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Analytical Review

Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines

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Abstract

Background: Viruses and virus-induced lymphokines may have an important role in the pathogenesis of autoimmunity (Schattner A. *Clin Immunol Immunopathol*; 1994). The occurrence and significance of autoimmune manifestations after the administration of viral vaccines remain controversial.
Methods: Medline search of all relevant publications from 1966 through June 2004 with special emphasis on search of each individual autoimmune manifestation and vaccination, as well as specifically searching each viral vaccine for all potential autoimmune syndromes reported. All relevant publications were retrieved and critically analyzed.
Results: The most frequently reported autoimmune manifestations for the various vaccinations, were: hepatitis A virus (HAV) — none; hepatitis B virus (HBV) — rheumatoid arthritis, reactive arthritis, vasculitis, encephalitis, neuropathy, thrombocytopenia; measles, mumps and rubella vaccine (MMR) — acute arthritis or arthralgia, chronic arthritis, thrombocytopenia; influenza — Guillain–Barre syndrome (GBS), vasculitis; polio — GBS; varicella — mainly neurological syndromes. Even these 'frequent' associations relate to a relatively small number of patients. Whenever controlled studies of autoimmunity following viral vaccines were undertaken, no evidence of an association was found.
Conclusions: Very few patients may develop some autoimmune diseases following viral vaccination (in particular — arthropathy, vasculitis, neurological dysfunction and thrombocytopenia). For the overwhelming majority of people, vaccines are safe and no evidence linking viral vaccines with type 1 diabetes, multiple sclerosis (MS) or inflammatory bowel disease can be found.

Keywords: Pathogenesis; Viral vaccines; Autoimmune manifestations

Contents

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The enigma of autoimmunity and autoimmune diseases appears to be driven by a complex interplay of genetic, hormonal and environmental factors [1]. Despite significant recent advances in our understanding of the pathogenesis of autoimmunity, many basic questions remain and others are fraught with controversy. A good example is the putative role of infectious agents as a triggering event in the pathogenesis of autoimmune diseases [2,3]. *I*n a few discrete illnesses such as reactive arthritis, rheumatic fever or vasculitis associated with hepatitis B virus (HBV), the inciting microbial agent is relatively well defined. However, in most other autoimmune diseases, no exogenous infectious agent could be identified although, based on much data, viral infections have been proposed to play an important role [4].

Can viral vaccines be included among the environmental factors positively associated with the subsequent development of clinically important autoimmunity? This question has many significant implications. On the practical level, it has a direct bearing on vaccine safety in general and in patients with autoimmune diseases in particular [5]. On the theoretical level, it could help clarify the pathogenesis of autoimmunity and afford valuable insights into the role of viruses in it [6,7]. We examined this association by a comprehensive computerized search using a search strategy that was not previously utilized for looking at the viral vaccine/autoimmune disease association.

1. Methods

All Medline records from 1966 through June of 2004 have been scanned and all articles relevant to vaccines (or immunizations) and safety, adverse reactions, autoimmune diseases or autoimmunity have been identified and all reports relating to viral vaccines were selected and retrieved. Additional searches were performed separately on each autoimmune disease or potentially autoimmune syndrome (e.g. SLE, arthritis, vasculitis, uveitis, thrombocytopenia, Guillain–Barre syndrome, etc.) and each one of the specific viral vaccines administered to children or adults (Table 1). Each of the viral vaccines was then crosschecked separately for autoimmune diseases in general, and for each potential autoimmune syndrome in particular. All relevant articles identified have been retrieved. The references of all articles were scanned, and any relevant citations not previously identified were added to the collection. Also included were the author's previous files of articles on the subject. We limited our search to articles in the English language, either with or without an abstract.

Table 1
Viral vaccines recommended for routine use[a]

Adult immunizations
Hepatitis B vaccine (adults at risk)
Measles–mumps–rubella vaccine
Varicella vaccine
Influenza vaccine (age >50; healthcare workers)
Pediatric immunizations
Hepatitis B vaccine
Inactivated polio vaccine
Varicella vaccine
Hepatitis A vaccine (selective)
Influenza vaccine (selective)

[a] Adapted from the National Immunization Program, Centers for Disease Control and Prevention [5]. Also included in the search were rabies and smallpox vaccinations.

2. Results

The findings regarding varied autoimmune manifestations reported in association with viral vaccines will be discussed separately for each of the vaccines studied.

2.1. Hepatitis A virus (HAV) vaccine

Although millions of patients have received HAV vaccination as part of clinical trials or routine use, we could find hardly any reports on autoimmunity associated with its use (encephalopathy or vasculitis in one patient each, and two who developed joint disease). Thus, it remains one of the safest vaccines in this regard and the call to implement universal early-childhood immunization [8] can be wholeheartedly supported.

2.2. Hepatitis B virus (HBV) vaccine

The case for HBV vaccine is quite different since apart from liver disease, chronic hepatitis B *infection* is known to be associated with the frequent detection of circulating immune complexes and some patients develop immune-mediated extrahepatic manifestations. These include skin rash, joint symptoms, polyneuritis, glomerulonephritis and most notably – polyarteritis nodosa (PAN) – a distinct form of necrotizing angiitis with multisystem involvement [9].

Perhaps in line with that, and with the fact that vaccination can lead to prolonged hepatitis B surface antigenemia [10], as well as to increased production of multiple cytokines [11–13], the list of autoimmune manifestations reported in patients *vaccinated* against HBV is remarkable in both length and diversity (Table 2) [14–23]. However, the small number of patients involved is striking, particularly when considering the dozens of millions of HBV vaccinations administered. Only arthritis, thrombocytopenia, demyelinating encephalitis and demyelinating neuropathy have been reported in detail for somewhat more than 10 patients (Table 2).

Nevertheless, when HBV vaccine was compared with two control vaccines in the Vaccine Adverse Events Reporting System (VAERS) database, it seemed to have an increased number of reports [24]. These accumulating reports have led to much concern, to publicized press reports and even lawsuits [25]. However, when the results of several large-scale case-control studies on the safety of HBV vaccine became available recently, no evidence linking HBV vaccination with