ASIA OR SHOENFELD'S SYNDROME: HIGHLIGHTING DIFFERENT PERSPECTIVES FOR DIFFUSE CHRONIC PAIN

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Is the Gulf War Syndrome (GWS) and the silicone related scleroderma –like syndrome spectres of the same disease? What do they have in common with a rare aluminium induced myopathic syndrome described for the first time in France in 1998? The logic answer was suggested by an elegant integration of the existing evidence into the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) proposed recently by Shoenfeld in a paper published in *Journal of Autoimmunity*[1]. A mosaic of environmental factors can be classified as adjuvants. In fact, we know for decades a variety of compounds that are able to induce autoimmunity in animal models and used in clinical practice to increase the immunogenicity of vaccines, but also known to be able, in genetic susceptible individuals, to induce autoimmune diseases[2,3]. In this vast group of substances bacterial antigens, hormones, aluminium, silicone and several other molecules have been included[4].

The GWS was described in veterans that were suffering from atypical rheumatic symptoms, such as arthralgia, myalgia, lymphadenopaty, chronic fatigue syndrome, malar rash and autoimmune thyroiditis[5].

A cohort study performed 10 years ago compared the titter of anti squalene antibodies of 144 Golf War immunized veterans or medical employees, 48 blood donors, 40 systemic lupus erythematosus patients, 34 silicone breast implant recipients and 30 chronic fatigue syndrome patients. The majority (95%) of overtly ill deployed GWS patients had antibodies to squalene. All (100%) GWS patients immunized for service in Desert Shield/ /Desert Storm who were not in the fighting front had antibodies to squalen. In contrast, none (0%) of the veterans that were in the fighting zone and were not showing signs and symptoms of GWS have antibodies to squalen. Neither patients with idiopathic autoimmune disease nor healthy controls had detectable serum antibodies to squalene. The majority of symptomatic GWS patients had serum antibodies to squalene[6]. The authors proposed that GWS was not a result of the exposition to weapons but rather induced by the intense vaccination program that they were submitted to. It is ironic that more solders were ill due to an oil adjuvant injected in their organisms than fighting against the hostile environment and the armed enemies.

Silicon was considered an inert material and thus unable to induce immune reactions. Recent metanalysis have supported this view, as the risk of silicon exposed individuals for developing a diffuse connective tissue disease is only 0.8%, not significantly higher than the risk of the general population. However, that is not the case for more unspecific symptoms such as arthralgia and myalgia and even some diffuse neurologic manifestations that appear to be more common in individuals exposed to silicon implants[7]. The possible association between chronic fatigue syndrome, fibromyalgia, and previous silicone mammoplasty was proposed almost two decades ago[8].

The post vaccination muscle disease described by Gehardi *et al.* in 1987 is of particular interest as it is based in well defined histologic features[9]. It is a miofasceitis that has the presence of macrophages with aluminum inclusions, which occurs associated with vaccination. Clinically the disease is expressed by systemic symptoms such as fatigue, myalgia, arthalgia, fever and, in some cases, by a demyelinating condition similar to Guillain-Barré, with electromyographic changes. Elevated acute

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Table I. Criteria suggested by Shoenfeld for ASIA diagnosis

Major Criteria

- Exposure to an external stimuli (infection, vaccine, silicone, adjuvant) prior to clinical manifestations
- The appearance of 'typical' clinical manifestations:
  - Myalgia, myositis or muscle weakness
  - Arthralgia and/or arthritis
  - Chronic fatigue, un-refreshing sleep or sleep disturbances
  - Neurological manifestations (especially associated with demyelination)
  - Cognitive impairment, memory loss
  - Pyrexia, dry mouth
- Removal of inciting agent induces improvement
- Typical biopsy of involved organs

Minor Criteria

- The appearance of autoantibodies or antibodies directed at the suspected adjuvant
- Other clinical manifestations (i.e. irritable bowel syndrome)
- Specific HLA (i.e. HLA DRB1, HLA DQB1)
- Evolvement of an autoimmune disease

For ASIA's diagnosis: at least 2 major criteria or 2 minor and 1 major.

phase proteins and creatine quinase also occur. The same group determined that the disease occurs only in HLA DRB1*01 positive individuals[9]. On top of that, it was shown that aluminum can persist in the local of injection, up to 10 years after vaccine administration, which can explain the persistence of this condition in some individuals[10].

These conditions and other observations, regarding for instance de H1N1 vaccination, have motivated the definition of the ASIA syndrome, with the criteria proposed by Shoenfeld listed in Table I[1]. These criteria, if properly validated, are of great clinical relevance, as they raise a major clinical doubt on the classification of some patients with chronic pain syndromes, as chronic fatigue syndrome, or even fibromyalgia. In fact, if we compare the cardinal symptoms of the Shoenfeld's ASIA syndrome with the typical clinical manifestations of patients with diffuse chronic pain we came quickly to the conclusion that reviewing the recent exposition to adjuvants and other potential exogenous stimulus seems to be a wise attitude. This is also in line with the characteristic symptoms of fibromyalgia and chronic fatigue syndrome that frequently occur in patients with well-defined Lyme disease, even after adequate treatment. Lyme disease is caused by an infection due to *Borrelia burgdorferi* spirochete and most of the clinical symptoms are in fact a consequence of an immune response to this infectious agent. Although a biological relationship between Lyme disease and diffuse pain syndromes has not been established, in fact this can be encompassed by the ASIA syndrome[11]. In addition, recent studies have detected the presence of retroviral sequences like xenotropic murine leukemia virus-related virus (XMRV) and polytropic murine leukemia virus related--virus (PMLV) in chronic fatigue syndrome patients, expanding, in fact, the need for thinking on alternative diagnosis in patients classified into these conditions[12]. Consequently, countries such as Australia, Canada, New Zealand and the UK elaborated restrictive guidelines for "blood donors with a history of current diagnosis of CFS". If upcoming research will confirm these observations and validate the ASIA/Shoenfeld criteria, a major paradigm shift will have to occur in the way rheumatologists perceive some cases of diffuse chronic pain. Interestingly, in this issue of Acta Reumatologica Portuguesa 2 case reports related to the ASIA/Shoenfeld are reported[13,14].

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