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Review

Predicting post-vaccination autoimmunity: Who might be at risk?

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ABSTRACT

Vaccinations have been used as an essential tool in the fight against infectious diseases, and succeeded in improving public health. However, adverse effects, including autoimmune conditions may occur following vaccinations (autoimmune/inflammatory syndrome induced by adjuvants – ASIA syndrome). It has been postulated that autoimmunity could be triggered or enhanced by the vaccine immunogen contents, as well as by adjuvants, which are used to increase the immune reaction to the immunogen. Fortunately, vaccination-related ASIA is uncommon. Yet, by defining individuals at risk we may further limit the number of individuals developing post-vaccination ASIA. In this perspective we defined four groups of individuals who might be susceptible to develop vaccination-induced ASIA: patients with prior post-vaccination autoimmune phenomena, patients with a medical history of autoimmunity, patients with a history of allergic reactions, and individuals who are prone to develop autoimmunity (having a family history of autoimmune diseases; presence of autoantibodies; carrying certain genetic profiles, etc.).

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Introduction

In the last two centuries, vaccinations have been used as an essential tool in the fight against infectious diseases, and succeeded in improving public health and in eradicating or minimizing the extent of several diseases around the world [1]. However, adverse effects may occur following vaccinations, ranging from

local reactions to systemic side effects, such as fever, flu-like symptoms, and autoimmune conditions (autoimmune/inflammatory syndrome induced by adjuvants – ASIA syndrome) [2,3].

Considerable data have recently been gathered with regard to involvement of the immune system following vaccination, although its precise role has not been fully elucidated [4]. It has been postulated that autoimmunity could be triggered or enhanced by the vaccine immunogen contents, as well as by adjuvants, which are used to increase the immune reaction to the immunogen [1].

The relationship between vaccines and autoimmunity is bidirectional [5]. On one hand, vaccines prevent infectious conditions, therefore preventing the development of overt autoimmune

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Table 1
Persons who might be at risk of developing vaccination-related autoimmune, inflammatory, or allergic phenomena.

1. Persons with prior post-vaccination autoimmune phenomena
2. Persons with a medical history of autoimmunity
3. Persons with a history of allergic reactions (especially vaccination-related reactions)
4. Persons who are prone to develop autoimmunity (having a family history of autoimmune diseases, presence of autoantibodies, certain genetic profiles, etc.)

diseases which in some individuals are triggered by infections. On the other hand, many reports that describe post-vaccination autoimmunity strongly suggest that vaccines can indeed trigger autoimmunity. Defined autoimmune diseases that may occur following vaccinations include arthritis, lupus (systemic lupus erythematosus, SLE), diabetes mellitus, thrombocytopenia, vasculitis, dermatomyositis, Guillain-Barré syndrome and demyelinating disorders [6]. Almost all types of vaccines have been reported to be associated with the onset of ASIA [6].

It is important to emphasize that a temporal relationship between autoimmunity and a specific vaccine is not always apparent. This matter is complicated by the fact that a specific vaccine may cause more than one autoimmune phenomenon and, likewise, a particular immune process may be triggered by more than one type of vaccine [2,3,6].

Throughout our lifetime the normal immune system walks a fine line between preserving normal immune reactions and developing autoimmune diseases [4]. The healthy immune system is tolerant to self-antigens. When self-tolerance is disturbed, dysregulation of the immune system follows, resulting in emergence of an autoimmune disease. Vaccination is one of the conditions that may disturb this homeostasis in susceptible individuals, resulting in autoimmune phenomena and ASIA.

Fortunately, vaccination-related ASIA is uncommon. Yet, by defining individuals at risk we may further limit the number of individuals developing post-vaccination ASIA. Who is susceptible to develop vaccination-induced ASIA? It is assumed that four groups of individuals are at risk (Table 1): patients with prior post-vaccination autoimmune phenomena, patients with a medical history of autoimmunity, patients with a history of allergic reactions, and individuals who are prone to develop autoimmunity (having a family history of autoimmune diseases; presence of autoantibodies; carrying certain genetic profiles, etc.).

Patients with prior post-vaccination autoimmune phenomena: “rechallenge” cases

The notion that there is a tendency of progression to full-blown immune-mediated disease in patients who experienced initial nonspecific symptoms (such as fever, arthralgia, transient skin reactions) following the initial administration of vaccination, if they continue with the scheduled regimen, is controversial. Thus, the question of whether halting the vaccination protocol would have been beneficial for some susceptible groups is still a matter of debate.

In the analysis by Zafrir et al. [7] of 93 patients who experienced new immune-mediated phenomena following hepatitis B vaccination, 47% continued with the vaccination protocol despite experiencing variable adverse events following administration of the first vaccine dose. Additionally, a personal or familial history of immune-mediated diseases was documented in 21% of the cohort, which may have rendered this particular population more genetically predisposed to developing immune-mediated adverse reactions following vaccination (see below). Gatto et al. [8] recently described 6 cases of SLE following quadrivalent anti-human

papilloma virus (HPV) vaccination (Gardasil®). In all six cases, several common features were observed, namely, a personal or familial susceptibility to autoimmunity and an adverse response to a prior dose of the vaccine.

In regard to quadrivalent anti-HPV vaccine, a case of sudden death of a teenage girl approximately 6 months following her third Gardasil® booster has been reported [9]. The patient experienced a range of non-specific symptoms shortly after the first dose of Gardasil injection including dizziness spells, paresthesia in her hands, and memory lapses. After the second injection, her condition worsened, and she developed intermittent arm weakness, frequent tiredness requiring daytime naps, worsening paresthesia, night sweats, intermittent chest pain and sudden unexpected palpitations. A full autopsy analysis revealed no anatomical, histological, toxicological, genetic or microbiological findings that might be linked to a potential cause of death. On the other hand, the post-mortem analysis of blood and splenic tissues revealed the presence of HPV-16 L1 gene DNA fragments, thus implicating the vaccine as a causal factor [9]. In particular, the sequence of the HPV DNA found in blood and spleen corresponded to that previously found in 16 separate Gardasil® vials from different vaccine lots [10]. It was also determined that these HPV 16L1 DNA contaminants were complexed with the aluminum adjuvant [11], which would explain their long-term persistence in the body of this teenager (more than 6 months following her third injection). Adjuvants indeed can persist in tissues for a long time (up to 8–10 years) [12] where they stimulate the immune system. This chronic stimulation may lead in certain cases to the development of a specific autoimmune disease.

Konstantinou et al. [13] reported two successive episodes of leukoencephalitis associated with hepatitis B vaccination after administration of the second and third doses of vaccine in a previously healthy 39-year-old woman. Soriano et al. [14], in their case-series of giant cell arteritis and polymyalgia rheumatic (PMR) following influenza vaccination, described a patient who developed PMR 8 weeks after influenza vaccination; 2 years later, the patient was in clinical remission when she received another influenza vaccination, and experienced recurrence of PMR.

Quiroz-Rothe et al. [15] also described a case of post-vaccination polyneuropathy resembling human Guillain-Barré syndrome in a Rottweiler dog. The dog suffered two separated episodes of acute polyneuropathy after receiving two vaccines (both adjuvanted). Inactivated rabies vaccine was administered 15 days before clinical signs were first noted. Clinical remission was achieved with steroid therapy, but 3 months later the dog had recurrence of polyneuropathy, following another vaccination 12 days earlier. The presence of antibodies against peripheral nerve myelin was demonstrated.

Although data is limited, it seems preferable that individuals with prior autoimmune or autoimmune-like reactions to vaccinations, should not be immunized, at least not with the same type of vaccine. If vaccination is of utmost importance, it might be given, but the patient should be followed closely and treated if necessary.

Patients with established autoimmune conditions

The efficacy of vaccination in patients with autoimmunity may be reduced. On the other hand it is important to realize that the immune system is stimulated by vaccinations (especially when adjuvants are added), and therefore the chance of side effects is increased, in particular for patients with autoimmune diseases, where the immune system is already stimulated. There is a potential risk of flares following vaccination in such cases. Adjuvanted vaccines were reported to trigger autoantibodies and ASIA [3,6].

Live vaccines including *Bacillus Calmette-Guérin* (BCG) and vaccines against herpes zoster, yellow fever (YF) and measles, and mumps measles and rubella triple vaccine (MMR) are generally

contraindicated in immunosuppressed patients with autoimmune conditions due to the risk of an uncontrolled viral replication [16]. Regarding inactivated or recombinant vaccines, these have the disadvantage of inducing a suboptimal immune response, requiring sometimes the addition of adjuvants, which may be associated with ASIA [6]. Several prospective controlled studies targeted safety issues of vaccination in patients with autoimmune conditions. In most studies, no increased risk for severe adverse events or increase of activity of pre-existing disease was observed after vaccination.

HPV vaccine was well tolerated and reasonably effective in patients with stable SLE and did not induce an increase in lupus activity or flare. Disease flares in patients with SLE occurred at a similar frequency to that of 50 matched SLE controls (0.22 and 0.20/patient/year, respectively) [17].

The safety of hepatitis B vaccine has been assessed in prospective studies in rheumatoid arthritis (RA) and SLE. In RA patients, hepatitis B vaccination was not associated with an appreciable deterioration in any clinical or laboratory measure of disease. The measures of disease activity of the patients and controls during the study period did not differ significantly [18]. In SLE, hepatitis B vaccination was safe in patients in remission or mild disease. No significant change in mean SLEDAI score was detected after vaccination [19].

Several studies targeted the safety of influenza vaccination in patients with autoimmune conditions. A large-scale study of 1668 patients with autoimmune rheumatic diseases and 234 controls evaluated the short-term (3 weeks) safety of non-adjuvanted Influenza A (H1N1) vaccination. Although no major relapses occurred in this short period of follow up, patients with autoimmune rheumatic diseases had significantly more arthralgia (9% compared to 3.8% in controls, $p=0.005$), and fever (3.9% and 1.2%, respectively, $p=0.04$) [20]. In another study, the autoantibody response to influenza vaccination in patients with autoimmune rheumatic diseases was reported. Female patients had statistically significant elevation in anti-nuclear antibody (ANA) titers following vaccination. In addition, a small subset of patients, especially ANA-positive patients, had a tendency to develop anti-extractable nuclear antibodies (ENA). One month after vaccination 8% of previously anti-cardiolipin (aCL)-negative patients presented with elevated aCL IgG and 4% with elevated aCL IgM antibodies. There was significantly more aCL IgG/IgM induction after the H1N1 compared to seasonal influenza vaccine. Elevated aCL were mostly transient but one female patient developed persistent high levels of aCL IgM [21]. In another study on Influenza H1N1 safety in patients with autoimmune rheumatic diseases, no change in disease activity scores was observed during a 4-week post vaccination period [22]. 15 other studies on influenza vaccination (reviewed in [23]) did not report significant adverse effects in patients with autoimmune conditions.

For the overwhelming majority of patients with established autoimmune diseases, vaccines carry no risk of significant disease flares. However, most studies did not address certain subsets of patients with autoimmune diseases, such as vaccinating patients with severe, active disease, or vaccination in conditions other than SLE or RA. In such subsets, the potential benefit of vaccination should be weighed against its potential risk.

Patients with a history of allergy

Historically, vaccine trials have routinely been excluded vulnerable individuals with a variety of pre-existing conditions. Some of these include personal or immediate family history of developmental delay or neurologic disorders (including convulsive disorders of any origin), hypersensitivity to vaccine constituents and any condition that in the opinion of the investigators may interfere with

the study objectives. Because of such selection bias, the occurrence of serious adverse reactions resulting from vaccinations in the real life where vaccines are mandated to all individuals regardless of their susceptibility factors may be considerably underestimated [24]. In particular, the number of true allergic reactions to vaccines is not known, with an estimated range from 1 per 50,000 doses to 1 per 1,000,000 doses [25]. A higher rate of serious allergic reactions is probable if allergens such as gelatin (as in the case of Japanese encephalitis vaccine) or egg proteins are included in the formulation.

Apart from infectious agents, vaccine components include potential allergens such as animal-derived proteins or peptides (hen's egg, horse serum, etc.), antibiotics (gentamycin, neomycin, streptomycin, polymyxin B), preservatives (aluminum, formaldehyde) and stabilizers like gelatin and lactose. In addition, exposure to inadvertent allergenic contaminants such as latex (in vial stoppers and syringe plungers) may also occur.

The classification of allergic reactions distinguishes mainly two categories: immediate, most likely IgE-mediated reactions, and delayed reactions. IgE mediated reactions to vaccines may present with skin manifestations (urticaria, angioedema), respiratory signs (rhino-conjunctivitis or bronchospasm), gastrointestinal disorders (diarrhea, abdominal pain and vomiting), and life-threatening cardiovascular complications such as hypotension and shock within minutes following the vaccination. It has been estimated that immediate anaphylactic life-threatening reactions to vaccines are a rare event, while reactions to vaccines limited to the injection site are more frequent [25].

Delayed reactions comprise a wide spectrum of manifestations. Fever and local swelling are the most commonly observed, and usually are not considered a contraindication for future administration of the vaccine [26,27]. Less frequent delayed immunologic reactions include serum sickness, polyarthritis and erythema nodosum. These cases represent a contraindication for future vaccination [28,29].

Gelatin is one of the most common causes of allergic reactions to varicella, MMR, Japanese encephalitis vaccines and influenza vaccine [30]. Egg protein is present in yellow fever, influenza, MMR and some rabies vaccines. Influenza vaccination in patients with egg allergy is an important clinical issue and relevant guidelines are frequently updated (see www.cdc.gov/vaccines). Currently, the amounts of egg protein in most influenza vaccines are small ($\leq 1 \mu\text{g}$ per 0.5 ml dose in most cases). In addition, egg-free influenza vaccines are now available for adults with egg allergy. Thus, influenza vaccine can be safely administered to the vast majority of patients with egg allergy, as adverse reactions have generally been very rare [31–33].

Thimerosal and phenoxyethanol, used as preservatives, have been associated with delayed-type hypersensitivity reactions. Thimerosal has been recently removed from vaccine formulations. Aluminum salts are contained in several vaccines, including diphtheria tetanus and pertussis, hepatitis A and B vaccine, human papilloma virus (HPV) and *Haemophilus influenzae* vaccine. Aluminum sensitization manifests as nodules at the injection site that often regress after weeks of months, but may persist for years [34]. In subjects with suspected aluminum-induced granuloma a patch test for aluminum may be used to confirm the sensitization.

Hepatitis B vaccine and anti-HPV vaccines are prepared by harvesting the antigens from cell cultures of recombinant strains of the yeast *Saccharomyces cerevisiae*, also known as baker's yeast. Yeast-associated anaphylactic reactions have also been reported as rare events. DiMiceli et al. [35] reviewed the adverse events described in the Vaccine Adverse Event Reporting System (VAERS) focusing on reports that mentioned a history of allergy to yeast and related anaphylactic reactions following vaccinations. Among 107 reports of anaphylaxis in subjects with pre-existing yeast allergies, 11 were

described as 'probably' or 'possibly' related to administration of hepatitis B vaccine.

Finally, antibiotics may also be responsible for anaphylactic reactions. Thus, an accurate allergy history has to be taken in cases with previous allergic reactions to antibiotics prior to administrations of vaccines containing these agents.

Individuals who are prone to develop autoimmunity

Family history of autoimmune diseases and the genetic profile

Numerous studies have found that autoimmune diseases have a genetic predisposition. The abnormal immune response probably depends upon interactions between susceptibility genes and various environmental factors. Evidence for genetic predisposition to autoimmunity includes increased concordance for disease in monozygotic compared to dizygotic twins, and an increased frequency of autoimmunity in patients with affected family members.

Family history of autoimmunity was prevalent among patients developing SLE following HPV vaccination [8]. In another study, 19% of 93 patients with autoimmune conditions following hepatitis B vaccination had a family history of autoimmunity [7].

Certain HLA profiles are associated with autoimmunity. The most potent genetic influence on susceptibility to autoimmunity is the major histocompatibility complex (MHC). Different HLA alleles are linked to different autoimmune diseases. Examples are DR2 and increased risk for multiple sclerosis and Goodpasture's syndrome; DR3 and increased risk for SLE, celiac disease, type 1 diabetes and Graves' disease; DR4 and increased risk for RA, pemphigus and type 1 diabetes; and DR5 and increased risk for Hashimoto's thyroiditis and pernicious anemia. HLA profiles were reported in only few patients with vaccination-triggered autoimmunity [36].

Non-HLA genes also play a role in the genetic etiology of autoimmune diseases. Non-HLA genes that have been associated with autoimmunity can be divided into two groups: the first group consists of immune-regulatory genes such as the cytotoxic T lymphocyte antigen-4, or the protein tyrosine phosphatase gene, or mutations leading to complement deficiencies or IgA deficiency [37–40]. Deficiencies in the earlier components of the classical pathway (especially C4) have been linked to autoimmune diseases, and autoimmune disorders occur more frequently in individuals with selective IgA deficiency. The second group of non-HLA genes that have been associated with autoimmunity consists of tissue-specific genes, such as polymorphisms associated with the insulin gene, the thyroglobulin gene and the thyroid-stimulating hormone receptor gene [reviewed in 37].

Presence of autoantibodies

Autoantibodies can be detected in the preclinical phase of autoimmune diseases many years before the disease becomes apparent. Examples are anti-citrullinated protein antibodies (ACPA) in RA, anti-mitochondrial antibodies (AMA) in primary biliary cirrhosis, anti-thyroid antibodies in Hashimoto's thyroiditis, and anti-dsDNA in SLE [41]. Many autoantibodies have the ability to predict the development of an autoimmune disease in asymptomatic persons. The progression towards an autoimmune disease and its severity can be predicted from the type of antibody, its level, and the number of different antibodies present. The ability to predict the development of an autoimmune disease in asymptomatic individuals is especially important when disease progression can be prevented by avoiding environmental factors, such as vaccinations, that may trigger or worsen the disease.

Smoking

Tobacco smoking is one of the most potent environmental factors that influence autoimmune diseases. Smoking has been associated with SLE [42,43] and with an increased risk of RA, an effect that was more pronounced in males and in seropositive patients [43]. Studies documenting an increased prevalence of smokers exist for many autoimmune disorders [43]. Smoking could lead to autoimmunity by several mechanisms: it interacts with genetic risk factors such as specific HLA-DR alleles, it induces tissue damage, increases apoptosis, induces leukocytosis and elevates levels of C-reactive protein, intercellular adhesion molecule-1 and E-selectin, resulting in inflammation [44,45]. To date, no specific association was documented between smoking and vaccination-related ASIA.

Hormonal factors

The hormonal panel, which affects the process leading to autoimmunity, involves estrogen, prolactin and vitamin D [46,47]. Exposure of the immune system to estrogens may be exogenous, in the form of oral contraceptives or hormone replacement therapy for post-menopausal women. Both forms may be associated with disease flare-up. Ovarian stimulation may also lead to the development of SLE or induction of SLE flares [48]. The mechanisms by which other potential sources of environmental estrogens, such as phytoestrogens, pesticides and other chemicals, could alter the immune system are yet to be established. Estrogen leads to increased survival and activation of autoreactive B cells [49]. Indeed, in large-scale reports of vaccination-induced ASIA, females seem to be affected more frequently than males [7].

Low vitamin D status has been implicated in the etiology of autoimmune diseases. There is an inverse relationship between vitamin D status and incidence of multiple sclerosis [50]. High vitamin D intake was also associated with lower risk for type 1 diabetes mellitus, rheumatoid arthritis and inflammatory bowel diseases [51]. Vitamin D status has not been established in cases with vaccination-related ASIA.

Summary

Appropriate epidemiological studies should be undertaken to confirm reports of individual cases or case series where familial, genetic, hormonal or other risk factors for autoimmune conditions were found in patients who developed post-vaccination ASIA. However, it is important to remember that for the overwhelming majority of individuals, vaccines carry no risk of systemic autoimmune disease and should be administered according to current recommendations. Reports on autoimmune reactions after vaccination would constitute probably less than 0.01% of all vaccinations performed worldwide, although this rate may be biased by under-reporting. In addition, many of those reactions are mild and self-limited. Nevertheless we should be cautious, especially in cases with previous post-vaccination phenomena and those with allergies, but also in individuals who are prone to develop autoimmune diseases, such as those with a family history of autoimmunity or with known autoantibodies. In such subsets, the potential benefit of vaccination should be weighed against its potential risk.

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