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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; asymptomatic carriers of autoantibodies; carrying certain genetic profiles, etc.).
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Contents

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 the 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 bi-directional [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, asymptomatic carriers of autoantibodies, with 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 the 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; asymptomatic carriers 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 the 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. 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 both 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 the administration of the second and the third vaccine dose in a previously healthy 39-year-old woman. Soriano et al. [14], in their case-series of giant cell arteritis and polymyalgia rheumatica (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 administered 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 have been reported to trigger autoantibodies and ASIA [3,6].

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