

THE RELATIONSHIP BETWEEN VACCINATION AND THE DEVELOPMENT OF AUTOIMMUNE DISEASES

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Abstract

The potential association between vaccination and autoimmune diseases has been largely questioned in the past few years, but this assumption has mostly been based on clinical case reports, and not on scientifically demonstrated mechanisms. In this regard, the safety aspects of vaccination in patients with previously diagnosed autoimmune disease is of particular relevance. Experimental and clinical research performed in this field showed that acquired autoimmunity syndromes occur usually after *viral* vaccinations. One of the proposed hypothesis is molecular mimicry, when a structural similarity exists between some viral antigen (or other component within the vaccine formulation) and a self-antigen. This similarity may be the trigger to the autoimmune reaction. Molecular mimicry in itself is not sufficient to trigger autoimmune pathology, but other factors, intrinsic to infections, such as tissue damage and long-lasting inflammatory reaction, might be required as well.

Therefore a potential correlation between vaccines and autoimmune diseases cannot be definitely ruled out and should be carefully explored during the development of new candidate vaccines.

Rezumat

Literatura științifică modernă evidențiază posibilitatea existenței unei corelații între vaccinare și incidența bolilor autoimune. Această ipoteză are la bază, în mod special cazuri clinice, și mai puțin mecanisme moleculare demonstrate științific.

Una dintre ipotezele descrise în literatură este cea a mimetismului molecular, privind similaritatea structurală dintre un antigen viral, sau alt component din formularea vaccinului, și antigenul propriu-zis. Această similaritate pare a fi corelată cu incidența reacțiilor autoimune. Mimetismul molecular nu poate fi considerat un factor unic pentru patologia autoimună, fiind necesare cercetări moleculare și preclinice, precum și studii epidemiologice extrem de riguroase.

Keywords: vaccination, autoimmunity, molecular mimicry

Introduction

The potential association between vaccination and autoimmune diseases has been largely questioned in the past few years, but this assumption has mostly been based on clinical case reports, and not on scientifically demonstrated mechanisms. In this regard, the safety aspects of vaccination in patients with previously diagnosed autoimmune disease is of particular relevance.

There should be a strict definition of the autoimmune adverse event in clinical, pathological, and biochemical terms, as far as is achievable. A vaccine containing inactivated pathogens would be less likely to induce autoimmunity compared to a vaccine containing live-attenuated pathogens. Also, an effective vaccine should generate protective immunity while keeping to a minimum molecular mimicry and bystander activation [23].

It is known that inactivated vaccines can induce the formation of autoantibodies in humans. Live viral vaccines have been suggested to cause autoimmunity by infecting the recipient's tissue and inducing an autoimmune response. The advent of new vaccines and the increasing number of articles that report a link between certain immunizations and autoimmune diseases have led to a serious concern over the risk of inducing autoimmune disease by immunization.

Appropriate experimental research and epidemiological studies should be performed in order to correlate a particular autoimmune clinical condition with a certain vaccine [26, 28].

The implications of molecular mimicry in the development of autoimmune diseases

Experimental and clinical research performed in this field showed that acquired autoimmunity syndromes occur usually after *viral* vaccinations. One of the proposed hypothesis is **molecular mimicry**, when a structural similarity exists between some viral antigen (or other component within the vaccine formulation) and a self-antigen. This similarity may be the trigger to the autoimmune reaction. **Molecular mimicry** may be described as an autoimmune reaction caused by a host receiving an antigen that has aminoacids homology with aminoacid chains in organs of the host's body.

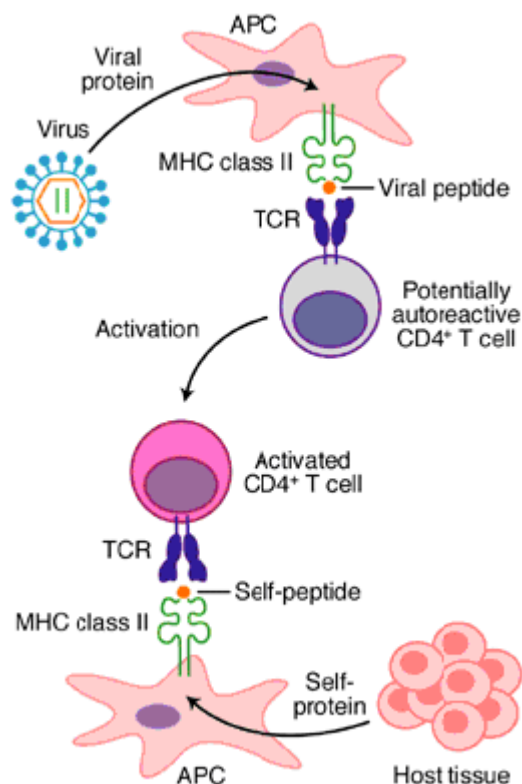


Figure 1

The implications of molecular mimicry within the innate system (APC= antigen-presenting cells; MHC= major histocompatibility complex; TCR= T cell receptor) (<http://journals.cambridge.org>)

Molecular mimicry in itself is not sufficient to trigger autoimmune pathology, but other factors, intrinsic to infections, such as tissue damage and long-lasting inflammatory reaction, might be required as well.

There exist no general criteria for diagnosing vaccine-related autoimmune disease.

Vaccines associated with the onset of autoimmune diseases

The association between infection and autoimmune disease has stimulated controversial research regarding whether such diseases might also be triggered by vaccines [27].

Criteria underpinning the assessment of adverse events of vaccines have been established by the World Health Organisation (WHO), and the four basic principles that apply to autoimmune diseases are the consistency,

strength, and specificity of the association between the administration of a vaccine and an adverse event, and the temporal relation [5].

Some vaccines may influence the T helper (T_H) lymphocyte balance (T_{H1}/T_{H2}), and this may favour either T_{H1} or T_{H2} responses. The mechanism for inducing autoimmunity appears to involve a cytokine drive phenomenon where the vaccine activates the immune system and an immune response develops to autoantigens that are attached to the major histocompatibility complex (MHC) molecules on the same antigen presenting cells [6, 9].

Vaccination is also incriminated in the formation of immune complexes resulting in vasculitis or the exacerbation of an underlying autoimmune disease. Therefore autoimmune responses should always be considered in the design of new vaccines [4].

As a general rule, patients diagnosed with an autoimmune disease are not at risk of exacerbation after administration of any of the available vaccines. Conversely, several vaccine-preventable infections are known to negatively affect the course of defined autoimmune diseases. Only in a few rare cases autoimmune pathology was associated with particular vaccines [15].

Several vaccines were associated in the literature with the onset of **Guillain-Barré syndrome**, but **influenza vaccine** was the most frequently cited. The estimated attributable risk of vaccine-related Guillain-Barré syndrome in the adult population was just less than one case per 100.000 vaccinations, and the period of increased risk in swine-flu vaccinated versus non-vaccinated individuals was concentrated primarily within the 5 weeks after vaccination (relative risk 7.60) [19, 25].

Another example of confirmed autoimmune adverse effects after vaccination is **idiopathic thrombocytopenia**, which might arise after administration of the **measles-mumps-rubella vaccine**. The reported frequency of clinically apparent idiopathic thrombocytopenia after this vaccine is around one in 30000 vaccinated children. Patients with a history of immune thrombocytopenic purpura are prone to this complication, and in these individuals the risk of vaccination should be weighed against that of being exposed to the corresponding viral disease [18,19].

Over the past few decades, there has been a regular increase in the incidence of **type 1 diabetes mellitus** in most countries of the world. Childhood vaccines have been identified as a potential trigger event for this disease. Certain vaccines (anti-*Haemophilus influenzae* type b, **Hib**) might increase the risk of type 1 diabetes if given at age 2 months or older. A reported clinical study in literature demonstrated that there was no increased risk of diabetes when children who had received four doses of vaccine at

age 3, 4, 6, and 14-18 months were compared with those who received only one dose at age 2 years [10]. Furthermore, the risk of diabetes did not differ between children in the latter two cohorts and those in a non-concurrent unvaccinated group. The mechanisms by which vaccines alter the risk of an autoimmune disease such as type 1 diabetes mellitus is not completely understood. Several cytokines are potentially released following immunization, and the therapeutic use of interferon-alpha was associated with the occurrence or the worsening of a large number of autoimmune diseases [16].

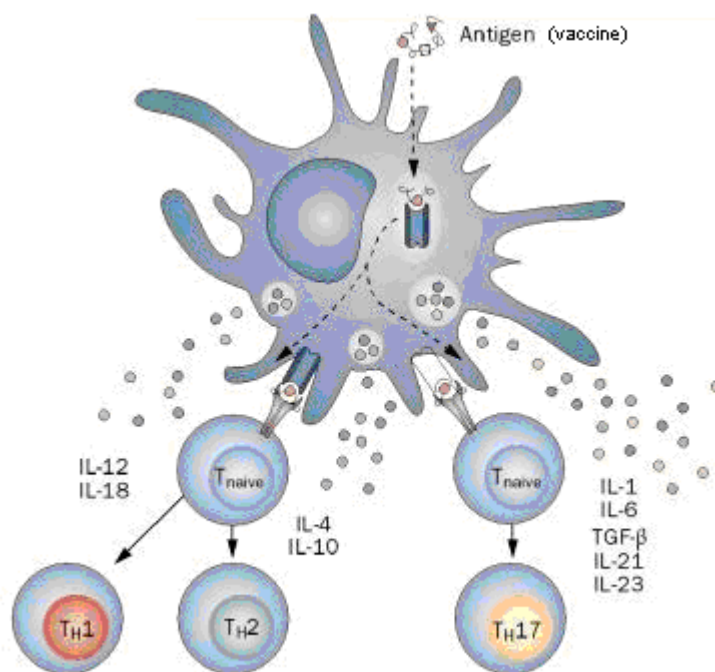


Figure 2

Cytokines implicated in immunization (T_H=T helper cell; IL₁₋₂₃=interleukine 1-23
TGF-β=tumor growth factor-β)

When autoimmune events seem to be attributable to a vaccine, investigators should then ascertain whether they are studying a predisposed set of individuals (by age, population, or genetic, immunological, environmental, ethnic, sociological, or underlying disease conditions) [21].

The development of autoimmune diseases depends on organisms predisposition

The human leukocyte antigen (HLA) pattern of the organism is an important factor for the occurrence of autoimmune responses. Patients who

suffered an syndrome after a viral vaccine had certain HLA patterns. In literature there are many articles stating that **anti-hepatitis B** vaccine induced **autoimmune demyelination**, with consequent development of **multiple sclerosis**. The correlation between the anti-hepatitis B vaccination and development of multiple sclerosis was first raised in France. The neurological manifestations were similar to those observed in multiple sclerosis. These neurological manifestations arose in individuals with a high risk of multiple sclerosis (a preponderance of women, mean age around 30 years, over-representation of the HLA-DR2 antigen, a positive family history of the disease [12,22]. There was no significant association between hepatitis B vaccination and the occurrence of demyelinating events or multiple sclerosis in any of these studies. There was no increase in the specific short-term risk of relapse associated with the hepatitis B vaccine. The possibility that several vaccines may cause or exacerbate multiple sclerosis usually originates from case reports describing the onset or recurrence of demyelinating symptoms shortly after vaccination [8,17] .

The presence of HLA B27 antigen in the majority of patients who developed rheumatoid arthritis suggests a possible role of vaccination in susceptible individuals [13].

Patients with immune deficiency disorders and their household contacts should not be vaccinated. Persons with defects in lymphocyte function, including people with leukemia and other forms of cancer, are at high risk of developing a serious and frequently fatal complication called **progressive vaccinia**. Although patients with mild defects in the immune system that do not affect lymphocyte function may not be at increased risk, there is no reason for these people to be vaccinated at this time. Patients with a condition that requires the use of **prednisone** or other **immunosuppressive agents** should not receive the **smallpox vaccine** at this time. Although low doses of prednisone do not usually cause any problems with live viral vaccines, these patients might require higher doses of prednisone if their underlying condition became more severe [1,2].

Although a temporal relationship between several vaccines and the occurrence of autoimmune diseases has been suggested in many case reports, there is so far no conclusive evidence for a causal link.

Clinical surveillance of potential autoimmune adverse effects and appropriate experimental tests should be considered for inclusion in the monitoring protocol.

The issue of the risk of vaccination remains a philosophical one, since the advantages of this policy have not been refuted, while the risk for autoimmune disease has not been irrevocably proved.

Although the post-vaccination risk of autoimmune diseases in the general population appears to be extremely low, epidemiological studies did not completely analyzed the role of **genetic predisposition**. In addition, a complex interplay of genetic, environmental and microbial factors may trigger a disease in subgroups of highly susceptible patients. This hypothesis should be carefully explored during the development of new candidate vaccines and new adjuvants. Therefore a potential correlation between vaccines and autoimmune diseases cannot be definitely ruled out and should be carefully explored during the development of new candidate vaccines.

Conclusions

Autoimmune effects should always be considered in the design of new vaccines. The correlation between vaccination and autoimmune illness is surrounded by controversy. The association between an autoimmune event and the administration of a vaccine should be very well defined, scientifically demonstrated through consistent experimental and clinical research. The association should be distinctive and the adverse event linked uniquely or specifically to the vaccine concerned.

The mechanisms of autoimmune reactions following immunization have not been elucidated yet. Only in a few rare cases, autoimmune pathology was associated with particular vaccines. Therefore, the findings should be the same if the vaccine is given to a different group of people, by different investigators not unduly influencing one another, and irrespective of the method of investigation.

An adverse event could be caused by a vaccine adjuvant or additive, rather than by its active component, hence spuriously affecting the specificity of the association between vaccine and adverse event.

There should be a clear temporal relationship between the vaccine and the adverse event. The administration of the vaccine should precede the earliest manifestation of the event or should occur a few weeks before a clear exacerbation of a continuing condition.

Special attention should be paid to new vaccine adjuvants, especially when they produce strong, innate responses. Clinical surveillance of potential autoimmune adverse effects and appropriate laboratory tests should be considered for inclusion in the monitoring protocol.

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