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EDITORIAL

Vaccination as an additional player in the mosaic of autoimmunity

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Vaccination against infectious agents is one of the greatest achievements of modern medicine; it has significantly reduced mortality and led to population growth. Even though vaccinations are highly effective, with a low incidence of serious systemic adverse events, numerous reports have raised the question as to whether or not vaccines can cause autoimmune disease (Table I).

These reports focus on the occurrence of neurological manifestations (Guillain-Barre syndrome, multiple sclerosis, autism), joint manifestations (arthritis, rheumatoid arthritis), and other autoimmune phenomena (systemic lupus erythematosus, diabetes mellitus) following various vaccines administered either alone or in combination [reviewed in (1, 2)]. Even though Guillain-Barre syndrome has been reported following various vaccines, including rabies, tetanus toxoid, smallpox, mumps, rubella, hepatitis B, poliovirus and diphtheria (3, 4), its strongest association is with the influenza vaccine. A slight increase of one to two additional Guillain-Barre syndrome cases per million vaccinated persons has been reported following an influenza vaccination program in 1992-1993 (5). Similarly, multiple sclerosis has been reported mostly in association with hepatitis B vaccine (6). Systemic lupus erythematosus (SLE) was also primarily associated with hepatitis B vaccine (7); however, lupus vulgaris was reported following BCG vaccine (8). Diabetes mellitus, on the other hand, has been connected most specifically to the vaccination for Haemophilus influenza type b (1, 2).

In this issue 2 cases of post-vaccination arthritis are presented (9). In one of the cases, knee arthritis developed 3 to 4 weeks following combined booster injection of vaccine against diphtheria,

Table I. Autoimmune diseases reported after immunizations [reviewed in (1, 2)].

Disease	No. of cases	Vaccine
Systemic lupus erythematosus	10	HBV
	3	Typhoid/Paratyphoid
	4	Combination
	1	Anthrax
	1	Tetanus
Rheumatoid arthritis	15	HBV
	13	Tetanus
Multiple sclerosis	> 20	HBV
Autism	> 10	MMR
Reiter's syndrome	1	BCG
	1	Typhoid
	1	Salmonella
	1	Combination
Dermatomyositis	1	Smallpox
	2	BCG
	2	Diphtheria
	1	DPT
Polyarteritis nodosa	4	Influenza
	1	Pertussis
Guillain-Barre syndrome	> 10	Influenza
	2	Polio
	2	Tetanus
Reactive arthritis	1	DPT
	2	MMR
	29	HBV
	1	Influenza

poliomyelitis and tetanus toxoid, and a hepatitis B vaccine injection few days later. Five years thereafter, she had recurrence of the arthritis following another booster injection of all the vaccinations apart from hepatitis B. In the other case, one day after these combined 3 vaccinations, ankle arthritis developed. The occurrence of arthritis has been described after different types of vaccines including smallpox, parvovirus B19, hepatitis C, mumps, typhoid, paratyphoid and, as in the presented 2 patients - following tetanus, poliomyelitis, diphtheria and hepatitis B vaccines [reviewed in (1, 2)]. Post-vaccination arthritis is most closely associated, however, with the rubella vaccine. In a study that compared children who were immunized or not immunized with the MMR vaccine, the former had an increased risk of arthralgia or arthritis 6 weeks post-immunization (10). Nonetheless, the risk of frank arthritis was estimated to be less than that after rubella infection. It has also been suggested that vaccination might trigger rheumatoid arthritis (RA), as 12 patients with RA reported the onset of their arthritis in the 6 weeks following tetanus immunization (11).

Arthritis post-vaccination has been described both as an isolated phenomenon, and as part of systemic syndromes such as SLE, Reiter's syndrome (12, 13) and even occasional cases of frank RA. Some of the patients who developed SLE or RA (11) following vaccination were found to be carriers of HLA-B27 and/or HLA-DR1 or HLA-DR4 (14). However, not all of those who contracted the disease were carriers of the genetic markers signaling the potential for the autoimmune illness. Similarly, not all of those carrying the genetic baggage developed the autoimmune syndromes after receiving various immunizations. Therefore the connection between vaccination and arthritis (as with all other autoimmune manifestations) is so far only temporal, and no conclusive causal relation has been proved. Currently, we are not capable of predicting who among those vaccinated will be most prone to develop any autoimmune side effect.

The occurrence of autoimmune phenomena shortly after vaccinations might have a similar pathophysiology to autoimmune diseases outside the post-vaccination setting. The underlying pathogenic mechanisms in autoimmune diseases are multifactorial and include genetic, environmental, hormonal and infectious factors (15). Therefore, instead of infectious agents triggering molecular mimicry, an antigen of a recombinant vaccine or of a live attenuated virus may resemble host antigen and trigger autoimmunity. Some of the molecules implicated in this process are proteins from a group called "stress proteins" (16). These substances are involved in reactions occurring in the body during stress and have been very well preserved among species during evolution. Specifically, there is great structural similarity between these molecules among different species: viruses, microbes and mammals. One such stress protein is the heat-shock protein-65kD of the mycobacterium TB. Another possibility is an increase in immune complex formation following immunization, which in turn might cause vasculitis.

Nevertheless, as infections do not cause overt autoimmune disease in most individuals, the interplay of several factors rather than a single one (i.e., vaccination) must lead to the development of autoimmunity, and hence patients with a genetic predisposition for autoimmunity could be at increased risk for post-vaccination autoimmune diseases. With respect to post-vaccination arthritis, 3 different explanations have been suggested (11). It is possible that the co-occurrence of the vaccination and the arthritis represents only a coincidental finding, as both are quite frequent. Another possibility is that under certain circumstances vaccination can trigger a specific form of, usually self-limited, arthritis. This might be the case of the second patient presented in this issue (9). Finally, vaccination might trigger a full-blown autoimmune disease such as RA.

It is also possible that several concomitant vaccinations, as occurred in the 2 presented cases, have a synergistic effect that can induce autoimmunity. Theoretically, the more complex a vaccine is and the more varied the array of its antigens, the more likely it would be to trigger an immune response that may eventually turn into an autoimmune reaction. Nevertheless, the relationship between vaccines and autoimmune conditions in general has yet to be established, and there are only coincidental suggestions that poly-vaccines may be more likely to trigger such conditions. This is best exemplified by a recent report of 5 cases of SLE that developed following immunization (17). In 3 of these 5 cases the patients had received multiple immunizations. The efforts towards revealing whether certain vaccinations predispose to autoimmune diseases should comprise epidemiological studies as well as basic studies in order to elucidate the mechanisms and the immune system response to vaccinations. An example for the latter is a study in which dogs received several vaccines and subsequently developed anti-fibronectin and anti-laminin antibodies (18).

The relationship between vaccinations and autoimmunity is bi-directional. On the one hand, vaccinations prevent infectious diseases, and thus in turn prevent the development of an overt autoimmune disease which in some individuals is triggered by infections. Furthermore, Singh (19) suggests that immunization with certain vaccines may stimulate the immune system to modulate or prevent the generation of pathogenic cells by the induction of regulatory cells, and thus prevent autoimmunity. On the other hand the case reports and series that describe various autoimmune diseases post-vaccination strongly suggest that vaccinations can trigger autoimmunity in a similar way to the infections which they are attempting to prevent. This dual relationship of vaccination and autoimmunity has a resemblance to the association of bone marrow transplantation, thymectomy and splenectomy with autoimmunity (Fig. 1). While bone marrow transplantation can induce clinical remissions in animal models and patients with autoimmune diseases (20), there are also reports of the induction of autoimmune diseases such as myasthenia gravis and autoimmune cytopenias following bone marrow transplantation (21). Similarly, while thymectomy is an optional treatment for myasthenia gravis and splenectomy is occasionally used in immune thrombocytopenic purpura, the occurrence of autoimmune phenomena have been reported following both (22-25).

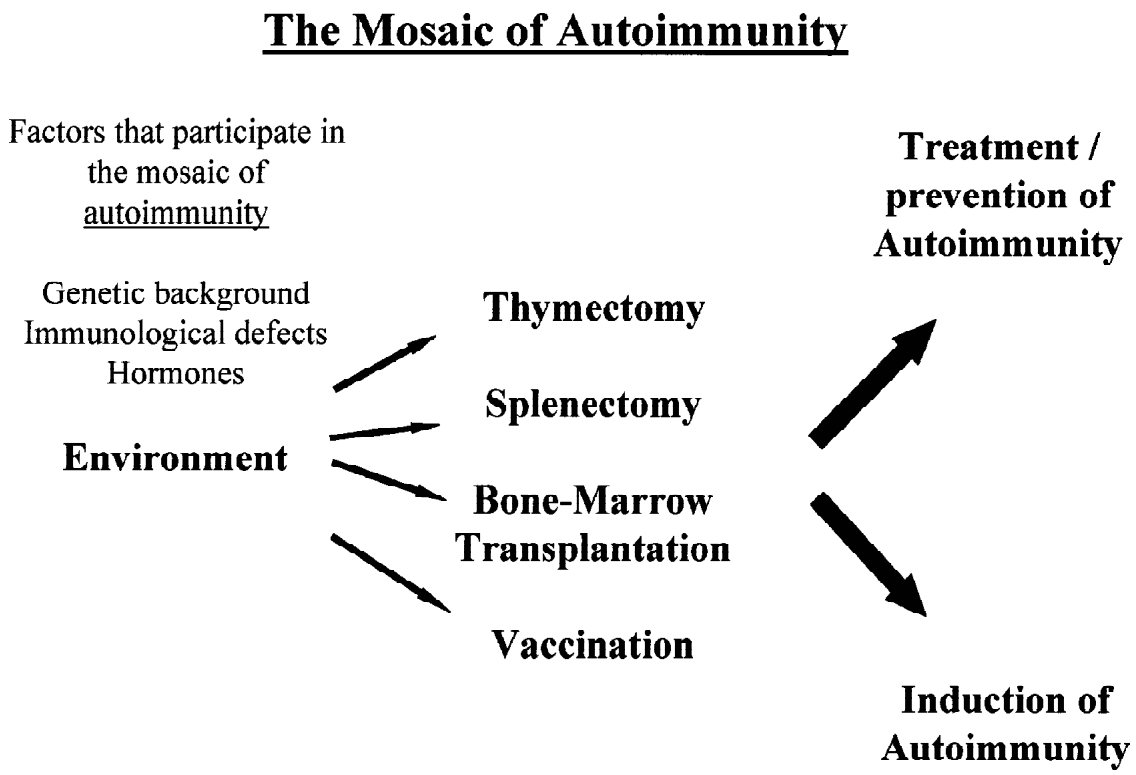

Fig. 1. Vaccination and the mosaic of autoimmunity. The pathogenesis of autoimmune diseases involves several factors. In addition, similarly to bone marrow transplantation, thymectomy and splenectomy, therapies that are used to treat autoimmune disease but occasionally can induce them, vaccination most often prevents infections and thus may prevent autoimmunity, but occasionally can also induce autoimmunity.

In this way, vaccination should be considered as part of the mosaic of autoimmunity, in which abrogation of an autoimmune disease (and in the case of vaccination, the prevention of an autoimmune disease) could concomitantly induce another autoimmune disease. However, bone marrow transplantation, thymectomy and splenectomy represent rare therapeutic interventions. On the contrary, vaccination is widely used in healthy subjects rather than in patients. Therefore while it is clear that the significant reduction in morbidity and mortality produced by vaccinations far outweighs the detrimental effects of post-vaccination autoimmunity, great efforts should be made to maximize as far as possible the safety of vaccine preparations (26).

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