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Vaccinations and multiple sclerosis

Abstract Two problems must be considered in regard to the relationship between vaccinations and MS: Do vaccinations favour the first attack of MS? Do they increase the short- or long-term risk in patients with known disease? Answers to these questions are difficult due to the paucity of reported cases, our ignorance of the precise frequency of neurological adverse events in vaccines based on prospective studies, and finally by the lack of a well established pathophysiology. In most instances, the role of the vaccine is based on a temporal link between the injection and the onset of neurological disease, and more rarely to a positive reintroduction. Acute disseminated encephalomyelitis (ADEM), a monophasic and multifocal illness of the white and grey matter, has been observed following various viral or bacterial infections as well as vaccine injections for diseases such as pertussis, tetanus and yellow fever. The similarities between ADEM and experimental allergic encephalitis (EAE) are suggestive of an immunological process. In addition to the dramatic presentation of ADEM, more limited white matter involvement, such as optic neuritis or myelitis, has been reported following vaccine injections, and has occasionally been counted as the first attack of MS. In France, 25 million inhabitants, almost half of the population, were vaccinated against hepatitis B (HB) between 1991 and 1999. Several hundred cases of an acute central demyelinating event following HB vaccination were reported to the pharmacovigilance unit, leading to a modification of vaccination policy in the schools and the initiation of several studies designed to examine the possible relationship between the vaccine and the central demyelinating events. The results of these studies failed to establish the causality of the HB vaccine. Nevertheless, molecular mimicry between HB antigen(s) and one or more myelin proteins, or a non-specific activation of autoreactive lymphocytes, could constitute possible pathogenetic mechanisms for these adverse neurological events.

Key words Multiple sclerosis • Vaccination • Hepatitis B

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Introduction

The benefits of modern immunization programs are well known and beyond question. Vaccination has reduced the mortality and morbidity of infectious diseases more than any other measures including improvements of public health and the introduction of anti-infectious drugs. No one knows the exact frequency of neurological adverse events because these complications are rare, and are not detected by pre-approval clinical trials involving a small numbers of subjects. The results of post-marketing surveillance are biased by incomplete reporting. Nevertheless, it has been known for many years that some vaccines can induce severe neurological side effects. Most of these post-vaccinal neurological manifestations involve an immunological process.

Post-vaccinal adverse neurological events

Besides the serum sickness observed after passive immunization, neurological complications include inflammatory disorders of the central nervous system (e.g. acute disseminated encephalomyelitis (ADEM) and its variants, acute transverse myelitis, optic neuritis and acute cerebellar ataxia and multi-

ple sclerosis) and of the peripheral nervous system (e.g. brachial plexitis, Guillain-Barré syndrome and mononeuropathies). The discovery of experimental allergic encephalomyelitis (EAE) was in part linked to the use of the antirabies vaccine discovered by Pasteur in the last century. In 1928, Stuart and Krikorian described encephalitis and polyneuritis after antirabies vaccination, and hypothesized that the neurological side effects were due to some components of the neural matter in the vaccine rather than to the virus. This led Rivers and Schwenker, in 1935, to inoculate monkeys repeatedly with homogenates of normal rabbit brain, which resulted in the first induction of EAE. Later, the encephalitogenic antigen was identified as the myelin basic protein, and EAE became the prototype of experimental immune disease. Thus it was that early observations of neuroparalytic accidents due to rabies vaccine provided the foundation for the current concepts of immunopathological mechanisms in demyelinating diseases.

Vaccine and CNS demyelinating events

Since the report by Miller et al. [1] of nine cases of the first attack of MS following various vaccine injections (e.g. smallpox, yellow fever, typhoid fever, tuberculosis and rabies), numerous similar case reports have appeared in the English literature. A decade later, following the debate on the safety of swine influenzae vaccine, Myers and Ellison conducted a double-blind placebo-controlled study in multiple sclerosis (MS) patients which showed no increase in the relapse rate following the vaccination [2]. In 1997, Miller et al. [3] conducted another double-blind placebo-controlled trial of influenza immunization in 104 MS patients followed for six months and found no differences in attack rate or disease progression between the vaccinated and non-vaccinated groups. Smaller studies by Michielsens et al. [4] and Salvetti et al. [5], which examined changes on magnetic resonance images after influenza vaccination, revealed no increased activity, except for one of Salvetti's series who already had very high activity as seen on magnetic resonance imaging (MRI) before vaccination. A recent 10-year survey by Behringwerke, a company that distributes about 10 million doses of bacterial and viral vaccines each year, resulted in an estimated incidence of 3.5 cases of central nervous system (CNS) demyelination per 10 million vaccinations within a month of vaccination; for 2.4 cases per 10 million, the symptoms were the first manifestation of neurological disease [6].

Hepatitis B vaccine and MS

The first-generation hepatitis B vaccine was based on the hepatitis B virus (HBV) surface antigen (HbsAg) derived from the plasma of HBV carriers. Post-marketing surveillance of this vaccine for adverse neurological events did not suggest a definitive association.

Second-generation HB vaccines include several recombinant DNA products: Recombivax (Merck Sharp and Dohme), Engerix (Smith Kline and Beecham), and GenHevac B (Pasteur Vaccins). Recombivax HB and Engerix B are yeast-derived vaccines based on the coding sequence for the S gene. GenHevac B is a Chinese hamster ovary cell-derived vaccine based on the coding sequence for the pre-S2 and S genes. The availability of these second-generation HB vaccines made possible extensive vaccination programs which targeted not only high-risk individuals but also neonates and children. As early as 1991, a few case reports of central demyelinating events following HB vaccine appeared in the English literature. Between 1991 and 1997, 35 cases of primary demyelinating events within eight weeks of recombinant HB vaccine injection were seen at the Salpêtrière in Paris [7-9]. The neurological manifestations were similar to those observed in MS: optic neuritis, sensorimotor disturbances, ataxia and vertigo. There were inflammatory changes in the cerebrospinal fluid (CSF), and high signal intensity lesions were observed in the cerebral white matter on T2-weighted MR images. After a mean follow-up of three years, half of them became clinically definite MS. Moreover, these neurological manifestations occurred in individuals at higher risk for MS: a preponderance of women, mean age near 30 years, over-representation of the DR2 antigen and a positive family history of MS.

From 1993 through 1999, the French pharmacovigilance system identified several hundred cases with similar demographic and clinical characteristics. No cases were reported in children under the age of three years. Almost 25 million inhabitants were vaccinated during this period, of which 18 million were adults. It is extremely difficult to differentiate between coincidence and causal relationship. Various calculations of expected versus observed cases gave results that could be interpreted as supportive of a possible association between HB vaccine and CNS demyelinating events, especially given the widespread underreporting of these events. Because of the concerns about the safety of the HB vaccine expressed by the media, it was not possible to conduct a prospective study in France.

A first retrospective, hospital-based case-control study was carried out at the Salpêtrière, on patients experiencing the first episode of CNS demyelination (FECD) during the 2-year period January 1994-December 1995 [10]. There were 121 cases with a FECD and 121 controls (matched for age, sex, socioprofessional status, and date of consultation). Data on vaccination history of cases and controls were collected by means of a postal questionnaire and checked by phone interview. Adjusted odds ratio (OR) obtained from conditional logistic regression between a FECD and any vaccination were 1.4 (95% CI, 0.5-4.3) for an exposure during the previous 60 days, and 2.1 (95% CI, 0.7-6.0) for an exposure during the previous 61-180 days. Similar results were found for HB vaccine exposure during the previous 60 days, adjust-

ed OR = 1.7 (CI 95%, 0.5-6.3) and during the previous 61-180 days, adjusted OR = 1.5 (CI 95%, 0.5-5.3). However, the power of the study was quite low and the probability of detecting a relative risk of 2 was only 35%. The conclusion was that these findings could not confidently exclude an association between HB vaccine and the occurrence of a FECD.

The Vaccinations, Demyelination and Multiple Sclerosis Study (VDAMS) conducted by Sturkenboom et al. [11] was a population-based case-control study using the general practice database in the UK which represents approximately 8% of the UK population. There were 343 cases with incident MS and 138 cases of central demyelination. Each case was matched for age, gender and practice with up to 6 controls. The index date was defined as the date of first symptoms consistent with disease. The vaccination history was obtained from automated medical, prescription and prevention records. The OR for exposure to HB vaccine in the 0-12 months period was 1.5 (CI 95%, 0.6-3.9). A prospective study of 753 MS patients during 1997-1998 identified 92 who were vaccinated against HBV [12]. Of these, 46 had a FECD, 20 in less than 2 months following vaccination, and 22 had probable and 24 had definite MS. The conclusion was that HB-vaccinated MS patients had the same relapse rates before and after the vaccine, and that patients with a FEDC after receiving HB vaccine have the same characteristics as those who did not, except for a younger age of onset. In two patients, a second injection was followed by a second attack.

Possible mechanisms

Possible pathogenetic mechanisms include: (i) molecular mimicry between HBV proteins and myelin components; (ii) indirect immunological stimulation by the large quantity of exogenous HbsAg; and (iii) direct or indirect immunological toxicity of vaccine contaminants. Genetic background may also play a role in the incidence of post-vaccinal complications.

In the molecular mimicry hypothesis, immunization with a viral peptide activates cross-reactive T cells that also recognize myelin antigen. After activation, clonal expansion and passage through the blood-brain barrier, T cells recognize the myelin antigen and initiate autoimmune inflammation. In 1985 Fujinami and Oldstone [13] showed that it was possible to induce EAE in rabbits with a peptide derived from the HBV polymerase, which is not included in HB vaccine but which shares six amino acids in common with the encephalitogenic site of rabbit myelin basic protein. More recently, Gran et al. [14] reported the identification of a T cell line specific for HB antigen that cross-reacts with PLP-derived peptide 179-197; the cell line was closed from a $DR2^+$ patient who developed MS after HB vaccination. This suggests that the mechanism of molecular mimicry warrants further investigation. Activation of the cytokine network by immunization with HbsAg may lead to the endogenous production of interferon gamma and tumor necrosis factors, which have been suggested or demonstrated to have a deleterious effect in the progression of MS. The yeast-derived recombinant vaccine Engerix is contaminated with thiomersal, yeast-derived lipids and DNA, and the cell-derived vaccine GenHevac B is contaminated with formaldehyde and Chinese hamster ovary-derived protein. Because neurological complications have been observed after both these two vaccines, these different contaminants do not appear implicated, except possibly for aluminum which is present in both vaccine. Aluminum-containing vaccines have been blamed for macrophagic myofasciitis (MMF) believed to be due to the impaired ability to clear the metal from muscle. Chronic deposits of aluminum may lead to chronic immune activation, which is suggested by the presence of autoimmune disorders in 34% of MMF patients [15]. A possible genetic predisposition is suggested by the over-representation of DR2 positivity and by the existence of relatives with MS for some of these patients.

Conclusions

Epidemiological studies have not demonstrated a relationship between HB vaccination and MS, but a trend is definitely present. Although HB vaccines do not cause MS, they could be a triggering factor in susceptible individuals in the same manner as infections. Further studies should clarify these observations. Careful studies of patients with CNS demyelination after recombinant hepatitis B vaccination may help demonstrate the importance of molecular mimicry in the pathogenesis of CNS demyelination.

Sommario *La relazione fra sclerosi multipla (SM) e vaccinazioni solleva due problemi: 1) La vaccinazione contribuisce all'esordio della malattia? 2) Esistono rischi a breve e/o medio termine in pazienti con SM sottoposti a vaccinazione? È difficile rispondere a queste domande, in ragione soprattutto della rarità dei casi riportati, ma anche per la mancanza di studi prospettici che permettano di determinare la frequenza precisa di eventi neurologici avversi in una popolazione vaccinata ed infine di un'ipotetica fisiopatologia di base. Nella maggior parte dei casi riportati, la responsabilità della vaccinazione è basata su una relazione temporale tra la prima somministrazione del vaccino e la comparsa di disturbi neurologici e, meno spesso, dalle somministrazioni del richiamo. L'encefalomielite acuta disseminata (ADEM), malattia monofasica e multifocale della sostanza bianca e grigia del sistema nervoso centrale, è stata osservata in concomitanza di varie infezioni di tipo virale o batterico, così*

come dopo iniezioni vacciniche (contro pertosse, tetano, febbre gialla, ecc.). La somiglianza tra la ADEM e l'encefalite allergica sperimentale (EAE) è suggestiva per un comune processo immunologico. Oltre alla manifestazione drammatica della ADEM, riesacerbazioni infiammatorie della sostanza bianca più contenute, quali neuriti ottiche e mieliti, sono state riportate dopo iniezioni vacciniche, e alcune sono state considerate esordio di SM. In Francia, dove il programma di vaccinazione contro l'epatite B (HB) ha incluso circa metà della popolazione (25 milioni di abitanti) tra il 1991 ed il 1999, le unità di farmacovigilanza hanno riportato centinaia di casi di demielinizzazione acuta del sistema nervoso centrale dopo la vaccinazione anti-HB. Queste osservazioni hanno condotto ad una modificazione della strategia di vaccinazione nelle scuole e ad un approfondimento della possible correlazione tra vaccinazione anti-HB e demielinizzazione del sistema nervoso centrale. I risultati di tali studi non consentono tuttavia di concludere che il vaccino anti-HB sia coinvolto nella demielinizzazione. Possibili meccanismi patogenetici alla base di questi eventi neurologici potrebbero essere inquadrati in un fenomeno di mimetismo molecolare tra l'antigene HB e costituenti proteici della mielina o in una non specifica attivazione di linfociti autoreattivi.

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Addendum

Since the submission of the manuscript, two important papers have been published. Confavreux et al. (2001) reported that the relative risk of relapse associated with exposure to any vaccination during the previous 2 months was 0.71 (IC 95%, 0.40 to 1.26). However the study is inadequate to conclude. In fact, the vaccinated population with at least one confirmed vaccination in the 12 months preceding the index relapse, composed of only 89 patients, is quite different from the original population and is no more representative of an MS population. This population seems to be composed of benign relapsing MS (for a median duration of illness of 7 years the median EDSS being 1, and the median number of relapses 2). Furthermore, only a small number of patients have been vaccinated with a specific vaccine (39 with HB vaccine, 25 with influenza vaccine, 2 with hepatite A vaccine, 2 with yellow fever vaccine...) and 12% of this population received immunosuppressive and immunomodulatory drugs. Finally, the only way to prove that vaccination is safe in MS would be to conduct a large randomized, double blind, placebo-controlled trial with each specific vaccine, as it has been done by Miller et al. (1997) for the influenza vaccine.
In another study, Ascherio et al. (2001) reported that the multivariate relative risk of MS associated with exposure to the hepatitis B vaccine at any time before the onset of the disease was 0.9 (IC 95%, 0.5 to 1.6) and was 0.7 (IC 95%, 0.3 to 1.8) within 2 years before the onset of disease. The study by Ascherio et al. excludes a possible link between hepatitis B (HB) vaccine and multiple sclerosis (MS). The discrepancies with the French studies could be due to the fact that Ascherio et al. have considered only patients with a diagnosis of MS, so they have excluded all possible central demyelinating events which can be either a first MS attack or a limited form of acute disseminated encephalomyelitis. Furthermore, they choose a long period at risk (2 years) which may have had a diluting effect. Finally, the number of vaccinated persons in the study is quite low (32) and if we consider the patients with MS who have been vaccinated in the 2 years before the onset of their disease the number drops to 9.

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