Infections More than Vaccines are Inducers of Autoimmune Diseases

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KEY WORDS: infections, autoimmunity, vaccination, molecular mimicry

IMAJ 2010; 12: 635–637

The evolvement of immune responses against self-antigens and the development of autoimmune diseases are multifactorial in origin. The most important of these factors are the genetic susceptibility of the individual and the environmental factor, mainly viruses and bacteria. Molecular mimicry and increased expression of modified, cryptic, or new antigenic determinants are among the many antigen-specific mechanisms. Nonspecific mechanisms known as bystander activation include enhanced processing, presentation of self-antigens, immune cell activation, cytokine release, and cell apoptosis [1].

INFECTIONS AND AUTOIMMUNE DISEASES

The correlation between cytomegalovirus and Raynaud's phenomenon in lupus nephritis was demonstrated in early studies. In this regard, serologic analyses for CMV, parvovirus B19 and Epstein-Barr virus were performed in 60 patients with systemic lupus erythematosus and evaluated for the presence of vascular events, Raynaud's phenomenon and antiphospholipid syndrome. It was observed that CMV seropositivity was a highly significant risk factor for Raynaud's phenomenon but not for venous vascular events [2]. The molecular mimicry of the EBV peptide PPPGRRP by the peptide PPPGMRPP from SmB'/B of the human nuclear antigen strengthened the possibility that in some cases EBV infection is associated with the onset of SLE. With this in mind, James et al. [3] tested SLE patients and matched controls for evidence of previous infection with EBV. All but one of the196 patients with SLE had been exposed to EBV, whereas 22 of 392 healthy controls had no previous EBV exposure (odds ratio 9.35, 95% confidence interval 1.45–infinity, $P = 0.014$). These findings strongly supported the role of EBV in the development of SLE.

In order to identify environmental agents that could potentially induce autoimmunity, autoantibodies against 60 kDa Ro in SLE were found to cross-react with a peptide from the latent viral protein EBV nuclear antigen-1. Animals immunized with each of these antigens progressively developed autoanibodies binding multiple epitopes of Ro autoantigens, but they also developed clinical symptoms of lupus such as leukopenia, thrombocytopenia and renal failure. This further supports the notion that autoimmune responses in human SLE arise through molecular mimicry between viral antigens and autoantigens [4].

Assessing the impact of acute viral infections on the diagnosis and management of 88 SLE patients, Ramos-Casals and co-authors [5] noted that 25 patients were diagnosed with new-onset SLE associated with infection by human parvovirus B19 (n=15), CMV (n = 6), EBV (n = 3), and hepatitis A virus (n = 1). The remaining 63 cases of acute viral infections arose in patients already diagnosed with SLE. The most common viral infections in patients with SLE were parvovirus B19 (predominantly mimicking SLE presentation) and CMV infection, which was shown to mimic a lupus flare or present with specific organ involvement such as pulmonary infiltrates [5].

The role of viral infections in the induction of other autoimmune diseases has also been explored. Early epidemiologic studies suggested an association between EBV infection and risk of multiple sclerosis. Antibody titers to EBV viral capsid antigen, nuclear antigens (EBNA-1, and EBNA-2) and diffuse and restricted early antigen (EA-D and EA-R) as well as to CMV were analyzed. Of 62,439 women who gave blood samples, definite or probable MS was found in 144, while 288 age-matched women were defined as normal. Compared with healthy controls, women with MS had higher serum geometric mean titers of antibodies to EBV but not to CMV. The strongest association was found for antibodies to EBNA-2; and a fourfold difference in titers was associated with a 3.9 relative risk of MS (95%CI 1.1–13.7). These results strongly support a role for EBV in the etiology of MS [6]. In a later study, blood specimens for the detection of anti-EBV were collected up to 30 years prior to the onset of MS. Titers of antibodies to EBNA-1 were significantly higher in the MS cases when compared with matched controls, suggesting again that elevation of anti-EBV titers is probably an early event in the pathogenesis of

CMV = cytomegalovirus

EBV = Epstein-Barr virus
SLE = systemic lupus erythematosus

EBNA = EBV nuclear antigen-1
MS = multiple sclerosis
CI = confidence interval

MS [7]. In line with this is the proposal that vaccination against EBV may prevent MS, and that effective antiviral drugs will inhibit disease progression in patients with MS and may even be curative [8].

Many microbial antigens were also shown to induce cross-reactive immune responses against self-antigens and enhance their presentation to the immune system. For example, about a third of all cases of Guillain-Barré syndrome were preceded by *Campylobacter jejuni* infection, which expresses a lipopolysaccharide molecule that mimics gangliosides that were found to be increased in peripheral nerves [9]. These observations raised the debate regarding whether autoimmune diseases could also possibly be triggered by vaccines.

VACCINATION AND AUTOIMMUNE DISEASES

Most vaccines "work" better when adjuvants are added to them. Adjuvants, from the Latin word "adjuvare" meaning "to help," are compounds used to enhance a vaccine's ability to elicit a strong, durable and protective immune response. They make vaccines more effective by inducing higher T cell activity and a better B cell memory with higher neutralizing and long-lasting antibodies. Of all the adjuvants, the use of Toll-like receptor agonists (in many vaccines, e.g., for human papillomavirus, hepatitis B and influenza A) greatly improves the vaccines' efficacy and established the era of modern, efficient and safe vaccination [10].

The medical literature is replete with case reports exemplifying the risk of autoimmune diseases as a possible consequence of vaccination. Whereas autoimmune diseases occur in 5% of individuals in developed countries, vaccination-related autoimmunity remains very rare and in most reported cases lacks firm confirmation [11-13]. During the last 100 years, billions of people received a variety of vaccines, many of which are adjuvanted with different compounds (aluminum salts, oils, Toll-like receptors). In the vast majority of all vaccine recipients, there were no side effects. Therefore, the issue of linking autoimmune diseases with vaccination remains highly questionable.

SURVEILLANCE STUDIES FOR SAFETY AFTER VACCINATION

The Vaccine Adverse Event Reporting System was established in the United States in 1990 to register spontaneously reported vaccination-induced adverse events. This repository comprises the largest cohorts from which one can learn about the incidence of adverse events following any vaccination. According to these reports, GBS after influenza vaccinations in persons 18 years or older were evaluated for each influenza season from 1990 through 2003. During this period VAERS received 501 reports of GBS following influenza vaccination in adults. The annual reporting rate decreased fourfold from a high of 0.17 per 100,000 vaccinees in 1993–1994 to 0.04 in 2002–2003 ($P < 0.001$) [14]. In a VAERS report from 2003 summarizing adverse events from 1991 through 2001, the overall dose-based reporting rate for the 27 frequently reported vaccine types was 11.4 reports per 100,000 net doses distributed. The most commonly reported adverse event was fever, which appeared in 25.8% of all reports, followed by injection site hypersensitivity (15.8%), rash (unspecified) (11.0%), injection site edema (10.8%), and vasodilation (10.8%). Of all the reports 14.2% described serious adverse events, which by regulatory definition include death, life-threatening illness, hospitalization, or permanent disability. Reviews of VAERS reports during this period demonstrated that vaccines are usually safe and that serious adverse events do occur but are extremely rare [15]. Later, in a report from the U.S. Centers for Disease Control / Food and Drug Administration / VAERS, analyzing 54 reports of GBS following vaccination against influenza, hepatitis and other diseases, it was concluded that vaccines other than influenza could be associated with GBS [16]. Contrary to the above, other studies showed no significant increase in the development of GBS, and the risk of its development after vaccination was judged to be substantially lower than the risk for severe influenza and influenza-related complications [12].

It appears that the association between hepatitis B infection and the development of MS does not occur in individuals following vaccination. This possibility was first noted in France following a report of 35 cases of primary demyelinating events occurring between 1991 and 1997 and within 8 weeks of recombinant hepatitis B vaccine injection [17]. Of importance is that definite MS was diagnosed in only half the patients after a mean follow-up of 3 years. Nearly 25 million people (40% of the population of France) received the hepatitis B vaccine during this period, of whom 18 million were adults. At least ten studies did not find a possible significant association between hepatitis B vaccination and the occurrence of MS in any of these vaccinees. In support of these results, findings of another two large-scale studies showed no significant association between hepatitis B vaccination and the development of MS [18].

There are numerous reports in the literature demonstrating a connection between vaccination and the development of immune mediated inflammation or autoimmunity. A transiently or persistently increased level of autoantibodies (antinuclear, cardiolipin, or extractable nuclear antigen antibodies) was demonstrated in up to 15% of apparently healthy adults after influenza vaccination [19]. However, the development of autoimmune diseases such as autoimmune thrombocytopenia, or SLE-like phenomena, antiphospholipid syndrome and rheumatoid arthritis is quite rare. Some researchers, though rarely, have claimed that post-vaccination morbidity may appear even 10 years after vaccination [20].

The possible development of antiphospholipid syndrome 6 months after a diph-

GBS = Guillain-Barré syndrome
VAERS = Vaccine Adverse Event Reporting Systems

theria-tetanus vaccination is discussed by Meyer and co-authors in this issue of *IMAJ*, who suggest a potential connection between this vaccination and the appearance of this autoimmune disease [21].

The question whether vaccination is safe in patients with rheumatic diseases such as rheumatoid arthritis or SLE is continuously raised. Addressing this question, many studies proved vaccines (against influenza or *Streptococcus pneumoniae*) to be safe in these diseases, especially in remission [22-24]. It is crucial that the incidence of vaccine-related disorders be compared with that associated with the corresponding natural infection for the whole population. Clearly, vaccine-related autoimmunity is possible and we should be aware of it. Furthermore, appropriate prospective and multicenter epidemiologic studies should be designed. Both clinical and laboratory data should be included in the process of long-term post-vaccination monitoring. At this stage it is our duty to encourage the wide use of vaccination, especially when indicated, but to keep our eyes open and be aware of possible vaccine-related adverse events.

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