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Is the immune neuroendocrine system the connection between epipharyngitis and chronic fatigue syndrome induced by HPV vaccine?

Editorial

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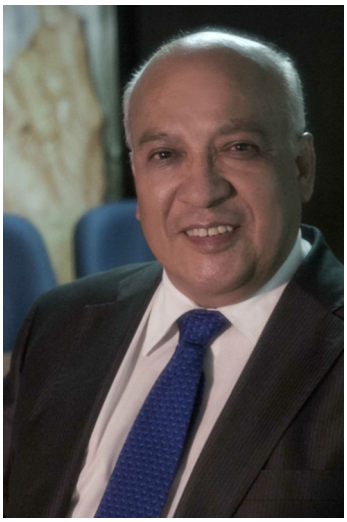

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An interesting study published in this issue of Immunologic Research, by Hotta et al. [1], analyzed forty-one patients who develop chronic fatigue syndrome (CFS) after HVP vaccine. All patients had at least two major criteria of the autoimmune/inflammatory syndrome induced by adjuvants or ASIA proposed by Shoenfeld et al. in 2011 [2], and all patients had severe chronic epipharyngitis. Sixteen patients were treated with abrasive $ZnCl_2$ procedure on epipharynx mucosa, and the authors observed significant improvement of CFS symptoms in 81.2 %, with a complete cure in four patients (25 %). These findings are relevant, because at this time, CFS is an untreatable disease opening the door for a clinical trial. The authors proposed that the possible explanations of improvement of patients treated with abrasive $ZnCl_2$ could be related to hypothalamic pituitary adrenal (HPA) axis normalization, which probably it was previously altered after HPV vaccine with the consequent development of CFS, suggesting an abnormal immune neuroendocrine interaction.

In 1976, Besedovsky and Sorkin [3], in order to incorporate immune system to an integral response after antigen challenge, proposed an immune neuroendocrine network based on the existence of afferent and efferent pathways between the immune and neuroendocrine structures. This hypothesis has been confirmed and amplified by several investigators, and actually consider that the immune neuroendocrine system controls growth and cell differentiation, immune response, metabolism and human behavior. Hormones, such as estrogens, growth hormone, prolactin, thyroid hormones and insulin, stimulate the immune response. On the contrary, cortisol, corticotrophin releasing hormone, adrenocorticotropic hormone, androgens and progesterone decrease the innate and adaptive immune responses. On the other hand, proinflammatory and anti-inflammatory cytokines released by the immune system cells stimulate or decrease the neuroendocrine system. All these actions are mediated by receptors for cytokines, hormones, neuropeptides and neurotransmitters present in the cells of the three systems, and the ability of these cells to synthesize these messengers. It has been proposed that the chronic stress triggers neuroendocrine hormones causing immune alterations, which may result in a risk factor for the development of autoimmune disease, by amplifying cytokine production. In human and experimental models, under stress situations, an integral response occurs, through the following stress axes: hypothalamic–pituitary–adrenal (HPA), hypothalamic–pituitary–gonadal (HPG), hypothalamic–pituitary–thyroid (HPT), prolactin–growth hormone

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system (PGHS) and autonomic nervous system (ANS) [4–8].

During a systemic or local inflammatory process, the immune cells are activated and release proinflammatory cytokines, which travel via peripheral blood to the central nervous system. The blood–brain barrier is an integral part of the neuroendocrine immune system, which divides circulating factors of the immune system and the CNS components. There are evidences that tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) during blood–brain barrier injury participate in neuroinflammation; TNF-α allows depolarization on endothelial cells of the blood–brain barrier and activates IL-6 production and signaling with consequent stimulation of neuroendocrine system. TNF-α-dependent generation of reactive oxygen species, down-regulation of endothelial junctions and permeability increase could be attenuated using an IL-6 neutralizing antibody [9, 10].

Based on the above, it is clear that chronic pharynx inflammation could activate the immune neuroendocrine system. In support of this concept, several authors have found highly activated T and B lymphocytes, and ciliated epithelial epipharynx cells, express class II antigen and act as antigen-presenting cells, with production of proinflammatory cytokines (IL-1beta, TNF-α, IL-6, IL-8, IL-2, IFN gamma, IL-10 and IL-4) [11]. Also, the relationship has been described between autonomous system and vasomotor symptoms of nasal mucosa and pharynx. In this study, the authors compared habitual tonsillitis with cases of simple tonsillitis, measuring the quantities of beta-adrenergic receptors and catecholamines. There were no significant differences in quantity of beta-adrenergic receptors. However, they found a major quantity of catecholamines in habitual tonsillitis [12].

In addition, multiple evidences support the relationship between CFS and HPA axis dysfunction. Patients with CFS have hypocortisolism; attenuated diurnal variation of cortisol; enhanced negative feedback to the HPA axis; and blunted HPA axis responsiveness [13]. Recent studies suggest that neuroendocrine pathways are involved in energy regulation (EnR). In chronic inflammatory/immune diseases (CIDs), balanced energy-rich fuel allocation to stores and consumers, normally aligned with circadian rhythms, is largely disturbed due to the vast fuel consumption in a chronic activated immune system (up to 2000 kJ day). During acute and chronic stress, proinflammatory cytokines altered the regulatory mechanism of EnR, which switched on to supply energy-rich fuels. Thus, EnR is inadequate in CIDs leading to many abnormalities as CFS. These signs and symptoms become comprehensible in the context of an exaggerated call for energy-rich fuels by the immune system [14]. In support of this hypothesis, it is suggested that patients with CFS have a decrease ability to increase mitochondrial energy production. A study demonstrated that the plasmatic levels of coenzyme Q10, a mitochondrial nutrient, essential for the production of ATP were significantly lower in CFS patients in comparison with normal controls [15].

CFS has been defined already in new diagnosis criteria by the Institute of Medicine IOM [16] as follows:(1) A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion and is not substantially alleviated by rest; (2) postexertional malaise (often described by patients as a "crash" or "collapse" after even minor physical or mental exertion); (3) unrefreshing sleep; and (4) cognitive impairment and/or orthostatic intolerance.

Chronic recurrent pharyngitis is a symptom sign frequently observed in patients with CFS and was one of the old criteria. However, the epipharyngitis was not previously described in CFS. Therefore, these clinical manifestations should be search for in these patients.

As we know, the etiology of CFS is still unknown. It has been associated with various infectious agents, vaccines and autoantibody production without definite causal relationship [17]. In relation to HPV vaccine, several case reports described CFS after exposition to HPV vaccine [18, 19]. In the study of Hotta et al., the interval between exposure to HPV vaccine and symptoms of CFS was from a few days to months. There are evidences that an interval of 6 weeks supports a causal-effect association. However, the development of CIDs has a long incubation time [20, 21].

In conclusion, the link between CFS and epipharyngitis after HPV vaccine could be the alteration in the immune neuroendocrine system. It is possible that an abrasive $ZnCl_2$ procedure on the epipharynx mucosa induced improvement in CFS by restoration of the immune neuroendocrine system. This hypothesis should be confirmed with a controlled clinical trial and determinations of cytokines and hormones before and after treatment of patients with chronic fatigue syndrome.

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