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REVIEW ARTICLE

The sick building syndrome as a part of the autoimmune (auto-inflammatory) syndrome induced by adjuvants

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Abstract Sick building syndrome (SBS) is a term coined for a set of clinically recognizable symptoms and ailments without a clear cause reported by occupants of a building. In the 1990s the term "functional somatic syndromes" was applied to several syndromes, including SBS, multiple chemical sensitivity, repetition stress injury, the side effects of silicone breast implants, the Gulf War syndrome (GWS), chronic fatigue syndrome, the irritable bowel syndrome, and fibromyalgia. Recently, Shoenfeld and Agmon-Levin suggested that four conditions—siliconosis, macrophagic myofascitis, the GWS, and post-vaccination phenomena—which share clinical and pathogenic resemblances, may be included under a common syndrome entitled the "autoimmune (auto-inflammatory) syndrome induced by adjuvants". Comparison of the clinical manifestations, symptoms, and signs of the four conditions described by Shoenfeld and Agmon-Levin with those described for SBS shows that nine out of ten main symptoms are present in all 5 conditions. Shoenfeld and Agmon-Levin further propose several major and minor criteria, which, although requiring further validation, may aid in the diagnosis of this newly defined syndrome. We propose here that SBS may also be included as a part of "Shoenfeld's syndrome".

Keywords Sick building syndrome · ASIA · Adjuvants · Autoimmune · Vaccination

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Introduction

Sick building syndrome (SBS) is a term coined for a set of several clinically recognizable symptoms and ailments without a clear cause reported by occupants of a building. The phenomena have occurred predominantly in offices, but also in schools, healthcare centers, and residential areas. The American Society for Heating, Refrigeration and Air Conditioning Engineering (ASHRAE) has given a quantitative definition of a sick building, as one where at least 20% of occupants report health symptoms and discomfort associated with their staying in the building and relief upon leaving the building, but where no definitive cause of the problem can be identified [1]. When a clinically defined illness is clearly associated with a specific agent in the building, the term building-related illness (BRI) is used. In extreme cases where the causes of the syndrome have not been specified and remediation processes have not been effective, the occupants may abandon the building, thereby creating a "building crisis".

Evolution and prevalence of SBS

The concept of the SBS emerged in the mid-1970s when, following the global oil shortage and energy crisis, the recirculation of air in the heating, ventilation, and air-conditioning (HVAC) systems of buildings began to increase significantly in order to save energy. Attention was drawn to a higher prevalence of building-related symptoms in offices than in the normal population. In 1984, the World Health Organization (WHO) estimated that up to 30% of new and remodeled buildings worldwide might be linked to symptoms of SBS [2]. The concept has evolved beyond the mere search for environmental-related etiology, to include

psychological aspects, economic implications, energy-saving, and climatic changes [3]. Air-recirculated and air-conditioned buildings have been found to have significantly higher rates of occupant complaints than naturally ventilated buildings [4]. Women are more likely to be affected by the symptoms of SBS than men [5, 6].

Health characteristics and manifestations of SBS

The characteristic symptoms experienced by occupants of buildings in which SBS has been reported include headaches, fatigue and lethargy, eye and throat irritation, nasal congestion, shortness of breath, disturbed ability to concentrate, dry skin, itchy skin, and skin rash. Other symptoms such as nausea, dizziness, sneezing, nose bleeds, chest tightness, back and joint pain, tachycardia, sleep disturbances, and odor sensitivity have also been reported. Table 1 presents prevalences of SBS-related symptoms, the most prevalent being lethargy, mucous membrane irritation, and headache [7]. In addition to transient symptoms, variants of building-related disease have been identified in recent decades, and it has been suggested that they are influenced by the nature of the pollutants as well as the intensity and duration of exposure and the reactivity of the occupant's immune system [8]. In recent years, reference to the antigen-adjuvant coexposure mechanism [9–11] has allowed a more profound elucidation of the association between indoor environmental quality (IEQ) and the onset of an immune response.

Potential contributors to and causes of SBS

Since the 1970s, researchers have been trying to identify a definitive cause of SBS, but it remains a poorly understood phenomenon. Poor indoor air quality (IAQ)—a term used interchangeably with the term IEQ—has been pointed out as the cause of the development of SBS. It is hypothesized that SBS could be caused by a number of factors working in combination [12]. These include poor ventilation; low humidity; airborne pollutants such as dust, carpet fibers, mold, and other fungal spores; airborne proteins; chemical pollutants such as cleaning materials; volatile organic compounds (VOCs); tobacco smoke; ozone produced by photocopiers and printers; formaldehyde; and more, as well as psychosocial factors, such as stress and human relations. But even in the absence of complaints, the potential for continuous exposure to health risks evolving from a large variety of low levels of chemicals, radon, and incident bioaerosols is inherent in the indoor environment. HVAC systems have been recognized as a major source and cause of IEQ problems [13]. These systems may also be a significant source of the growth of microbial contamination, including bacterial and fungal colonies and spores, and the systems may also be a factor contributing to dispersion of chemicals in the indoor air. At present, biological contaminants in indoor air are considered to be predominantly responsible for known BRIs. Mycotoxins, secondary metabolites of indoor molds, and non-mold particles (proteins) are suspected of adjuvant activity in inducing allergic sensitization and provoking the appearance of auto-antibodies which may trigger an autoimmune disease outbreak [14–16]. The association of chemical environmental adjuvants with the onset of immune-based inflammatory reaction in the living cell and respiratory tracts has also been studied [17, 18]. Components in ambient particulate matter (PM) with recognized adjuvant activity are diesel exhausts and their polycyclic aromatic hydrocarbons (PAH). Gases studied as environmental adjuvants are ozone, nitrogen oxides, and sulfur dioxide. Ambient PM originating from vehicular traffic and found in indoor air was demonstrated to have an adjuvant effect in the promotion and enhancement of allergic sensitization by ovalbumin and the induction of allergic airway inflammation. The effect was correlated with the prooxidant potential of the PM [19–21]. Ambient ultrafine particles have been found to be more active than fine particles in their adjuvant activity.

Table 1 Prevalence of symptoms associated with sick building syndrome (SBS)

Work-related symptom	Prevalence (%)
Lethargy	57
Blocked nose	47
Dry throat	46
Headache	43
Itchy eyes	28
Dry eyes	27
Runny nose	23
Flu	23
Difficulty in breathing	9
Chest tightness	9

Modified by permission from [7]

SBS and autoimmune (auto-inflammatory) syndrome induced by adjuvants

During the past two decades, different terms have been used to describe a group of medical conditions having similar symptoms. In the 1990s the term "functional somatic syndromes" was applied to several syndromes, including SBS, multiple chemical sensitivity (MCS), repetition stress injury, the side effects of silicone breast

Table 2 The prevalence of clinical manifestations: MMF, silicone-related disease, GWS, and post-vaccination events, and SBS

Symptoms	MMF ($N = 250$)	Silicone ($N = 100$)	GWS ($N = 4600$)	Post-vaccines ($N = 30000$)	SBS ($N = 20000$)
Myalgias/myopathy/muscle weakness	+++	+++	+	+	+
Arthralgias/arthritis	+++	+++	++	+	+
Chronic fatigue/sleep disturbances	+++	+++	+++	+	++
Neurological/cognitive impairments	+	++	++	+	+
Fever	+	NR	NR	+	+
Gastrointestinal	+	NR	+	+	+
Respiratory	NR	NR	+	+	+
Skin		+	+	+	+
Diagnosis of defined autoimmune disease	+ 33% MS	+	NR	+/−	NR
Antibodies	NR	+	+	NR	+
Increased ESR	++	NR	NR	+	NR

The prevalence of signs and symptoms was defined as (+) if reported in <30% of subjects, (++) if reported in 30–60%, and (+++) if present in more than >60% of subjects. Modified by permission from [11]

MMF macrophagic myofascitis, *GWS* Gulf War syndrome, *MS* multiple sclerosis, *NR* not reported, *ESR* erythrocyte sedimentation rate

implants, the Gulf War syndrome (GWS), chronic fatigue syndrome (CFS), the irritable bowel syndrome, and fibromyalgia (FM) [22]. Patients with these functional somatic syndromes have high self-diagnoses, and their symptoms are often refractory to reassurance, explanation, and standard symptomatic treatment. During the past decade, another term has been used to describe these syndromes—"medically unexplained symptoms" [23, 24]. These same syndromes—SBS, CFS, GWS, MCS, and FM—are defined solely on the basis of symptoms rather than by medical signs. The relationship of such symptoms and syndromes to environmental exposure is often debated, as is the distinction among the various syndromes.

Shoenfeld and Agmon-Levin [11] recently suggested that four conditions—siliconosis, macrophagic myofascitis (MMF), the GWS, and post-vaccination phenomena—sharing clinical and pathogenic resemblances, may be included under a common syndrome entitled the "autoimmune (auto-inflammatory) syndrome induced by adjuvants" (ASIA). Shoenfeld and Agmon-Levin further propose several major and minor criteria that, although requiring further validation, may aid in the diagnosis of this newly defined syndrome (Table 2). We propose here that SBS may also be included as a part of "Shoenfeld's syndrome". Comparison of the clinical manifestations, symptoms, and signs of the four conditions described by Shoenfeld and Agmon-Levin [11] with those described for SBS shows that nine out of the ten main symptoms (listed in Table 2; adapted from [11]) are present in all 5 conditions. These symptoms are myalgia, arthralgias, chronic fatigue, neurological cognitive impairment, fever, gastrointestinal and respiratory symptoms, skin manifestations, and the appearance of autoantibodies. The only missing denominator in SBS is the diagnosis of defined autoimmune disease. Symptoms of SBS have been described in tens of thousands of people worldwide, although in the relevant studies the proportions of patients suffering from each clinical manifestation have not always been reported in definite percentages [14, 25–28]. SBS as a medical condition also fits well with the criteria suggested by Shoenfeld and Agmon-Levin [11] for ASIA (Table 3).

Table 3 Suggested criteria for the diagnosis of 'ASIA'

Major criteria
Exposure to 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 demyelinization)
Cognitive impairment, memory loss
Pyrexia, dry mouth
Minor criteria
The appearance of autoantibodies or antibodies directed at the suspected adjuvant
Removal of inciting agent induces improvement
Typical biopsy of involved organs
Other clinical manifestations (e.g., irritable bowel syndrome)
Specific HLA (i.e. HLA DRB1, HLA DQB1)
Evolution of an autoimmune disease (e.g., MS, SSc)

Modified by permission from [11]

SSc systemic sclerosis

The first and most relevant major criterion consistent with Shoenfeld's syndrome is "exposure to external stimuli (infection, vaccine, silicone, adjuvant) prior to clinical manifestations". In SBS there is always pre-exposure to external stimuli in the building environment. Most of the environmental compounds implicated in SBS—VOCs, hydrocarbons, organic allergens, molds, mycotoxins, phthalates, etc.—may be regarded as environmental adjuvants [16, 29–32]. Environmental factors that have an immune adjuvant effect have been recognized for several decades. These adjuvants (e.g., silicone, aluminium, pristane, infectious components) have been found to induce autoimmunity by themselves in different animal models and may possibly provoke autoimmune or auto-inflammatory diseases (AI/AIFD) in humans [9, 10, 33–35]. Exposure to these substances has been documented in the four medical conditions included in ASIA, suggesting that the common denominator of these syndromes is a trigger entailing adjuvant activity.

The other major criterion suggested by Shoenfeld for ASIA is: "the appearance of 'typical' clinical manifestations", among which a large proportion are symptoms typical of SBS, including myalgia, chronic fatigue, sleep disturbances, neurological manifestations, cognitive impairment, and dry mouth. Some of the minor criteria suggested by Shoenfeld for ASIA are also met in SBS patients: "the appearance of antibodies directed at the suspected adjuvant, or in some cases auto-antibodies" [36–39]; patients with documented exposure to molds in SBS have elevated titers of antibodies (IgA, IgM, and IgG) to neural-specific antigens when compared with healthy controls [36]. In a mouse model, exposure to molds caused a significant increase in total serum IgG(2a) and interferon gamma [37], and the presence of serum IgE specific to fungi was found to be connected with building-related syndrome in individuals working in damp and moldy buildings[39].

The next criterion of ASIA—"the removal of the inflicting agent induces improvement"—is very typical of SBS [3, 28]. The last minor criterion—"evolution of an autoimmune disease", is not met distinctively by SBS, but, as shown by Gray et al., there is evidence to suggest an increased risk of autoimmunity [38]. In this study, Gray et al. showed that subjects exposed to mixed mold mycotoxins in a water-damaged building exhibited a high risk of producing autoantibodies to nuclei, smooth muscle, and central nervous system (CNS) and peripheral nervous system (PNS) myelin (IgG, IgM, IgA) and neurofilament. Odds ratios for each autoantibody were significant at 95% confidence intervals, showing an increased risk for autoimmunity. The patients reported a greater frequency and intensity of symptoms, particularly neurological and inflammatory symptoms, when compared with controls. (Other abnormal immune parameters were detected in the patients: immune activation markers, with elevated levels of CD+CD26+, CD8+HLR-DR+, CD5+CD25+, and CD8+CD38+ phenotypes in peripheral blood; and decreased complement-receptor-bearing T-suppressor, CD8+CD11b+, cells.)

Neurogenic switching has been proposed as a crossover mechanism between immunogenic inflammation and neurogenic inflammation [40].

Neurogenic inflammation occurs when substance P and other neuropeptides released from sensory neurons produce an inflammatory response, whereas immunogenic inflammation results from the binding of antigen to antibody or leukocyte receptors. Neurogenic switching has been proposed to result when a sensory impulse from a site of activation is rerouted via the CNS to a distant location, producing neurogenic inflammation at the second site. Exposure to an allergen or chemical irritant at one site leads to a sensory nerve impulse. For allergens, mast cell degranulation leads to the release of histamine and other mediators, and histamine binds receptors on sensory nerves. Both histamine and substance P can bind effector cells, such as endothelial cells, mucus-secreting cells, and bronchial smooth muscle cells to produce inflammation. For chemical substances, receptors on peripheral nerves are directly triggered, and when the impulse reaches the CNS it is redirected to another peripheral location, leading to the release of substance P and other neuropeptides, and producing inflammation at the second site. An alternative hypothesis is that immunogenic switching occurs, with the release of cytokines which act on distant cells even in the brain. These two mechanisms may explain how allergens, infectious agents, adjuvants, etc. can exacerbate conditions such as asthma, migraine, and arthritis, and other symptoms described in SBS and in the other ASIA-related syndromes. These two mechanisms can also explain how respiratory or gut irritants lead to symptoms at other sites in these disorders.

Conflict of interest None.

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