

Cannabidiol as a Therapy for ASIA Syndrome? An Editorial on a Novel Study

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First described by Shoenfeld et al. in 2011 [1], the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) is a novel syndrome unifying immune mediated pathologies via a common etiology – adjuvant exposure. The word ‘adjuvant’ comes from the Latin word *adjuvare*, meaning to aid, and is defined as “any substance that acts to accelerate, prolong, or enhance antigen-specific immune response.” Unfortunately, the ability of adjuvants to enhance the body’s immune reactions is not only the foundation for both successful vaccination but also for adverse autoimmune reactions [1,2]. Hence, adjuvant exposure in genetically predisposed individuals can potentially induce ASIA syndrome, forged from the following conditions: post-vaccination phenomena, macrophagic myofasciitis syndrome, Gulf War syndrome, and sick building syndrome [3].

Common clinical presentations, comprising some of the ASIA diagnostic criteria as well, include: pyrexia, myalgia, arthralgia, chronic fatigue, cognitive impairment and other neurological manifestations [Table 1]. Yet, ASIA can manifest

in numerous ways, as presentation can vary from clusters of symptoms forming undefined connective tissue diseases to full-blown autoimmune diseases such as systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, among others [3]. Since ASIA syndrome was first described in 2011 [1], case reports have been accumulating, numbering more than 4000, of which 305 were classified as severe and 11 resulted in death [4].

Focusing on the human papillomavirus (HPV) vaccine reveals an even more troubling picture, with HPV vaccine being the leading cause of ASIA syndrome. Moreover, the majority of severe ASIA cases as well as reported deaths were found to be related to the HPV vaccine [4]. Utilizing the vaccine adverse event reporting system (VARES) database in the United States, Pellegrino et al. [5] assessed about 2000 probable ASIA cases occurring post-HPV vaccination between 2006 and 2013. Furthermore, based on this analysis, an estimated rate of 3.6 cases per 100,000 doses of HPV vaccine was calculated. Typical manifestations include pyrexia (58%), myalgia/myositis (27%) and arthralgia/arthritis (19%). Still, rare manifestations should not be disregarded since they can have potentially devastating effects, for example, primary ovarian failure following HPV vaccination [5,6]. HPV vaccine’s possible toxicity is postulated to be due to its vast homology with human proteins as well as its high potency in the immune system [7].

In contrast to major advances made in deciphering the pathogenesis and characterization of ASIA syndrome, progress in the search for a possible cure is scarce. Currently, only sporadic studies exploring a therapeutic option for Gulf War syndrome exist, with some suggesting exercise, mindfulness combined with psychiatric medication, cognitive behavioral therapy, coenzyme Q10 or nicotinamide adenine dinucleotide (NADH) as possible treatments [8-11].

Unlike previous studies on Gulf War syndrome, an innovation by Palmieri and team, reported in this issue of *IMAJ* [12] – namely, targeting the ASIA syndrome as an immune mediated disease – has opened a new line of possible treatment for the disease. Hence, cannabidiol (CBD), a non-psychoactive anti-inflammatory constituent of *Cannabis sativa*, appears to be a natural candidate for treating ASIA patients [13]. Focusing on CBD’s anti-inflammatory traits, CBD has been shown to decrease the

Table 1. Diagnostic criteria for ASIA syndrome: either two major criteria or one major criteria accompanied by two minor criteria required

Major criteria
<ul style="list-style-type: none"> • Exposure to an external stimuli (i.e., adjuvant, silicone, infection) prior to clinical manifestation • Appearance of typical clinical manifestation <ul style="list-style-type: none"> ▶ Myalgia, myositis, or muscle weakness ▶ Arthralgia and/or arthritis ▶ Chronic fatigue, unrefreshing sleep or sleep disturbances ▶ Neurological manifestation (especially associated with demyelination) ▶ Cognitive impairment, memory loss ▶ Pyrexia, dry mouth ▶ Removing of inciting agents induces improvement ▶ Typical biopsy of involved organ
Minor criteria
<ul style="list-style-type: none"> • The appearance of autoantibodies or antibodies directed at the suspected adjuvant • Other clinical manifestation • Specific HLA (HLA DRB1, HLA DQB1) • Involvement of an autoimmune disease

number of B, T helper and T cytotoxic cells, reduce the secretion of B cells' IgM and IgG antibodies and of T cells' IL-17 and IL-6, and increase transcription of T cells' IL-10 [14-16].

Working on the assumption that CBD's immunomodulating properties might be the source for this therapeutic potential raises the question whether measured outcomes should include markers for inflammation. Additionally, in light of the authors' acknowledgment of a possible bias in the health survey questionnaire on quality of life administered to the study participants, the question of supplementary measured outcomes still remains. Tackling the issue of the subjective questionnaire also raises concern about a placebo effect, underlining the need for placebo control.

Two additional factors also give rise to concern. Firstly, the overall dropout rate of 32% of the study participants, with 16% dropping out due to adverse effect and 16% due to lack of improvement. Data on these patients were excluded from the final analysis, which hampers the reliability of the results. Secondly, in the Discussion section of their article, Palmieri et al. [12] mention a sudden 1 week interruption in therapy without providing further explanation, again eliciting concern about the trial's accuracy.

CONCLUSIONS

Palmieri and colleagues [12] are the first to embark on a search for a cure of ASIA syndrome in humans, while Kivity et al. [17] were the first to explore this in mice. The approach towards an immune modulating treatment for ASIA syndrome is groundbreaking, opening a new field to be explored. Alas, due to reliability issues, conclusions regarding the potential of cannabidiol treatment in ASIA patients cannot yet be drawn.

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