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Review article

Delayed-type hypersensitivity to metals in connective tissue diseases and fibromyalgia

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ABSTRACT

Rheumatic diseases include a group of autoimmune disorders with environmental and genetic etiology that are characterized as a subgroup of connective tissue diseases (CTD). Rheumatoid arthritis (RA) often involves the small joints of the hands in a symmetrical fashion that can lead to loss of joint function, and RA, as well as Sjögren's syndrome (SS) and other rheumatic diseases, are often accompanied by sensitivity to metals. Numerous investigations on metal sensitivity were evaluated in this review. A detailed metal exposure history was collected by different evaluation of studies. In all subjects, the main source of metal exposure was nickel, mercury, gold, palladium, titanium, and chromium. All of SLE (systemic lupus erythematosus), RA and SS patients appeared to have an increased frequency of metal delayed-type hypersensitivity (DTH) (Type IV allergy). As dental restorative materials release minor amounts of their metals (including mercury, gold, and nickel), many adults are commonly exposed to these metal ions by vapor or corrosion into saliva. Metal-related DTH in these patients will induce an inflammatory response. Such inflammations are important factors in CTD progress. It is hypothesized that metal-specific T cell reactivity can act as an etiological agent in the propagation and chronification of rheumatic inflammation. The key responses of metal delayed-type hypersensitivity in autoimmunity are precipitating as an appealing challenge for further investigations.

1. Introduction

Rheumatoid arthritis (RA) is the most frequent type of autoimmune arthritis that is characterized as a disease with heterogeneity in phenotypes, chronic inflammatory disorder, low disease incidence, and geographic variation in prevalence. It usually presents in the third to the seventh decades (Sparks and Costenbader, 2014; Stejskal et al., 2015). Systemic autoimmune disorders are characterized by a variety of clinical features reflecting a multisystemic involvement (Iaccarino et al., 2013). It is supposed to have a 0.8% prevalence in the adult population (Di Giuseppe et al., 2014), with three times higher in women than men. These conditions are commonly described by swelling and pain in the musculoskeletal system, problems in the mobility, eyes, and lungs. It is a progressive and chronic persistent fluctuating synovial inflammation that can simulate fibromyalgia but often leads to loss of joint function and in some cases Sjögren's syndrome (SS) and also sensitivity to metals (Stejskal et al., 2015). Systemic lupus erythematosus (SLE), RA and SS belong to the group of connective tissue diseases (CTD) (Iaccarino et al., 2013). SLE is a chronic, heterogeneous, systemic autoimmune disorder (Izmirly et al., 2017) that can affect many different body systems, including the skin, joints, kidneys, heart, and brain (Askanase et al., 2012). RA is characterized by persistent and progressive synovial inflammation (Salt and Crofford, 2012), resulting in pain, swelling, stiffness, and loss of function in joints. SS attacks the immune cells and destroys the exocrine glands that produce tears and saliva (Delaleu et al., 2008). It has been demonstrated that similar to SLE, the prevalence of the disease is higher for women with a ratio of approximately 9:1 (Alani et al., 2017). It may occur alone (primary SS) or accompany other rheumatologic conditions (secondary SS). It has been revealed that 30% of patients with SLE and RA suffer secondary SS (Oğütcen-Toller et al., 2012). The incidence of SLE varies between different ethnical groups and races. The disorder is much more common in black people than in white people (Chakravarty et al., 2007). The annual incidence rate in Norway is 4.6 per 100,000 women, and 0.6 per 100,000 men (Nossent, 2001; Izmirly et al., 2017). More than 90% of lupus patients are women (Lahita, 1999; Urowitz et al., 2015), indicating rates are ~9 times higher in women in compared with men (Izmirly et al., 2017). SLE may occur at any age but occur most

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frequently in young women between the ages of 15 and 44 (Blank et al., 2009; Askanase et al., 2012). Symptoms vary from person to person. Almost all patients with SLE have joint pain and swelling. Some patients experience only mild rashes and arthritis; other SLE patients suffer from fatigue, debilitating fever, joint pain, or severe organ and/or life-threatening disease (Lahita, 2004).

RA often starts between ages 25 and 60, and the prevalence is higher in women and older people (Salt and Crofford, 2012). The disorder can affect any joint but is most common on the wrist and fingers. It can also affect eyes, mouth, and lungs. Left untreated RA may lead to the destruction of joints due to the destruction of cartilage and bone (McDougall, 2006; Salt and Crofford, 2012). Most of the RA patients experience a chronic, fluctuating disease course (McDougall, 2006). Also, severe fatigue could be seen in one out of every two rheumatic patients (Overman et al., 2016).

The prevalence of SS is four cases per 100,000 of the population, and nine of 10 patients with the disorder are women (Oğütcen-Toller et al., 2012). The disorder can affect any age but the onset is most common in people older than 40, and 2–5% of people aged 60 years and above have primary SS (Oğütcen-Toller et al., 2012). The main symptoms of SS are dry mouth and dry eyes. People with dry mouth may experience difficulty in chewing, swallowing, and speaking. They often also have a very high rate of tooth decay and mucosal infection (Oğütcen-Toller et al., 2012).

Fibromyalgia (FM) is a chronic rheumatic disease with an unknown etiology characterized by widespread pain in 11 of 18 tender points experienced for at least three months (Wolfe et al., 1990; Marques et al., 2017). Symptoms of the disease are general fatigue, widespread musculoskeletal pain and stiffness, cognitive impairment, sleep disorders, and cognitive and somatic symptoms that affect the quality of life (Salaffi et al., 2009; Arranz et al., 2010). FM often leads to working and social inability. The prevalence of FM is between 0.2% and 6.6% in the general population, 2.4–6.8% in women, 0.7–11.4% in urban areas, 0.1–5.2% in rural areas, and 0.6–15% in special populations (Arranz et al., 2010; Branco et al., 2010; Lawrence et al., 2008; Wolfe et al., 2013; Marques et al., 2017).

FM has a considerable overlap in non-musculoskeletal symptoms with allied conditions such as chronic fatigue syndrome (CFS)/myalgic encephalopathy (ME), tension headaches, migraine, affective disorders, and irritable bowel syndrome (Claliw, 1995; Sivri et al., 1996). This overlap is sufficiently impressive to warrant the question if it is at all correct, except for legal purposes (where it might perhaps still be convenient), to consider FM as a disease entity in its own right (with a distinctive etiopathogenesis of its own) rather than as a combination of various other diseases, known under other names, with the only important difference, as far as skeletal muscle pain is concerned, from better understood diseases such as e.g. tension headache. It has been suggested that mercury from dental amalgam fillings may play a role in the etiology of fibromyalgia (Kötter et al., 1995). Other studies suggest a link between nickel allergy and fibromyalgia (Marcusson, 1996; Marcusson et al., 1999; Regland et al., 2001). Since fibromyalgia appears to be an inflammatory disease, metal-induced inflammation might be one of the risk factors. Although C-reactive protein levels and cytokine pattern in FM patients are usually within the normal range, elevated levels of substance P in cerebrospinal fluid has been reported as a characteristic sign (Russell et al., 1994).

The underlying causes of autoimmune and rheumatic disorders are not fully known, but both genetic and environmental/lifestyle factors are considered to play a role. It has been reported that mercury, as well as gold, induces autoimmunity in genetically susceptible animals (Warfvinge et al., 1995; Bagenstose et al., 1999; Havarinasab et al., 2009; Suzuki et al., 2011; Stejskal et al., 2015). Research also indicates that some non-essential metals have a potential to induce or promote the development of autoimmunity and thereby also autoimmune disorders in man (Stejskal and Stejskal, 1999), in contrast to some micronutrients that apparently alleviate autoimmune diseases, e.g., vitamin D, A, and E and also selenium (Aaseth and Teigen, 1993; Rennie et al., 2003; Røsjø et al., 2014; Jeffery et al., 2016). Metal pathology may be due to toxic or allergic mechanisms where both may play a role. Various factors such as vaccines (Bruzzese et al., 2013), cosmetics (Kumagai et al., 1984; Kjøller et al., 2001), silicon (Sánchez-Guerrero et al., 1995), and cigarette smoke (Churg et al., 2002) have been suggested to play a role in the etiology of CTD. Research indicates that RA and SLE are associated with tobacco smoking (Hart et al., 2009; Selmi et al., 2011). Other known risk factors in RA include occupational exposure to silica and mineral oils, and traffic pollution (Hart et al., 2009) - all containing heavy and transition metals such as nickel, mercury, and palladium. Ambient particles (particulate matter), implicated in the pathogenesis of RA, may induce local lung inflammation as well as systemic inflammation. Increased frequency of SLE has been described in a community exposed to petroleum products and mercury (Dahlgren et al., 2007). Dental patients are exposed to mercury and other metals used in dental restorative materials via vapor, corrosion products in swallowed saliva, and direct absorption into the blood from the oral cavity (Eneström and Hultman, 1995).

The aim of the present article is to evaluate and discuss a possible disease-promoting role of metal intolerance in rheumatic diseases.

2. Nickel

Nickel allergy is the most common type of contact allergy in the Western world (Nielsen et al., 2001; Uter et al., 2005). It is often triggered by exposure to earrings, other nickel-containing jewelry (including piercing), belts, glasses, watches and trouser buttons (Dotterud and Falk, 1994; Pizzutelli, 2011). Nickel is used in silver and nickel plating, as well as in many types of alloys; e.g., white silver, stainless steel, and silver-like copper alloys (Hansen and Kroon, 2008). Other sources of nickel exposure include food, cigarette smoke, some detergents, soaps and cosmetics (Forsell et al., 1997; Schäfer et al., 2001). It may also be found as an impurity in amalgam and dental silver-alloys or as a component of dental crowns and bridges (Forsell et al., 1997). The patch test is the specific test of allergic contact dermatitis and explores local reactions of delayed cell-mediated hypersensitivity. The prevalence of nickel allergy is as high as about 20% of a general European population (Nielsen and Menné, 1992) but varies between populations (ESSCA Writing Group, 2008; Hansen and Kroon, 2008). Nickel allergy is more common in women, which may be due to women being more easily sensitized to various allergens and having a stronger immune response than men (Smith-Sivertsen et al., 1999). It may in part also be due to a use of nickel-containing earrings in women (Sterzl et al., 1999). In men, occupational exposure is the most responsible factor for raising sensitization to nickel (Pizzutelli, 2011). Nickel has been shown to induce scleroderma-related autoantibodies and cutaneous sclerosis in rats (Al-Mogairen et al., 2010).

Nickel is considered to be an essential nutrient in mammals (Stangl and Kirchgessner, 1996), although biochemical functions are unknown, and studies from Finland have shown that more than 90% of the total dietary intake, similarly as for manganese, comes from plant foods, spices and plant-derived beverages (Bjørklund et al., 2017a). Nickel occurs in soil, water, air and in the biosphere. It is present in most of the constituents of a normal diet and is a very common metal contained in many everyday objects. Most of the nickel produced worldwide is used for the production of stainless steel (Sharma, 2007; Pizzutelli, 2011). Other sources of exposure are cigarette smoke, and piercing (Dotterud and Falk, 1994; Schäfer et al., 2001). The daily intake of nickel from food is highly variable both among different populations and in a single individual, in different seasons and even on different days (Pizzutelli, 2011). The average daily intake of nickel in humans is approximately 0.2–0.6 mg (Grandjean, 1984). A half-part of the average daily nickel supply is provided by cereals and pulses, followed by fats, dairy products and fruits (Tsoumbaris and Tsoukali-Papadopoulou, 1994).

The patch test that is the used as a specific test of allergic contact