Vaccination in Autoimmune Animal Models

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Different studies have proved the concept of autoimmune/inflammatory syndrome induced by adjuvants (ASIA) in animal models [1]. Hence, vaccination remains a concern especially in genetically susceptible patients or those with immune mediated diseases such as systemic lupus erythematosus (SLE), as autoimmune diseases can be triggered by environmental factors. Therefore, it is important to determine if the use of vaccines or adjuvants in susceptible populations can initiate or aggravate the course of these diseases. For this reason, analyzing environmental effects in animal models is a good approach to identify risk in this particular population.

HEPATITIS B AND HUMAN-PAPILLOMA VIRUS VACCINES

Previously, both hepatitis B virus vaccine (HBVv) and human-papilloma virus vaccine (HPVv) were associated with SLE diagnosis or exacerbation in a minority of patients [2-4]. In the case of HBVv, we described 10 cases of SLE where the mean latency period from first vaccination to onset of autoimmune symptoms was 56.3 days [2]. In this case series, two patients had a personal history of autoimmunity and two a familial history of autoimmunity. Neurological symptoms were the most common manifestation in this group, present in 8 of 10 patients. Interestingly, 70% of patients continued with vaccination although adverse events were documented [2]. The aggravation of post-vaccine adverse phenomena in subjects who previously reacted adversely to vaccine administration has been documented previously by our group and others [3-5]. For instance, a case series of six patients with SLE post-HPVv was recorded, where several common features were observed among the patients, namely, personal or familial susceptibility to autoimmunity and an adverse response to a prior dose of the vaccine, both of which were associated with a higher risk of post-vaccination full-blown autoimmunity [4].

These observations from case series prompted further research in animal models to determine whether there might indeed be more solid proof for a causal association between vaccination and subsequent development of autoimmunity. Initially we evaluated the effects of immunization with HBVv and its adjuvant, aluminum, on NZBWF1 mice which are genetically prone to develop SLE-like disease. We chose this approach since it appears that in many cases there seems to be a genetic predisposition towards development of autoimmunity, which explains the relative rarity of such adverse phenomena when compared to the number of individuals receiving routine vaccinations. Our study demonstrated acceleration of the disease following immunization with the HBVv. Three groups of animals were immunized with HBVv, aluminum hydroxide or phosphate-buffered saline. The results demonstrated a differential effect of immunization. The group immunized with the whole vaccine, which contains HBV surface antigen, showed advanced kidney damage with severe inflammation, the presence of crescents and higher deposition of immunoglobulin, as well as higher urine protein levels and anti-ds-DNA antibodies. In contrast, immunization with the adjuvant alone was not associated with kidney aggravation. Nonetheless, there were notable hematological and neurobehavioral manifestations in the group of mice that received aluminum. In particular, neurocognitive deficits and brain inflammation were observed following both HBVv and aluminum injections, suggesting that these effects may have been induced by the aluminum adjuvant component of the HBVv [6]. Notably, similar neurocognitive effects were observed among C57BL/6 naïve mice 3 months following immunization with HPVv or aluminum (unpublished data).

ADJUVANT RELEVANCE

Recent experiments in animal models have revealed that injected nano-aluminum adjuvant particles have a unique capacity to travel to distant organs including the spleen and brain [7], inciting deleterious immuno-inflammatory responses in neural tissues [8,9]. In particular, following injection, antigen-presenting cells (APCs) avidly take up aluminum particles, and in so doing, become long-lived cells, impeding aluminum solubilization in the interstitial fluid. Thus, a pro-

portion of aluminum nanoparticles escape the injected muscle, mainly within immune cells, travel to regional draining lymph nodes, then exit the lymphatic system to reach the bloodstream, eventually gaining access to distant organs, including the spleen and the brain where aluminum deposits were still detected one year after injection [7]. Moreover, the 'Trojan horse' mechanism by which aluminum loaded in macrophages enters the brain results in its slow accumulation due to lack of recirculation and is likely responsible for neurocognitive adverse manifestations previously associated with administration of aluminum-containing vaccines [8,9].

The bioaccumulation of aluminum in the brain appears to occur at a very low rate in normal conditions, potentially explaining the presumably good overall tolerance of this adjuvant despite its strong neurotoxic potential. Nonetheless, according to Khan et al. [7], continuously increasing doses of the poorly biodegradable adjuvant may become insidiously unsafe, especially in cases of repetitive, closely spaced vaccinations and an immature/altered blood-brain barrier. In this context, the latest research by Lujan et al. [8] who described a severe neurodegenerative syndrome in commercial sheep, linked to the repetitive inoculation of aluminum-containing vaccines, is noteworthy. In particular, the "sheep ASIA syndrome" mimics in many aspects human neurological diseases linked to aluminum adjuvants. Notably, the adverse chronic phase of this syndrome affects 50–70% of flocks and up to 100% of animals within a flock. It is characterized by severe neurobehavioral outcomes (restlessness, compulsive wool biting, generalized weakness, muscle tremors, loss of response to stimuli, ataxia, tetraplegia, stupor, coma and death), inflammatory lesions in the brain, and the presence of aluminum in central nervous system tissues [8]. In summary, the ability of aluminum adjuvants to penetrate the blood-brain barrier, its subsequent retention in the brain where the adjuvant has the capacity to trigger severe neurological damage, may in part explain why the vast majority of reported adverse reactions following vaccinations are neurological and neuropshychiatric [3]. These observations are further consistent with the results obtained from our NZBWF1 mice model [6].

CONCLUSIONS

With respect to autoimmune manifestations, the importance of genetic background in autoimmune diseases is well documented. For instance, many human leukocyte antigen polymorphisms have been associated with different autoimmune diseases as well as many other polymorphisms in genes related to immune processes (innate immunity, T and B cell function and differentiation). In addition, ancestry plays a major role in the etiology of autoimmune diseases. For example, Amerindian ancestry has a higher risk for SLE. Moreover, autoimmune diseases are usually aggregated among closer relatives. And finally, the presence of one autoimmune disease in an individual implies a greater risk of developing another [10]. Therefore, susceptible individuals may be at higher risk for developing post-vaccine autoimmunity compared to individuals with no predisposition. Thus, in prophylactic approaches such as vaccinations, potential risks must be carefully considered and evaluated, especially in individuals who may be inherently more prone towards developing autoimmune diseases either because of their genetic background or prior history of adverse reactions to vaccinations.

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References

1. Cruz-Tapias P, Agmon-Levin N, Israeli E, Anaya JM, Shoenfeld Y. Autoimmune (auto-inflammatory) syndrome induced by adjuvants (ASIA) – animal models as a proof of concept. *Curr Med Chem* 2013; 20: 4030-6.
2. Agmon-Levin N, Zafrir Y, Paz Z, Shilton T, Zandman-Goddard G, Shoenfeld Y. Ten cases of systemic lupus erythematosus related to hepatitis B vaccine. *Lupus* 2009; 18: 1192-7.
3. Zafrir Y, Agmon-Levin N, Paz Z, Shilton T, Shoenfeld Y. Autoimmunity following hepatitis B vaccine as part of the spectrum of 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants' (ASIA): analysis of 93 cases. *Lupus* 2012; 21: 146-52.
4. Gatto M, Agmon-Levin N, Soriano A, et al. Human papillomavirus vaccine and systemic lupus erythematosus. *Clin Rheumatol* 2013; 32: 1301-7.
5. Stubgen JP. Immune-mediated myelitis following hepatitis B vaccination. *Autoimmun Rev* 2012; 12: 144-9.
6. Agmon-Levin N, Arango MT, Kivity S, et al. Immunization with hepatitis B vaccine accelerates SLE-like disease in a murine model. *J Autoimmun* 2014 Jul 16; Epub ahead of print
7. Khan Z, Combadiere C, Auther FJ, et al. Slow CCL2-dependent translocation of biopersistent particles from muscle to brain. *BMC Med* 2013; 11: 99.
8. Lujan L, Perez M, Salazar E, et al. Autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA syndrome) in commercial sheep. *Immunol Res* 2013; 56: 317-24.
9. Petrik MS, Wong MC, Tabata RC, Garry RF, Shaw CA. Aluminum adjuvant linked to Gulf War illness induces motor neuron death in mice. *Neuromolecular Med* 2007; 9: 83-100.
10. Anaya JM. Common mechanisms of autoimmune diseases (the autoimmune tautology). *Autoimmun Rev* 2012; 11: 781-4.

"Nature is often hidden, sometimes overcome, seldom extinguished"

Francis Bacon (1561-1626), English philosopher, statesman, scientist, jurist, orator, essayist, and author. Named the "father of empiricism," he established inductive methodologies for scientific inquiry (known as the Baconian or scientific method). His demand for a planned procedure of investigating all things natural marked a new turn in the rhetorical and theoretical framework for science, much of which still surrounds conceptions of proper methodology today