinating events, two optic neuritis, two reports of transverse myelitis, and one non-specific demyelinating condition are evaluated in this paper. Caution is raised on not actively looking for neurologic AE, and for not considering causation when the incidence rate is too low to raise a calculable difference to natural occurence.

Keywords: OspA, Lyme disease vaccine, outer surface protein A, neurologic adverse events

1. Introduction

Lyme disease (LD) is a tick-borne infectious disease [1, 2] caused by the spirochaete *Borrelia burgdorferi* (Bb). The Bb grows in an intermediate host, the tick, where it is found in the salivary gland. At that point, Bb expresses outer surface protein A (OspA). OspA has been shown to be a critical factor for *Bb* to colonize and live in the midgut of the tick, and its growth there is a necessary part of the natural enzootic life cycle of Bb [3].

Once the tick bites a person, the blood meal from the person enters the tick's mouth, and contents from the tick's salivary gland, including Bb, mix with the human blood. Some of this blood along with Bb is regurgitated back into the bite site, and re-enters the human. Once in the human, production of OspA by Bb is down-regulated.

In at least 80 percent of patients in the United States, LD begins with a slowly expanding skin lesion, erythema migrans, which occurs at the site of the tick bite. The skin lesion is frequently accompanied by influenza-like symptoms, such as malaise and fatigue, headache, arthralgias, myalgias, fever, or regional lymphadenopathy, suggesting dissemination of the spirochete. These symptoms may be the presenting manifestation of the illness. Overall, LD has a number of clinical manifestations, divided into early and late, as described in Table 1.

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Table 1
Clinical manifestations of Lyme disease

Stages of Lyme disease	Dermatologic	Neurologic	Cardiac	Musculoskeletal	General
Early	Erythema migrans	Headache		Arthralgias, myalgias	FLS, fatigue, fever, regional lymphademopathy
Early disseminated		Acute neuroborreliosis		Arthralgias, myalgias	
Late		Cognitive	block	Arthralgias, myalgias	

2. Neurologic involvement in Lyme disease

Within weeks, during or shortly after the period of early, disseminated infection, objective signs and symptoms of acute neuroborreliosis develop in about 15 percent of untreated patients in the United States. Possible manifestations include lymphocytic meningitis with episodic headache and mild neck stiffness, subtle encephalitis with difficulty with mentation, cranial neuropathy (particularly unilateral or bilateral facial palsy), motor or sensory radiculoneuritis, mononeuritis multiplex, cerebellar ataxia, or myelitis [4, 5]. Even in untreated patients, acute neurologic abnormalities typically improve or resolve within weeks or months. LD in many ways mimics the neurologic involvement of another spirochaetal infectious disease – syphilis.

By vaccinating individuals with OspA, it was anticipated [6] that individuals would produce anti-OspA antibody. When a tick would then bite an OspA vaccinated person, the blood meal, containing anti-OspA antibody would come into contact with Bb in the tick's mouth and salivary gland, and the spirochaete would become inactivated before it could be transferred into an infected individual [7]. One problem with this proposed immune mechanism of vaccine efficacy is the known down regulation of OspA production once the Bb is in the infected individual. Such down regulation would run counter to the necessity to have OspA on the surface of Bb for effective immune inactivation. Presumably the down regulation was incomplete or enough OspA was still present to account for the known but rather limited efficacy of OspA vaccine.

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 [8]. This includes including Guillan Barre syndrome from influenza vaccine, transverse myelitis caused by duck embryo rabies vaccine, and seizures from pertussis vaccine (Table 2) [9–25].

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 LD from a successful infection with 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 OspA from Bb and is designed to induce a protective immune response against Bb may have associated with its use a range of neurologic AE. This case series reports on a subgroup of neurological adverse events selected from a larger group of various AEs reported after vaccination with OspA vaccine.

Table 2
Neurological adverse effects of vaccines. The spectrum of neurological toxicities seen with various vaccines

Vaccine	Formulation	Neuro AE
Measles vaccine	Live attenuated virus	Autism
Hep B vaccine	Recombinant protein	Multiple sclerosis
Japanese encephalitis vaccine	Infected mouse brain extract	Meningoencephalitis
Influenza vaccine	Live attenuated, killed, or protein extract	Guillain-Barré syndrome and giant cell arteritis
Rabies vaccine	Attenuated	CNS demyelination
Pertussis	Purified protein	Seizures and hypotonic/hyporesponsive episodes
Tetanus	Tetanus toxoid conjugate	Acute disseminated encephalomyelitis
Varicella vaccination	Live attenuated	Encephalitis, aseptic meningitis, and cerebellar ataxia
Oral polio vaccine	Live attenuated	Vaccine-associated paralytic poliomyelitis
Vaccine aduvants (e.g. Freund's)	Aluminum, BCG, peanut oil	MS
Vaccine preservatives (thimerosal)	Mercury	Neurotoxicity, Autism
Vaccine contaminants	Aluminum	Macrophagic myofasciitis
Bovine-derived materials	Tissue culture	New variant Creutzfeldt-Jakob disease

3. Methods

Available medical records (outpatient and inpatient records, consultations, laboratory and radiology reports, etc.) were reviewed from ninety four patients who had suffered symptoms temporally related to having received Lymerix (SKB OspA) vaccination. When possible, the patient was examined, and neurology consults were reviewed, when they had previously been obtained. Standard rules of medical causation [26] were applied. Specifically, the following five criteria were used to evaluate whether a causal relatedness existed between vaccination with Lymerix and the symptom: 1) Was the vaccine given before the adverse event appeared, 2) Has that adverse event been reported before, for that vaccine, 3) Has that adverse event been reported for similar vaccines, 4) Is that adverse event consistent with known mechanisms of vaccine-related injury, 5) Is there a pre-existing injury or alternative explanation? Comparison was made to the known adverse event profile of Lymerix and other vaccines. Causation was ranked as Definite, Probable, Possible, or Unlikely. Disease case definitions were defined based on standard accepted expert descriptions.

4. Results

Twenty one of the ninety four cases reviewed complained of neurologic AE, as listed in Table 2. This represents 17 males, average age 49 years old, and 4 females. One case (#9) was definitely causally related, 15 were probably related, 2 were possibly related, one was unrelated, one was unlikely and one was indeterminate. Of those definitely, probably or possibly related, none were serious AE – fatal, life threatening or resulting in prolonged hospitalization. Seven cases involved complaints pointing to neurocognitive deficits, one optic neuritis, seven demyelinating neuropathy, and one Bell's palsy. These cases involved specialty examinations and testing by neurologists, which verified the diagnoses.

Table 3
Neurologic adverse effects reported with Lymerix

Case No	Age at onset	AE	No of vaccinations	Interval from vaccination to AE	IR to OspA	HLA DR4	Relatedness by std rules
1	30	Neurocognitive changes	2	1 yr	Reactive	Not available	Possible
2	31	Reactivation wide range of inflammatory and neurocognitive symptoms	2	Progressed several months after	Reactive	Not available	Probable
3	52	Neurocognitive	2	Next day	Non-reactive	Pos	Probable
4	48	Neurocognitive	2	Approx. 1 mo	Non-reactive	Pos	Probable
5	39	Neurocognitive	2	Within days	Reactive	Neg	Probable
6	43	Neurocognitive	3	Almost immediately	Reactive	Not available	Probable
7	47	Neurocognitive	3	After 2nd vaccine	Not available	Not available	Probable
8	34	Optic neuritis	2	Knee pain after/eye-2 months after	Reactive	Pos	Probable
9	60	Inflammatory demyelinating polyneuropathy	3	Same day	Non-reactive	Not Available	Definitely
10	61	Guillan Barre and demyelinating neuropathy	2	Approx. 2 mos	Reactive	Pos	Probable
11	62	Demyelinating syndrome	3	Days later	Reactive	Pos	Probable
12	68	Transverse myelitis	1	Approx. 2 weeks	Not available	Neg	Probable
13	26	Guillan Baree	3	Approx. 1 week	Reactive	Not available	Probable
14	74	Transverse myelitis	2	Several hours	Non-reactive	Pos	Probable
15	46	Demyelinating disease or central Lyme	1	2 days	Non-reactive	Not available	Probable
16	63	Bells' palsy	1	Awaiting more info	Non-reactive	Not available	Awaiting more info
17	39	Quadraplegia from spinal chord lesion	1	Approx. 10 mos	Reactive	Not available	Possible
18	61	Neuromuscular	2	5 days	Non-reactive	Not available	Probable
19	44	Bell's palsy and paresthesias	2	Approx. 3 months	Not available	Not available	Probable
20	49	Tinnitus	1	Over 1 year	Not available	Pos	Unlikely
21	53	Neuropathy	2	Approx. 2 months	Reactive	Neg	Unrelated

As shown in Table 3, the median age in the people who experienced neurological events was 62. The following AE were observed:

- 21 neurological events,
- median age 62 years,
- 7 reports of neurocognitive deficits,
- 5 reports of cerebral ischemia that included three cerebral vascular accidents, two transient Ischemic attacks,
- Five reports of demyelinating events,

- 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, 10 and 13 days after the vaccine.
- One non-specific demyelinating condition diagnosed 208 days after vaccination.
- The remainder of the neurological events didn't fall into any single diagnostic category.

5. Discussion

5.1. Neurological complications known for vaccines

The ability of a wide range of vaccines to cause neurologic AE is well-documented [18–23, 27–31]. A variety of vaccines are known or suspected of being able to cause significant neurologic AE, as listed in Table 2.

5.2. Mechanisms

The mechanism by which vaccines may cause neurological AE includes live replication (MMR, polio), autoimmune [32], molecular mimicry [33] and direct toxicity, and immune release [34].

5.3. Mechanisms for neurologic complications of OspA vaccine

OspA can cause induction and secretion of the inflammatory cytokine IL-6 by human glial cells [35, 36]. Production of IL-6 and INF have been associated with neurological damage in LD. OspA can stimulate a protective immune response against Bb [37]. 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) [38]. 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 [39].

5.4. OspA vaccine neurological experience

Lymerix vaccine was intended to produce an antibody response against the immunogenic antigen OspA, which is a lipoprotein. The lipid moiety, although strengthening the immune response against OspA, does not yield a maximal protective immune response unless presented along with a non-specific stimulator – an adjuvant. Realizing that in the natural infection with Bb, the switch from IgM to IgG, mediated by T cells, is delayed or absent in most patients, it is not surprising that a number of patients have a diminished IgG response to OspA vaccine.

Published reports of clinical trials for the Connaught Pasteur Merieux [40, 41] and the SKB [42] OspA vaccines mention headache, but do not described serious (fatal, life-threatening or resulting in prolonged hospitalization) or severe neurological adverse events. Yet, AE that are infrequent, although potentially serious and severe, might not be visible within relatively small size efficacy studies with a few thousand healthy persons. This illustrates the importance of post-marketing surveillance of AE, the VAERS system.

The data reported in this paper is post-marketing, and in most cases reported to VAERS. The data show that OspA vaccine is capable of causing neurologic AE. Some of these AE are similar to the known neurological AE causally related to other, completely different vaccines. Some of the AE are of the same type as seen in Lyme disease itself.

In addition to the data on cases reported here, the VAERS post-marketing data available (through FOI) were examined for neurological AE (regardless of causal relatedness) for the reporting period December 1998 through October 31st, 2000. This data period only includes OspA vaccine produced by SKB. In addition, the updated VAERS presentation was reviewed which covered the period up to January 31, 2001. There is limited data after this period, and in February of 2002 the sole manufacturer of OspA vaccine voluntarily discontinued making it available.

The VAERS data in the limited time period provided are consistent with the types of AE that are reported here. It is of interest that there were 7 cases of neurocognitive complaints which 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. Another issue 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, then that particular line of data might not be questioned for and captured [43, 44].

6. Conclusions

OspA vaccines are capable of initiating a wide array of acute and chronic neurological AE. Not surprisingly, some of these AE resembled neurological manifestations of Lyme disease, and point to reactivation of latent infection, molecular mimecry or aberrant immune responses as mechanisms. Adverse effect profiles from limited pre-licensure studies should not deter from making a clinical determination of relatedness for seemingly new or unreported AE, This is particularly true if the AE follows along a pattern seen for the disease being vaccinated against.

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