Vaccination may be Associated with Autoimmune Diseases

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Autoimmune diseases affect as many as 1 in 10 people in Europe and North America. Although the prevalence of most diseases is quite low, their individual incidence has greatly increased over the past few years, as documented for type I diabetes mellitus and multiple sclerosis [1–5]. Since some autoimmune disorders arise in age groups that are often selected as target populations for vaccination programs and reports have accumulated on observed side effects following vaccination, this is starting to emerge as a more complex issue than previously thought.

Autoimmunity and infection

Autoimmunity is generally assumed to result from complex interactions between genetic traits and environmental factors. Most often autoimmune responses are not followed by clinical disease manifestations unless an additional event favors such expression. Infections are usually considered to be key elements in the control of autoimmune responses and there is solid evidence that they might either prevent or more commonly precipitate autoimmune disorders [6,7].

An infection can trigger autoimmune disease via two mechanisms, antigen-specific or non-specific, which can operate either alone or together. Nevertheless, the disease itself will only arise in an individual who is genetically predisposed. The most appealing hypothetic mechanism for the triggering of autoimmunity by an infectious agent is molecular mimicry [8]. According to this hypothesis, antigenic determinants of the microorganisms can be recognized by the host's immune system as being similar to its own antigenic determinants. Owing to the structural resemblance, antibodies and autoreactive T cells not only destroy the invading pathogen but also attack host tissue. Such mimicry among sugar structures is common and has been shown to cause infection-associated neuropathies. This is mainly represented by Guillain-Barré syndrome in which about one-third of the cases are preceded by *Campylobacter jejuni* infection [8]. This bacterium expresses a lipopolysaccharide molecule that mimics various gangliosides presented in high concentrations in peripheral nerves. Furthermore, in sera taken from GBS patients in the acute phase of the disease, antibodies against different gangliosides can be found with a strong relationship between the specificity of the autoantibodies and the patterns of clinical features in these patients [9,10]. This mimicry is more complex when T cells are involved, because in order to serve as a molecular mimic for an autoreactive T cell a microbial antigen must copy the shape of a self-antigenic epitope bound to an appropriate major histocompatibility complex molecule. Such T cell mimicry was documented in an experimental model of multiple sclerosis in which a hepatitis B virus polymerase peptide was shown to cause histologically proven autoimmune encephalitis in rabbits [11].

In theory it is possible that any microorganism expressing an epitope that could serve as a molecular mimic for an autoantigen would be able to induce disease. This theory has been proven by our group in experimental antiphospholipid syndrome. In that study bacterial peptides homologous with beta-2 glycoprotein I induced pathogenic anti-β2 GP1 antibodies along with APS manifestations in mice [12]. Another mechanism involved in microorganism-induced autoimmune disorder involves a bystander activation. In this case microbial infection releases previously sequestered self-antigens, resulting in an activation of self-antigen-expressing antigen-presenting cells. Evidence for such a non-specific effect of infection was found in studies with transgenic mice containing high numbers of autoreactive T cells [13]. The same mechanisms that act in infectious invasion of the host apply equally to the host's response to vaccination. Based on these principles a killed vaccine would be less likely than a live attenuated vaccine to activate the innate immune response or cause tissue disruption.

Autoimmunity and vaccination

During the last decade reports have accumulated on various side effects following vaccination that had not been observed or acknowledged previously [14,15]. These reports focused on autoimmune phenomena as well as on the emergence of full-blown autoimmune diseases [16–19] [Table 1]. Since there is a wide spectrum of disorders that have been associated temporally and/or causally with vaccination, two main issues have arisen. The first is

GBS = Guillain-Barré syndrome
anti-β2 GP1 = anti-beta 2 glycoprotein 1
APS = antiphospholipid syndrome

Table 1. Autoimmune diseases reported after vaccination

Disease	Type of vaccine	Ref
Systemic lupus erythematosus	HBV, tetanus, anthrax	30
Rheumatoid arthritis	HBV, tetanus, typhoid/paratyphoid, MMR	29
Multiple sclerosis	HBV	18, 23, 24
Reactive arthritis	BCG, typhoid, DPT, MMR, HBV, influenza	15, 29, 31
Polymyositis/dermatomyositis	BCG, smallpox, diphtheria, DPT	14, 15
Polyarteritis nodosa	Influenza, pertussis, HBV	14, 15
Guillain-Barré syndrome	Influenza, polio, tetanus	16, 21, 22
Diabetes mellitus – type I	HiB	19, 26, 27
Idiopathic thrombocytopenia	MMR, HBV	14, 15

HBV = hepatitis B virus, BCG = Bacillus Calmette-Guerin, DPT = diphtheria-tetanus, MMR = measles-mumps-rubella

the difficulty in proving that a vaccination is the real cause of the autoimmune phenomenon. This will require large randomized controlled clinical studies or cohort studies, which are quite hard to conduct. The second issue is the lack of studies in large animals (dogs, monkeys) following the development of autoantibodies or autoimmune diseases after vaccination. To the best of our knowledge, only in one study were the effects of vaccination in dogs evaluated [20]. Although no evidence of autoimmune disease development following vaccination was detected in the dogs, a significant increase in antibodies to fibronectin and laminin was observed in the immunized animals.

Guillain-Barré syndrome

The first reported autoimmune disease following vaccination was documented in 1977 when a form of GBS was reported after a massive vaccination against "swine-flu" influenza [16]. While the estimated risk of GBS in the adult population following influenza vaccination is 1:100,000, the risk of GBS after "swine-flu" influenza vaccination was 7.6 times greater.

Following reports of influenza vaccine-induced GBS, Lasky et al. [21] retrospectively reviewed adults with GBS that developed 6 weeks following influenza vaccination in the years 1992–1993 and 1993–1994. They found that the adjusted relative risk of vaccine-associated GBS was 1.7, i.e., only one additional case of GBS per million vaccinated persons.

In a recent study reported by the Vaccine Adverse Events Reporting System in the United States, all cases of GBS from 1991 through 1999 were examined. In this study an increased risk of acute GBS (relative risk 4.3) and severe GBS (relative risk 8.5) following influenza vaccination was found, as compared to the incidence in an adult tetanus-diphtheria vaccine control group [22]. The authors found a maximal incidence of GBS following influenza vaccine approximately every third year (1993, 1996 and 1998), with significant variations in the incidence of GBS between vaccines produced by different manufacturers. Although in other influenza vaccinations no significant increase in GBS was noted, probably due to the change in the viral antigen, the chance that in the future another serotype of influenza virus included in a vaccine might induce autoimmune phenomena like those in the past still exists.

Multiple sclerosis

The possible association of MS and hepatitis B vaccination was first reported in France after immunization with hepatitis B recombinant vaccine [23]. More than 600 cases of illnesses, many with MS-like symptoms, have been reported in France among people who received recombinant hepatitis B vaccine. All cases of demyelinating disease occurred within 8 weeks of the immunization and there were definite inflammatory changes in the cerebral spinal fluid, with cerebral white matter lesions found on magnetic resonance imaging.

Although it has been postulated that neurologic manifestations appear in high risk individuals, and although two large-scale studies have not shown any significant association between hepatitis B vaccination and the occurrence of MS [16,24], it should be remembered that some changes that had been made in the vaccine could have changed their late toxic effect.

Another vaccine that has been investigated in connection with MS is the measles vaccine. The finding of higher titers of measles antibodies in MS patients raised the hypothesis that measles might be among the causes of MS. However, this hypothesis was rejected because despite the sharp drop in the incidence of measles since the institution of measles vaccination in the U.S. in 1963, the incidence of MS had not changed significantly 30 years later [25].

Diabetes mellitus

The fact that the incidence of type I diabetes is increasing rapidly in children in many countries around the world has raised the question about the role of vaccination as an important candidate contributing to this phenomenon. There are conflicting data concerning this issue. One group suggested that the timing of vaccination is important in the development of type I diabetes and that *Hemophilus influenzae* type B vaccine can increase the risk for the development of diabetes if given at age 2 months or older [19]. On the other hand, a 10 year follow-up of more than 100,000 Finnish children who participated in a trial of HiB vaccination did not find an increased risk for the development of type I diabetes [26]. Nevertheless, a recently published study in a non-selected cohort of 4,400 babies in southeast Sweden disclosed that HiB vaccination stimulates the immune system. This non-specific stimulation may have a polyclonal effect and thereby increase the production of glutamic acid decarboxylase antibodies and tyrosine phosphatase antibodies, thus increasing the risk of developing type I diabetes in this population [27]. Therefore, the authors postulate that HiB vaccination might be of importance under special circumstances when pancreatic β cell-related immune response is activated by other mechanisms. On the other hand, a recently published study following a cohort of Danish children did not reveal an increased risk of type 1 diabetes among children vaccinated with at least one dose of vaccine as compared with unvaccinated children [28].

MS = multiple sclerosis
HiB = *Hemophilus influenzae* type B

Other autoimmune disorders

A variety of additional autoimmune manifestations has been described in relation to vaccines. These include polyarthritis, systemic lupus erythematosus, polyarteritis nodosa, reactive arthritis, etc. [15,29,30]. Even intravesical inoculation with Bacillus Calmette-Guérin has been associated with arthritis in many reports published during the past 15 years [31,32]. Arthritis has been described in connection with rubella vaccine, hepatitis B vaccination as well as paratyphoid A and B vaccines [18]. The development of post-vaccination inflammatory arthritis occurs 1–3 weeks following immunization and, unlike the naturally occurring autoimmune disorders, affects males and females equally. It was recently reported that intranasal influenza vaccine used in Switzerland during the 2000–2001 season greatly increased the risk of Bell's palsy among vaccinees. This association was found to be strong, temporal and specific, and was highest during the second month after vaccination [33].

Concluding remarks

There is a clear indication that vaccination can and potentially does have autoimmune side effects and can even trigger a full-blown autoimmune disease, although it is quite rare. Secondly, the association of vaccination and autoimmunity can raise a serious medico-legal issue. The meaningful question of legal compensation to those patients who developed a life-long disease following mandatory vaccination might be tested. Thirdly, we are as yet unable to identify those who are prone to develop these complications. It is apparent that susceptibility to vaccine-induced autoimmunity is also determined by genetic predisposition, which further emphasizes the importance of "the mosaic of autoimmunity" [34]. Finally, vaccination has improved the quality and length of life, with decreasing morbidity and mortality, especially in children. Nevertheless, the dilemma of whom and when to vaccinate remains unresolved and future research will provide us with more definite answers.

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