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GUEST EDITORIAL

Role of environmental factors in autoimmunity: pearls from the 10th international Congress on autoimmunity, Leipzig, Germany 2016

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The astonishing setting of the 10th International Congress on Autoimmunity in Leipzig was the perfect frame for intense and vibrant discussions on the pathogenic mechanisms of autoimmune diseases. Several authors have focused their attention on the role played by environmental factors. The depiction of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) by Shoenfeld and Agmon-Levin in 2010 has added a piece to the complex mosaic of autoimmunity, and several scientists have put their efforts in deciphering such complex syndrome [1]. The adjuvant is any substance used to enhance a specific immune response [2]. Several effects of adjuvants on the immune system have been suggested: they can deliver antigens to the immune system; activate innate immune cells through Toll-like receptors (TLR), NOD-like receptors, helicases and C-type lectin receptors; promote the attraction of dendritic cells; increase the uptake of the antigen by antigen-presenting cells (APCs); promote the secretion of cytokines with secondary activation of APCs or activate the inflammasome [3]. A number of evidences have associated these substances with the development of autoimmune phenomena. Torres Ruiz et al. [4] have reviewed the animal models of adjuvants induced autoimmunity. These are of extreme importance because they allow a better understanding of the pathogenic mechanisms of autoimmune diseases as well as may be used to find novel potential treatments. What is becoming clearer is the fact that the development of an autoimmune reaction may require a genetically prone individual [5]. Arango et al. [6] have summarized the HLA-DRB1 haplotypes linked with different autoimmune conditions. Moreover, they revised those haplotypes associated with a higher production of antibodies against specific vaccines. It is evident that these interactions are crucial in determining the onset of an autoimmune response [7, 8]. From the clinical point of view, case reports and case series of suspected vaccine-induced autoimmunity are present in the literature. Ruhrman-Shahar et al. [9] reported on four cases of anti-tetanus vaccination and the appearance of dermatomyositis, systemic lupus erythematosus, type 1 diabetes mellitus and anti-phospholipid syndrome. These cases show a strict temporal relationship between vaccine administration and the development of the full-blown autoimmune disease. The pathogenic mechanism may be shared between an alum-induced autoimmune response and the abnormal immune reactions occurring in the course of the autoimmune conditions [10]. Nonetheless, most of the reports have been addressing the possible role of the human papilloma virus (HPV) vaccine and the development of adverse events, which may be of autoimmune origin [11].

Bizjak and colleagues [12] reported one case of a man who developed pancreatitis one week after being vaccinated with the quadrivalent HPV vaccine. It is intriguing that the HPV vaccine may contain molecules, which may work through a molecular mimicry mechanism in eliciting an autoimmune reaction at the pancreas level. Nonetheless, it is well known that infections can trigger autoimmunity through molecular mimicry [13], especially in genetically prone individual. Dreyfus, for instance, illustrated that infections may elicit autoimmunity through a "metagenome" mimicry. For instance, in that study, It was shown that many Epstein–Barr virus (EBV) encoded genes could be shared with human immunoregulatory genes required for the host suppression of

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autoimmune responses. This could explain the strong linkage between this pathogen and several autoimmune conditions such as systemic lupus erythematosus (SLE) [14].

One of the diseases, which has been associated with several infection agents, is Guillain–Barrè syndrome (GBS) [15]. Mahecha et al. [16] performed a review of those cases reported in Colombia with a special focus on a recent burden, the ZIKA virus. It is possible that such pathogenic agent may be related to at least some of the cases, and clarifying the mechanisms at the base of such phenomenon could help in the clarification of GBS development. Palmieri et al. [17] reported 12 cases of severe somatoform and dysautonomic syndromes possibly associated with HPV vaccination. All cases developed within 20 days from vaccine administration, the authors suggesting that HPV vaccine, and not others, may facilitate the entrance of substances to the CNS leading to such protean manifestations [18, 19]. What emerges from this case series, given the lack or poor response to several drugs, is the necessity of proper treatments. Looking at possible neurological consequences associated with the HPV vaccine, the animal model presented by Inbar et al. [20] is intriguing. The authors suggested that the quadrivalent HPV vaccine may trigger behavioural abnormalities in C57BL/6 female mice. They sought to find a possible explanation, revealing that anti-HPV antibodies from the sera of vaccine-injected mice showed cross-reactivity with the mouse brain protein extract leading to microglial activation in the CA1 area of the hippocampus. Nonetheless, it was shown in a murine model that alum-inoculated mice tend to be more anxious show an increment in the number of astrocytes and alum deposition in the brain [21].

Geier and Geier [22], who performed a review of cases with the serious autoimmune adverse event outcomes of the VAERS database, performed another huge work. They observed that adverse events in terms of gastroenteritis, rheumatoid arthritis, thrombocytopenia, systemic lupus erythematosus, vasculitis, alopecia, CNS demyelinating conditions, ovarian damage, and irritable bowel syndrome were associated with the quadrivalent HPV vaccine administration. The paper did not prove causal relationship; rather, additional studies must be conducted to evaluate the epidemiological outcome of such HPV-related autoimmune adverse events [23]. Besides "classical" autoimmune diseases, HPV vaccine seems associated with the development of chronic fatigue syndrome (CFS) [24]. Indeed, in this special issue, it was suggested that the neuro-endocrine system could be the connection between CFS and HPV vaccine with an inflammatory response probably starting at the pharynx leading, in turn, to cytokine production and activation of T and B cells [25]. This mechanism could be exploited in order to search for a treatment of CFS. Another treatment strategy was tested in mice by Arango et al. [26]. The authors administered 0.2 ml of a dietary supplement enriched with phosphatidylcholine to 60 C57BL/6 female mice previously immunized with the quadrivalent HPV vaccine, aluminium or the vehicle. Intriguingly, those mice supplemented with phosphatidylcholine significantly reduced the depressive symptoms that were developed after HPV vaccine or aluminium injection.

Besides HPV vaccine, silicone implants have been ascribed as potential triggers of ASIA [27]. Colaris et al. [28] reported on 200 cases of silicone-related ASIA showing that most common symptoms of affected patients were fatigue, arthralgia, myalgia and cognitive impairment. Intriguingly, they compared two cohorts: one retrospectively evaluated in the years 1985–1992 and another recently collected. Since no differences were observed in the clinical manifestations of these two cohorts, it is likely that silicone-related disease has not changed during the last 30 year. Furthermore, Jara and colleagues [29] performed the first systematic review on ASIA. They found that over 4479 identified ASIA cases, 305 were severe, with illegal injection of mineral oil and other substances for cosmetic purposes representing one of the most harmful causes of the syndrome [30].

Thus, a question arises: how should we treat patients with ASIA? De Boer and colleagues [31] suggested that at least in those with breast implants, explantation of the silicone prosthesis improved the complaints in 75 % of the patients. Such improvement was only infrequently observed without additional therapy with immunosuppressive therapy in those developing a full-blown autoimmune disease [32]. We should also observe that such drastic measure could be of benefit especially in those patients in which silicone migration to draining lymph nodes has not occurred or, at least, has not massively occurred [33]. Furthermore, hydroxychloroquine has been suggested for its potential immunomodulatory properties. In this view, Nuri et al. [34] found that in those patients displaying anti-phospholipid antibodies, hydroxychloroquine could be a helpful adjunctive measure since it appears able of reducing the level of the autoantibodies in patients with anti-phospholipid syndrome [35].

Within the novel environmental factors potentially associated with autoimmunity such as vitamin D [36, 37], obesity [38], smoke [39] and air pollution [40] is also electrosmog. Marshall [41] proposed a connection between these two, observing a structural instability of the activated receptor of vitamin D by electromagnetic waves. Large, well-conducted experiments are required to better clarify this issue .

To conclude, this was another perfect moment to learn and to share at the boiling pot of autoimmunity. The environmental factors implicated in the pathogenesis of autoimmune phenomena become more complicated as the world surrounding us [42], as we better understand the billion particles influencing our lives.

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