

Mercury-Induced Inflammation: Yet Another Example of ASIA Syndrome

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In this issue of *IMAJ*, the occurrence of a plethora of psychoneuro-immunological symptoms (also called ASIA or Shoenfeld syndrome) is described in three different patients. Segal and co-authors [1] present an 85 year old woman who underwent total hip replacement and experienced side effects. Patch testing showed hypersensitivity to cobalt and chromium. The metal components were replaced with ceramics and the symptoms disappeared. The second case, reported by Pineda and team [2], concerns a 53 year old woman with breast implants. Since silicone was found in her lymph nodes, removal of her implants was recommended. Finally, Cruz-Dominguez et al. [3] present the thought-provoking case of a patient exposed subcutaneously to a large amount of metallic mercury. The case illustrates that mercury might act as a potent adjuvant, inducing ASIA [4,5]. The patient, a 30 year old woman, had initially suffered from fever and profound weight loss. Later, fibromyalgia, excessive fatigue, anxiety, depression and granulomas developed. Laboratory findings were in the normal range, except for the presence of antinuclear antibodies and antibodies to double-stranded DNA. Since the patient fulfilled the criteria for ASIA (autoimmune/inflammatory syndrome induced by adjuvants), the authors suggested that mercury might be yet another trigger of ASIA syndrome. Despite some persistent

health issues such as depression and skin problems, no major illness (such as neurologic or kidney disease) had developed. This case illustrates the difficulty of making general risk assessment of the health effects of mercury since its toxicity varies considerably among exposed subjects.

Despite its toxicity, the use of mercury and mercury compounds has been widespread in medicine. Mercury chloride (calomel) has been used as a treatment for syphilis and for toothache in children, and the preservative thimerosal (merthiolate) is added to childhood and adult vaccines. In dentistry, amalgam containing 50% mercury is still used in many countries, although efforts to phase out mercury are being made worldwide.

Mercury and other heavy metals affect the body mainly in two ways: through toxic and immunological reactions – the latter causing hypersensitivity or autoimmunity. Studies show that metals, including mercury, can be a risk factor for the development of various autoimmune diseases, such as autoimmune thyroiditis [6,7], multiple sclerosis [8], kidney disease [9], and unspecific symptoms such as chronic fatigue and myalgia [10,11]. Animal studies have shown that mercury and other metals, such as nickel, chromium, silver and gold, might either cause no harm or induce more – or less – severe diseases, such as skin disease or autoimmunity, depending on the individual genotype. The situation is more complex in humans, since the genes responsible for metal-induced pathologies are not yet identified. Endocrine status and chronic infections, which have been discussed previously [4,5], are factors that might increase the risk of sensitization.

Studies indicate that there is no safe

level of mercury in humans. Even with the same amount of exposure, there is great variation in both the *effects* of the exposure and the *levels* stored in the body. Many different factors determine the toxicity of mercury; among others, a person's genes will regulate if, and which, side effects occur. This is illustrated by the study of a family of seven who were living in a trailer contaminated by metallic mercury. Only one child developed flu-like symptoms, anorexia, and the inability to talk. The four other children had similar levels of mercury in the blood but no symptoms [12].

Generally, exposure to organic mercury (which is lipophilic) and to metallic mercury (which can turn into gas at room temperature) is more harmful than the less soluble inorganic mercury used in the past as a treatment for syphilis and in teething powders. Nevertheless, a small number of children treated with calomel (1 in 500) developed a neurologic disease, acrodynia, and a hypersensitivity reaction to inorganic mercury was suggested as the cause [13].

The immunological effects of metals, including mercury, are immunomodulation, allergy or autoimmunity. Metals may act as immunosuppressants or as immune adjuvants. Allergy induced by metals is called delayed-type hypersensitivity and manifests often as contact dermatitis. However, the development of autoimmunity associated with dental, orthopedic or other surgical implants has been described, and the clinical manifestations resemble ASIA syndrome [1,10,14,15]. In the case described by Segal and colleagues [1], the condition of the patient with cobalt and chromium allergy improved after revision surgery which replaced the metal component with a ceramic one.

The evaluation of mercury allergy is usually done by the application of mercury on the skin, known as patch testing. Mercury compounds have a strong allergenic potential, as demonstrated by the results of patch testing as well as in vitro studies [16,17]. Thimerosal, ethyl mercury thiosalicylate, like nickel, is one of the most frequent allergens in children and adolescents. Studies are needed to investigate if thimerosal (used together with aluminium, an adjuvant) in vaccines could cause chronic inflammation in a subset of susceptible children sensitized by thimerosal by repeated vaccination. Thimerosal-specific memory lymphocytes have been found in the blood of thimerosal patch test-positive subjects as well as in some children suffering post-vaccination side effects (discussed in a government reform committee hearing on the status of research into vaccine safety and autism, U.S. House of Representatives, 2002).

Although less studied, mercury-induced autoimmunity in humans has been described; for example, the occurrence of autoimmune glomerulonephritis in 1/100 people using a skin-bleaching ointment containing mercury [9].

However, mercury is not the only metal with autoimmune potential; other transition metals such as nickel, chromium, gold and silver, may function in a similar way. Transition metals have a strong affinity to sulfur groups present in two amino acids: methionine and cystine. Consequently, they form a strong bond with enzymes and other proteins in the body, altering their structure and rendering them “foreign” to the immune system and susceptible to an autoimmune attack [11].

Despite widespread exposure to metals, only a minority of people develop allergic and autoimmune disorders such as ASIA syndrome. In order to protect these individuals, identification of clinical and laboratory markers of susceptibility is of huge importance. Since knowledge of human genes and other factors involved in metal susceptibility is limited, phenotypic markers of the effect of metals can be used. One biomarker used for this purpose is

the lymphocyte transformation test, which measures the proliferation of memory lymphocytes after exposure to metals in vitro. The MELISA® test [17], and beryllium-specific lymphocyte proliferation test (BeLPT) [18] are two examples. The clinical relevance of such testing has been demonstrated [18,19]. BeLPT is used in some countries (Canada, Israel, USA) as part of the routine screening of beryllium-exposed workers. Early identification of sensitized individuals, even before the appearance of symptoms, enables the relocation of workers to a beryllium-free environment. This will minimize the risk for development of chronic beryllium disease.

In conclusion, mercury and other metals can be added to the list of environmental agents that exert both specific and non-specific effects contributing to ASIA syndrome. Together with screening for autoantibodies, metal-specific T cells can be used for the identification of individuals at risk. In future, this approach could also be used for the demonstration of agents triggering ASIA syndrome, for example siliconosis, which is proposed by Pineda et al. [2] as the cause of their patient's symptoms. This constitutes a new kind of disease to consider as part of the diagnosis of autoimmune syndromes that affect muscles and lungs. The demonstration of increased immunological stimulation of T lymphocytes by silica in women with siliconosis has been described previously [20]. Finally, in autoimmunity research, longitudinal studies of susceptible populations before and after reduction of exposure to triggers are likely to be more beneficial than traditional case-control studies.

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