ASIA – Autoimmune Syndromes Induced by Adjuvants: Rare, but Worth Considering

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KEY WORDS: autoimmune (auto-inflammatory) syndrome induced by adjuvants (ASIA) syndrome, silicone, adjuvant, vaccination, autoimmunity

IMAJ 2012; 14: 121–124

The etiology of autoimmune diseases remains multifactorial, with genetic susceptibility and the environmental factor, mainly viruses, being the most important. Molecular mimicry and the expression of modified, cryptic or new antigenic determinants are among the main antigen-specific mechanisms involved in the tight association between autoimmunity and infectious diseases. Cytomegalovirus, parvovirus B19 and Epstein-Barr virus were evaluated in many studies and found to be triggers or associated with the flare of many autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and others [1].

Pavlovic and co-workers [1] assessed the impact of acute viral infections on the diagnosis of 88 SLE patients. Of the 25 patients who were diagnosed with new-onset SLE, acute parvovirus B19 infection was noted in 15, CMV in 6 and hepatitis B virus in 4 patients. In the remaining 63 cases, acute viral infections were reported after SLE had already been diagnosed. The most common viral infection was parvovirus (mimicking SLE presentation) and CMV infection, which was shown to mimic a lupus flare or present with specific organ involvement such as pulmonary infiltrates [2].

Genetic abnormalities in some toll-like receptors such as TLR3 and TLR4 have been associated with susceptibility to viral infections and the predisposition to autoimmunity. In this respect an association between TLR3 variant, L412F, and the development of recurrent viral infections and autoimmunity were shown. Patient's cells carrying the L412F variant showed both reduced interferon-gamma and tumor necrosis factor secretion in response to stimulation with CMV [3].

Finally, many microbial particles are galvanized by a non-specific mechanism identified as bystander activation. In this case, microbial antigens induce cross-reactive immune responses against self-antigens and enhance their presentation to the immune system. This is exemplified by the finding that many cases of Guillain-Barre syndrome were preceded by *Campylobacter jejuni* infection, which expresses a lipopolysaccharide molecule that mimics gangliosides. In a recent study it was shown that sialylation of *C. jejuni* lipo-oligosaccharide enhances human dendritic cell activation and subsequent B cell proliferation, which may contribute to the development of cross-reactive anti-ganglioside antibodies found in GBS patients [4]. This strong and well-established association between infections and autoimmune diseases begs the question whether autoimmune diseases could possibly be induced by vaccination.

VACCINATION-INDUCED AUTOIMMUNITY

The addition of adjuvants to many vaccines, such as mineral oils, aluminum salts and recently toll-like receptor agonists, enabled vaccines to become more effective in inducing higher T cell activity and a better B cell memory with higher neutralizing and long-lasting antibodies. The use of TLR agonists established the era of modern and efficient vaccination. Although considered safe, one should keep in mind that side effects (rarely serious) may occur following adjuvanted vaccines.

Adjuvants exert their immunostimulatory effect by many different actions. By translocating antigens to the lymph nodes they can be better recognized by T cells at sites of infection, leading to a net increase of immune cells as a whole. By interacting with pattern-recognition receptors, specifically TLRs on accessory cells, they enhance the innate immune response to antigens. Finally, they increase the capacity to cause local reactions at the injection site, thereby releasing danger signals by helper T and mast cells [5]. This is why adjuvants were reported to potentially inflict illness of an autoimmune nature. Defined as "the adjuvant-induced diseases," they are rare but do occur.

Mineral oils (generally considered non-toxic) were reported to induce sclerosing lipogranulomas at injection sites, but rarely in internal organs such as liver, spleen and lymph nodes. Aluminum hydroxide is known to potentially stimulate the immune system and to shift immune responses towards a Th2 profile. Th2-biased immune responses were considered a possible explanation for chronic fatigue, myalgia and low grade fever, considered by many to be post-vaccination manifestations. The above adjuvants were shown to induce lupus-related anti-nRNP/

SLE = systemic lupus erythematosus
CMV = cytomegalovirus
GBS = Guillain-Barre syndrome
TLR = toll-like receptor

Sm or -Su autoantibodies in non-autoimmune mice. In addition, anti-cytoplasmic, -ssDNA, and -chromatin antibodies were recorded in mice treated with MO-F and MO-S (medicinal mineral oils), suggesting pathogenic implications of these adjuvants in human autoimmune diseases [6]. Macrophagic myofasciitis is a condition that manifests as diffuse myalgias and chronic fatigue, both described in some cases of the so-called Gulf War Syndrome. It has been suggested that the GWS was a result of the adjuvant effect following multiple vaccinations performed over a short period. During the Gulf War in 1991, the veterans' vaccination protocol included the anthrax vaccination, administered in a six-shot regimen and adjuvanted by aluminium hydroxide and squalene. Antibodies to squalene were detected in almost all "ill" GWS patients (suffering from fatigue, myalgias, cognitive dysfunctions), compared to none of the healthy controls and veterans not showing signs of GWS. Though of vague pathogenesis, the data raise the possible role of this regimen of vaccination [7].

Silicone-elicited inflammatory fibroproliferative responses were hypothesized to contribute to the development of connective tissue diseases. Though considered by many to be inert, silicone is not a completely inert substance and microparticles from breast prostheses were shown to migrate and cause localized or generalized reactions. Silicone breast implantation was reported to induce the production of some autoantibodies and the development of the so-called adjuvant disease.

In this issue of *IMAJ*, Caldeira and Caldeira [8] describe another case of a woman in whom silicone prothesis was associated with immune mediated symptoms such as general fatigue and autoimmune markers. Frequently reported during the last decade, silicone prothesis was associated with even fully defined autoimmune diseases; however, in large cohorts of meta-analysis studies the relation between silicone breast implants and the development of connective tissue diseases was not established [9].

GWS = Gulf War syndrome

Suggested criteria for the diagnosis of ASIA

Major criteria

The appearance of "typical" clinical manifestations:

- Myalgia, myositis or muscle weakness
- Arthralgia and/or arthritis
- Chronic fatigue, non-refreshing sleep, or sleep disturbances
- Neurological manifestations (especially associated with demyelination)
- Cognitive impairment, memory loss
- Pyrexia
- Dry mouth

Minor criteria

- The appearance of autoantibodies or antibodies directed at the suspected adjuvant
- Other clinical manifestations (irritable bowel syndrome)
- Specific HLA (HLA DRB1, HLA DQB1)
- Evolvement of an autoimmune disease (multiple sclerosis, Sjögren's syndrome, SLE)

Source: *J Autoimmun* 2011; 36: 4-8

Aiming to include all the above mentioned conditions under one roof, a syndrome entitled "Autoimmune (Auto-inflammatory) syndrome Induced by Adjuvants" (ASIA) was recently described by Shoenfeld et al. [10]. The authors suggest using major and minor diagnostic criteria [Table], which still lack validation but grab the attention of physicians when symptoms such as arthralgia, myalgia, chronic fatigue and the appearance of autoantibodies emerge following vaccination [10]. Since then, ASIA is appreciated by many as a guide for physicians in characterizing and following less-defined immune mediated conditions than the fully defined ones with clear diagnostic criteria. Reviewing the literature, one can find many case reports and small series that fulfill the above proposed criteria of ASIA. Autoimmune diseases such as SLE, multiple sclerosis, antiphospholipid syndrome, and immune mediated inflammatory disorders such as giant cell arteritis, polymyalgia rheumatica, transverse myelitis, central nervous system inflammation, and less-defined disorders such as chronic fatigue syndrome (all considered an integral part of ASIA) are repeatedly reported as post-vaccination conditions related to vaccines such as HBV, human papillomavirus and influenza [11,12].

ASIA = autoimmune (auto-inflammatory) syndrome induced by adjuvants
HBV = hepatitis B virus

The causal relationship between vaccination and autoimmune manifestations is not well defined and cannot be measured. Causality was always suggested indirectly by the appearance of events in relation to any vaccination, taking into consideration the severity and consistency of the adverse events. In order to establish a causal relationship between a vaccine and autoimmune disease, a well-confirmed relationship over time is obligatory. In this respect the causal relationship between influenza vaccine and GBS that was reported after administration of the swine flu vaccine back in 1976 was not established by many meta-analysis studies. On the other hand, many new studies and case reports still appear in the literature considering causality between many vaccines and the development of various immune mediated situations. In a very recent study the records of 114 patients with immune-mediated diseases post-HBV vaccination were assessed, aiming to establish a correlation between the symptoms of these patients and the criteria of ASIA. Of these, 93 patients diagnosed with disease before applying for legal consultation were included in the study. Manifestations that were commonly reported included neuropsychiatric (70%), fatigue (42%), mucocutaneous (30%) and gastrointestinal (50%) symptoms. Elevated titers of various autoantibodies were also documented in 80% of sera tested. All the above manifestations fulfilled the required criteria for ASIA,

suggesting the syndrome to be useful in assessing post-vaccination events [13].

The other issue to be discussed is the latency period between vaccines and the appearance of post-vaccination adverse events. Whereas autoimmune disorders are noted to appear within days after vaccination, other studies report on the appearance of autoantibodies (antinuclear and antiphospholipid antibodies) in healthy medical workers up to 6 months after influenza vaccination [14]. In agreement with the fact that vaccine-induced autoimmunity is indeed rare, many studies alluded to the fact that vaccines may affect mainly subjects with a similar genetic background such as HLA-DRB1 [15].

It is important to note that even if strengthened by additional reports, and being related to individual genetic susceptibility, ASIA is a rare condition and its relevance as a syndrome is to raise the alertness of physicians when the above disorders do appear following vaccination.

VACCINATION EFFICACY AND SAFETY

The introduction of vaccination by Edward Jenner in 1798 was one of the most important steps in developing modern vaccination, leading to the eradication of lethal infectious diseases and widespread epidemics. During the last 100 years, billions of people received a variety of vaccines for the prevention of numerous infectious diseases. Millions are vaccinated every year to prevent the spread of influenza. Following the recent fear of swine flu and its identification as an almost epidemic of the influenza A/H1N1 virus, the World Health Organization called for wide vaccination of the population, primarily of professionals, those suffering from chronic diseases, pregnant women and other groups at risk. Monovalent anti-influenza vaccines, produced from adjuvant or non-adjuvant viral fragments, were as safe and effective as seasonal influenza polyvalent vaccines in the general population.

Serious adverse events such as GBS and other immune mediated disorders are still reported sporadically but are considered extremely rare. The majority of reported side effects were local, such as pain at the injection site, low grade fever, and myalgia – and all of short duration.

The Vaccine Adverse Event Reporting System (VAERS) was established in the United States in 1990 with the aim of registering all spontaneously reported vaccination-induced adverse events. Trying to assess whether GBS should indeed be recognized as even a rare side effect of the various influenza vaccines, and following the analyses of hundreds of reports on suspected cases of side effects, VAERS concluded that vaccines are mostly safe and that serious adverse events are indeed rare [16].

In a recent study, the risk of autoimmune disorders among people who were vaccinated against pandemic influenza A (H1N1) (n=1,024,019) compared with unvaccinated people (n=921,005) was analyzed over a period of 8–10 months. Excessive risks among vaccinated compared with unvaccinated people were of low magnitude for symptoms such as parasthesia after adjustment for age and gender. However, risks for GBS, multiple sclerosis and rheumatoid arthritis remained comparable to those who were unvaccinated. This strengthens previous findings of the safety of influenza vaccination, and that there was no change in the risk for GBS, multiple sclerosis, and other autoimmune disorders following this vaccination [17].

Many vaccines – such as against HBV and human papillomavirus – to which new adjuvants (such as ligands to toll-like receptors) were added to reduce the amount of viral particles and to increase the immune response – were shown by many large-scale studies to be totally safe. In a very recent study, 189,629 females who received more than one dose of human papillomavirus vaccine were followed during 2006–2008. The vaccine was considered safe over time and no autoimmune disorders were observed [18]. Furthermore, Hochwald et al. [19] assessed the efficacy of pertussis vaccination in day care centers and found that the incidence of pertussis was lower among vaccinated children (2/27) compared to unvaccinated (4/4) ($P = 0.001$), supporting the importance of this vaccination [19].

The issue of the safety of vaccination in rheumatic diseases such as SLE and rheumatoid arthritis was also studied by many. A recent study evaluated the safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Several vaccine-preventable infections occurred more often in these patients, but all vaccines were effective even in patients who were treated with immunomodulatory agents. No serious adverse events were reported in comparison with unvaccinated patients who suffered from the same rheumatic conditions, suggesting that vaccination is safe in this population [20].

In conclusion, post-vaccination autoimmunity is possible and physicians should take it into consideration when relevant symptoms appear. This is why the proposal of ASIA is of relevance, at least in order to place all the above mentioned disorders 'on the same page'. However, vaccine-related autoimmunity is very rare, and further appropriate prospective and multicenter epidemiologic studies should be designed. Until then, vaccination should be extensively encouraged and applied, mainly among medical workers, children, and patients suffering from chronic diseases.

VAAERS = Vaccine Adverse Event Reporting System

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References

1. Pavlovic M, Kats A, Cavallo M, Shoenfeld Y. Clinical and molecular evidence for association of SLE with parvovirus B19. *Lupus* 2010; 19: 783-92.
2. Ramos-Casals M, Cuadrado MJ, Alba P, et al. Acute viral infections in patients with systemic lupus erythematosus: description of 23 cases and review of the literature. *Medicine (Baltimore)* 2008; 87: 311-18.

3. Nahum A, Dadi H, Bates A, Roifman CM. The biological significance of TLR3 variant L412F, in conferring susceptibility to cutaneous candidiasis, CMV and autoimmunity. *Autoimmun Rev* 2011. In press.
4. Kuijf ML, Samson JN, van Rijs W, et al. TLR-4 mediated sensing of *Campylobacter jejuni* by dendritic cells is determined by sialylation. *J Immunol* 2010; 85: 748-55.
5. Israeli E, Agmon-Levin N, Blank M, Shoenfeld Y. Adjuvants and autoimmunity. *Lupus* 2009; 18; 1217-25.
6. Kuroda Y, Akaogi J, Nacionales DC, et al. Distinctive patterns of autoimmune response induced by different types of mineral oils. *Toxicol Sci* 2004; 78: 222-8.
7. Lippi G, Tragher G, Franchini M. Vaccination, squalene and anti-squalene antibodies: facts or fiction? *Eur J Intern Med* 2010; 21: 70-3.
8. Caldeira M, Caldeira Ferreira A. Siliconosis: autoimmune/inflammatory syndrome induced by adjuvants (ASIA). *IMAJ Isr Med Assoc J* 2012; 14: 137-8.
9. Hajdu SD, Agmon-Levin N, Shoenfeld Y. Silicone and autoimmunity. *Eur J Clin Invest* 2011; 41: 203-11.
10. Shoenfeld Y, Agmon-Levin N. ASIA – autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmune* 2011; 36: 4-8.
11. 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.
12. Bhat A, Naguwa S, Cheema G, Gershwin ME. The epidemiology of transverse myelitis. *Autoimmun Rev* 2010; 9: A395-9.
13. Zafir Y, Agmon-Levin N, Paz N, Shilton T, Shoenfeld Y. Autoimmunity following hepatitis B vaccine as part of the spectrum of autoimmune (auto-inflammatory) syndrome induced by adjuvant (ASIA): analysis of 93 cases. *Lupus* 2012; 21: 146-52.
14. Agmon-Levin N, Paz Z, Israeli E, Shoenfeld Y. Vaccines and autoimmunity. *Nat Rev Rheumatol* 2009; 5: 648-52.
15. Santoro D, Vita G, Vita R, et al. HLA haplotype in a patient with systemic lupus erythematosus triggered by hepatitis B vaccine. *Clin Nephrol* 2010; 74: 150-3.
16. Zhou W, Pool V, Iskander JK, et al. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VARES) – United States, 1991-2001. *MMWR Surveill Sum* 2003; 52: 1-24.
17. Bardage C, Persson I, Ortqvist A, Bergman U, Ludvigsson J, Granath F. Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden. *BMJ* 2011; 343: d5956.
18. Chao C, Klein NP, Velicer CM, et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. *J Intern Med* 2011. In press.
19. Hochwald O, Bamberger ES, Rubin L, Gershtein R, Srugo I. A pertusis outbreak among daycare children in northern Israel: who gets sick? *IMAJ Isr Med Assoc J* 2010; 12: 283-6.
20. van Assen S, Elkayam O, Agmon-Levin N, et al. Vaccination in adult patients with auto-immune inflammatory rheumatic diseases: a systematic literature review for the European League Against Rheumatism: evidence-based recommendations for vaccination in adult patients with auto-immune inflammatory rheumatic diseases. *Autoimmun Rev* 2011; 10: 341-52.

Capsule

Proliferation of *Legionella pneumophila* in a cell

The intravacuolar pathogen *Legionella pneumophila* injects the AnkB F-box effector into the host amoeba or human cell. Host-mediated farnesylation then anchors AnkB into the outer leaflet of the Legionella-containing vacuole (LCV) membrane, which is required for intravacuolar proliferation of *L. pneumophila* and for its virulence in vivo. Price et al. now show that AnkB promotes preferential docking of Lys48-linked polyubiquitinated host proteins to the LCV, which is followed by their proteasomal degradation. This generates an intracellular source of amino acids, which suppress an amino acid starvation response by *L. pneumophila*, and allows intravacuolar proliferation. Supplementation of amino acids completely rescued an ankB null mutant from its severe intracellular growth defect and suppressed its amino acid starvation response in amoeba and human cells.

Science 2011; 334: 1553

Eitan Israeli

Capsule

The rs4774 CIITA missense variant is associated with risk of systemic lupus erythematosus

The major histocompatibility complex (MHC) class II transactivator gene (CIITA) encodes an important transcription factor required for human leukocyte antigens (HLA) class II MHC-restricted antigen presentation. MHC genes, including the HLA class II DRB1*03:01 allele, are strongly associated with systemic lupus erythematosus (SLE). Recently the rs4774 CIITA missense variant (+1632G/C) was reported to be associated with susceptibility to multiple sclerosis. Bronson et al. (*Genes Immunity* 2011; 12: 667) investigated CIITA, DRB1*03:01 and risk of SLE using a multi-stage analysis. In stage 1, 9 CIITA variants were tested in 658 cases and 1363 controls (N=2021). In stage 2, rs4774 was tested in 684 cases and 2938 controls (N=3622). The authors also performed a meta-analysis of the pooled 1342 cases and 4301 controls (N=5643). In stage 1, rs4774*C was associated with SLE: odds ratio (OR) 1.24, 95% confidence interval (95% CI) = 1.07–1.44, $P = 4.2 \times 10{-}3$. Similar results were observed in stage 2 (OR 1.16, 95% CI = 1.02–1.33, $P = 8.5 \times 10{-}3$) and the meta-analysis of the combined data set (OR 1.20, 95% CI = 1.09–1.33, Pmeta = $2.5 \times 10{-}4$). In all three analyses, the strongest evidence for association between rs4774*C and SLE was present in individuals who carried at least one copy of DRB1*03:01 (Pmeta = $1.9 \times 10{-}3$). These results support a role for CIITA in SLE, which appears to be stronger in the presence of DRB1*03:01.

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