Metal-induced inflammation triggers fibromyalgia in metal-allergic patients

Vera Stejskal 1, Karin Öckert 2, Geir Bjorklund 3
1 Department of Immunology, University of Stockholm, Stockholm, Sweden
2 Gårdatandläkarna, Gothenburg, Sweden
3 Council for Nutritional and Environmental Medicine, Mo i Rana, Norway

Correspondence to: Prof. Vera Stejskal,
August Wahlströms väg 10, 18231 Danderyd, Stockholm, Sweden.
TEL: +46 8753 2322; FAX: +44 20 8711 5958; E-MAIL: vera@melisa.org

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Abstract

BACKGROUND: Fibromyalgia (FM) is a disease of unknown aetiology. Inflammation could be one of the mechanisms behind this disease.

OBJECTIVES: We studied the frequency and clinical relevance of metal allergy in FM patients.

METHODS: Fifteen female FM patients were included in the study. Metal allergy was measured by a lymphocyte transformation test, MELISA®. Ten healthy age-matched women were used as controls for in vitro studies. Reduction of metal exposure in the FM patients was achieved by replacement of dental metal restorations and by the avoidance of known sources of metal exposure. Objective health assessment was performed 5 years after treatment. Subjective health assessment was established by a questionnaire, completed 2, 5 and in some cases 10 years after the start of the study. Follow-up MELISA was also performed.

RESULTS: All FM patients tested positive to at least one of the metals tested. The most frequent reactions were to nickel, followed by inorganic mercury, cadmium and lead. Some healthy controls responded to inorganic mercury in vitro but most of the tests were negative. Objective examination 5 years later showed that half of the patients no longer fulfilled the FM diagnosis, 20% had improved and the remaining 30% still had FM. All patients reported subjective health improvement. This correlated with the normalisation of metal-specific responses in vitro.

CONCLUSION: Metal allergy is frequent in FM patients. The reduction of metal exposure resulted in improved health in the majority of metal-sensitized patients. This suggests that metal-induced inflammation might be an important risk factor in a subset of patients with FM.

Abbreviations:

FM - fibromyalgia
CFS - chronic fatigue syndrome
ME - myalgic encephalopathy
SI - stimulation index
MCS - multiple chemical sensitivity
Au - gold
EtHg - ethyl mercury
Hg - mercury (inorganic)
MeHg - methyl mercury
Ni - nickel
Pb - lead
Pd - palladium
PhHg - phenyl mercury
Sn - tin
Thim - thimerosal
Ti - titanium

INTRODUCTION

Fibromyalgia (FM) is a disease of unknown aetiology. It is characterised by widespread pain in 11 of 18 tender points experienced for at least three consecutive months (Wolfe et al. 1990). Patients with FM suffer from general fatigue, widespread musculoskeletal pain and stiffness, cognitive impairment, sleep disorders and other symptoms that affect their quality of life (Salaffi et al. 2009; Arranz et al. 2010). The disease also has a considerable overlap in non-musculoskeletal symptoms with allied conditions such as chronic fatigue syndrome/myalgic encephalopathy (CFS/ME), post-viral fatigue syndrome, migraine and tension headaches, affective disorders and irritable bowel syndrome (Clauw 1995; Sivri et al. 1996; Hamilton et al. 2005). Fibromyalgia often leads to working and social inability and no curative treatment is currently available. The prevalence of FM is 0.5% to 6% in the general population of the North America and Europe (Arranz et al. 2010; Branco et al. 2010; Lawrence et al. 2008; Wolfe et al. 2013). As FM is a frequently occurring condition, better knowledge is warranted to find an effective treatment.

It has been suggested that mercury from dental amalgam fillings may play a role in the aetiology of FM (Kötter et al. 1995). Other studies suggest a link between allergy to nickel and FM (Marcussen et al. 1999; Regland et al. 2001). Since signs of inflammation have been described in patients with FM (Kadetoff et al. 2012), metal-induced inflammation may be a risk factor. The present study aims to investigate if metals ubiquitous in our environment, such as nickel, and metals commonly used in dentistry might trigger inflammation in FM patients.

METHODS

Fifteen female patients with primary FM (mean age 47.6 years, range 34–66 years) provided informed consent to participate in this study. A specialist in rheumatology diagnosed the patients according to the American College of Rheumatology 1990 criteria for FM (Wolfe et al. 1990). The mean duration of illness at the time of study was 11 years (range 2–29 years). All patients had clinical metal allergy, such as eczema when wearing cheap metal earrings. Other allergies to food, pollen and drugs were also frequent and were reported by 80% of the patients. The evaluation of oral health, performed by one of our group (Karin Öckert), showed that all patients had amalgam fillings. All but three also had restorations containing gold, such as crowns and bridges. Most of the patients had root-filled teeth; some containing gold-plated metal posts (Table 1). Other known metal exposures were: living in a polluted area (near motorway, airport or crematorium), exposure to cigarette smoke, occupational exposure or contact with occupationally exposed family member. Further sources of metal exposure were thimerosal-containing vaccines and pills coated with titanium dioxide. All patients underwent amalgam replacement. In most patients, other metal restorations were removed as well. Maximal precaution was taken to minimize the metal release. Metal restorations were replaced with metal-free alternatives such as composites and non-metallic ceramics. In some patients, titanium-containing medication was replaced with a titanium-free alternative.

Five years after treatment, a rheumatologist evaluated the patients’ health. Subjective health assessment was done by patients using a questionnaire; 2, 5 and in some cases 10 years after the treatment.

In vitro testing

The presence of metal allergy in FM patients was measured by an optimized lymphocyte transformation test, MELISA (Stejskal et al. 1994; 2006; Valentine-Thon & Schiwara 2003; Valentine-Thon et al. 2006).

This test uses the property of memory cells to be re-stimulated by a specific allergen in vitro. If memory cells are present in the blood, they start to divide and differentiate to so-called lymphoblasts. When allergens are low-molecular substances, allergen-specific memory cells are found in the blood of patients experiencing exposure-related clinical symptoms but not in the majority of healthy subjects (Stejskal et al. 1986; 1990; 1999; Stejskal & Forsbeck 1996; Tibbling et al. 1995). Lymphocytes isolated from peripheral blood were cultivated for 5 days with various concentrations of metal salts in vitro. Lymphocyte proliferation was measured by the uptake of radiolabeled thymidine and calculated as a Stimulation Index (SI): the quotient of counts per minute in metal-treated cultures and mean counts per minute from control cultures cultivated in the absence of metal salts. SI <3 was regarded as negative, SI ≥3 was taken as a positive response and SI ≥10 as a strongly positive response. In addition to objective radioisotope measurement, the number of lymphoblasts in cultures was morphologically evaluated.

RESULTS

Lymphocyte responses to metals in 15 patients with FM and in 10 healthy controls are shown in Table 2. All FM patients responded in vitro to one or more of the metals tested. The most frequent reaction was to nickel followed by inorganic mercury and phenyl mercury. One third of patients responded to palladium and tin and one fifth to gold. Only patients who had both amalgam and gold restorations responded to gold and palladium salts in vitro; the three patients exposed to amalgams only did not. Titanium was tested in the form of titanium dioxide and induced low positive responses in 40% of FM patients. Four patients responded to thimerosal, a mercury-containing preservative. None of the patients responded to copper, silver or platinum (data not shown).
Three healthy controls responded to mercury with weak positive responses; one of the responders showed positive response to titanium dioxide as well.

Objective assessment performed by a rheumatologist 5 years after treatment, showed that half of the patients no longer fulfilled the diagnostic criteria of FM and thus were regarded as “cured”. One fifth of the patients had less trigger points than the 11 necessary for the diagnosis of FM and were therefore labelled as “possible FM”. The remaining one third of the patients still fulfilled the criteria for FM. Subjective health evaluations was done by patients 2, 5 and 10 years following treatment. All patients reported improvement of health. Follow-up MELISA, performed at the same time as the subjective evaluation, showed a marked decrease in lymphocyte reactivity to metals in vitro compared to the reactivity at the beginning of the study (Table 3).

DISCUSSION

In this small cohort of women with primary FM, metal allergy to nickel, mercury and other metals was frequent. Following reduced exposure to metals, most FM patients experienced long-term health improvement. Similar findings in CFS patients have previously been reported (Stejskal et al. 1999; 2006; Sterzl et al. 1999). In those studies, as well as in the current study, the most frequent metal allergens were nickel and inorganic mercury. Two recent studies, one from France and one from Italy, reached the same conclusion. In the French study, 100 patients with FM and CFS/ME were tested for metal allergy by the MELISA test. Nickel and mercury were found to be the most frequent sensitizers (Tournesac P. Fibromyalgia: nickel and mercury hypersensitivity in general practice. Poster presented at: Controversies in Rheumatology and Autoimmunity; 2013 April 4–6; Budapest, Hungary.)

In the second study, Pigatto and his colleagues from Italy studied 41 patients diagnosed with multiple chemical sensitivity (MCS) (Pigatto et al. 2013). Metal allergy had been diagnosed with patch testing and MELISA testing in vitro. The authors reported that 91% of the patients (39 women and 2 men) were sensitized to at least one metal, indicating a very high presence of metal allergy in the Italian MCS cohort. This high frequency of metal allergy in MCS patients corroborates the data obtained in this study. Another Italian group (De Luca et al. 2010) compared serum cytokine profiles in 226 MCS patients with the corresponding cytokine levels in 218 healthy Italians. Significant up-regulation of pro-inflammatory cytokines such as interferon (IFN)-gamma was found in the MCS group compared to controls.
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Other findings, such as changes in free radical/antioxidant homeostasis, and low levels of glutathione are all compatible with a metal-induced pathology in the MCS group.

Most patients suffering from nonspecific symptoms fulfilling the criteria of FM, CFS/ME and MCS, are women. It is well known that women suffer more frequently from nickel allergy than men. This may be due to exposure to nickel-containing earrings (Sterzl et al. 1999) as well as by widespread use of nickel-containing cosmetics (Liu et al. 2013). In men, occupational exposure is the most frequent factor behind sensitization to nickel (Pizzutelli 2011). Nickel occurs in soil, water, air and in the biosphere. It is present in most of the constituents of a normal diet and also in many metallic everyday items. In some countries, metal alloys with a high concentration of nickel are still used in dental crowns and bridges. Nickel can also be present as an impurity in amalgam and dental gold alloys (Forsell et al. 1997). Other sources of nickel exposure are cigarette smoke and piercing (Dotterud & Falk 1994; Schäfer et al. 2001).

Patch testing is the gold standard for diagnosis of delayed cell-mediated hypersensitivity. The prevalence of positive patch tests to nickel in the general population in Europe is about 20% (Nielsen & Menne 1992).

### Tab. 2. Lymphocyte responses to metals in patients with fibromyalgia and healthy controls expressed as Stimulation Index.

<table>
<thead>
<tr>
<th>Code</th>
<th>Inorganic mercury</th>
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<th>Tin</th>
<th>Copper</th>
<th>Silver</th>
<th>Gold</th>
<th>Palladium</th>
<th>Platinum</th>
<th>Lead</th>
<th>Cadmium</th>
<th>Titanium dioxide</th>
<th>Methyl mercury</th>
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1. P1–P15: patients with FM, C1–C10: healthy controls, SI: Stimulation index
2. SI ≥3 are positive responses and are shown in **bold**, SI ≥10 indicates strongly positive responses are shown in **bold cursive**, ND: Not done
Marcussen et al. (1999) reported on the increased prevalence of nickel positive patch tests in Swedish patients with FM and CFS/ME. In a previous study from this group, 397 patients were referred for metal patch testing in Sweden. Over 50% of the patients had systemic symptoms such as fatigue and muscular pain, while local oral symptoms were less frequent (Marcussen 1996). This confirms the in vitro data showing increased lymphocyte responsiveness in this patient group (Stejskal et al. 1994; Sterzl et al. 1999).

Muris and Feilzer (2006) describe two patients with a known nickel allergy that experienced the disappearance of symptoms and general health improvement after removal of nickel-containing dental appliances (a bridge and orthodontic wire respectively). One of the patients, a 45-years old woman, suffered from profound fatigue, migraine and joint pain of the wrists, hands and fingers. Two months after the removal of a nickel-containing orthodontic wire, the patient’s symptoms disappeared. Regland et al. (2001) investigated 204 women that fulfilled the criteria for FM and CFS/ME. About half of the patients in the present study had a positive history of nickel-induced contact dermatitis.

The second most common allergen found was inorganic mercury. Dental amalgams commonly consist of 50% mercury, ~22–32% silver, ~14% tin, ~8% copper, and other trace metals (Ferracane 2001). Mercury released from dental amalgams makes the predominant contribution to human exposure to inorganic mercury and vapour in the general population (Clarkson et al. 1988). No exposure to mercury vapour can be considered totally harmless since mercury vapour has no toxic threshold (IPCS 1991).

All mercury salts tested have immunomodulatory potential (Shenker et al. 1992) as well as allergenic properties (Stejskal et al. 1996). One third of the FM patients tested positive to thimerosal and nearly half reacted to phenyl mercury in MELISA. Both thimerosal, also called Merthiolate™, and phenyl mercury are organic mercury compounds used as antiseptics and preservatives in eye drops and vaccines (Rietschel & Fowler 2001). Organic mercurials are strong allergens and induce local and systemic delayed type hypersensitivity (Tosti et al. 1989; Seidenari et al. 2005). In our study, three out of four patients responding to thimerosal in vitro responded to ethyl mercury as well.

Lymphocyte responses to methyl mercury were rarely detected in this study. The most common source of methyl mercury in humans is from polluted fish. Methyl mercury is also produced by the anaerobic bacteria. This is important to note that memory lymphocytes induced by various mercury compounds do not cross-react (Santucci et al. 1998; Tosti et al. 1989). Therefore, to determine the presence of possible mercury allergy, both organic and inorganic mercury should be tested.

One third of the patients, but none of the controls, reacted to gold, palladium and tin. These metals are frequently used in dental restorations and the allergenic potential of gold and palladium has been discussed previously (Marcussen 1996).

Titanium is generally considered to be a safe option for metal allergic patients, although the risk of titanium allergy might be increased in patients already sensitized to other metals (Hallab et al. 2001). Around 40% of our FM patients tested positive to titanium dioxide. In addition to the titanium used in dentistry and orthopedic surgery, titanium is frequently used as a white pigment (E171) in pharmaceuticals, sunscreens, cosmetic products, toothpastes, foods and other items. As a consequence of a positive MELISA test to titanium dioxide, some FM patients limited their exposure to for example titanium-containing cosmetics and requested titanium-free medication from their physicians. Avoidance of titanium-containing cosmetics in a strongly titanium-positive patient, who was required to wear titanium-containing make up daily, resulted in resolution of her eczema and joint pain (Müller and Valentin-Thon 2006).

Fibromyalgia is often present as a co-morbidity with other inflammatory diseases. In a recent study, the frequency of metal allergy was determined in 41 patients suffering from systemic lupus erythematosus, rheumatoid arthritis and Sjögren’s syndrome (Stejskal V and Reynolds T. Metal allergy – the missing link in autoimmune connective tissue disorders? Poster session presented at: Controversies in Rheumatology and Autoimmunity (2013 April 4–6; Budapest, Hungary).

### Tab. 3. Frequency of positive lymphocyte responses to metals in fibromyalgia patients.

<table>
<thead>
<tr>
<th>Metal</th>
<th>Before treatment</th>
<th>%</th>
<th>After treatment</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercury</td>
<td>6/9</td>
<td>67%</td>
<td>0/9</td>
<td>0%</td>
</tr>
<tr>
<td>Phenyl mercury</td>
<td>2/4</td>
<td>50%</td>
<td>0/4</td>
<td>0%</td>
</tr>
<tr>
<td>Tin</td>
<td>3/3</td>
<td>100%</td>
<td>1/3</td>
<td>33%</td>
</tr>
<tr>
<td>Gold</td>
<td>3/5</td>
<td>60%</td>
<td>1/5</td>
<td>20%</td>
</tr>
<tr>
<td>Palladium</td>
<td>3/7</td>
<td>43%</td>
<td>1/7</td>
<td>14%</td>
</tr>
<tr>
<td>Lead</td>
<td>2/5</td>
<td>40%</td>
<td>1/5</td>
<td>20%</td>
</tr>
<tr>
<td>Cadmium</td>
<td>4/5</td>
<td>80%</td>
<td>0/5</td>
<td>0%</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>4/6</td>
<td>67%</td>
<td>0/6</td>
<td>0%</td>
</tr>
<tr>
<td>Methyl mercury</td>
<td>2/7</td>
<td>29%</td>
<td>0/7</td>
<td>0%</td>
</tr>
<tr>
<td>Thimerosal</td>
<td>2/5</td>
<td>40%</td>
<td>0/5</td>
<td>0%</td>
</tr>
<tr>
<td>Nickel</td>
<td>8/11</td>
<td>73%</td>
<td>3/11</td>
<td>27%</td>
</tr>
<tr>
<td>Total</td>
<td>39/67</td>
<td>58%</td>
<td>7/67</td>
<td>10%</td>
</tr>
</tbody>
</table>

1) Number of positive tests/total tests
2) The treatment consisted of replacement of metal with ceramic or composite restorations as well as removal of other known sources of metal exposure.

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The results showed that the majority of the patients had clinical metal allergy, and responded in vitro to nickel, mercury, gold, and palladium. In one patient, the symptoms of rheumatoid arthritis resolved after removal of stainless steel chest wires containing nickel, molybdenum and chromium; metals that the patient reacted to in the MELISA test. These findings, as well as previously published data (Stejskal et al. 2006; Prochazkova et al. 2004), suggest that metal-induced allergy might be a risk factor not only in CFS/ME, MCS and FM but also in rheumatoid diseases.

In conclusion, dental and environmental metals can trigger chronic inflammation in metal-sensitized FM patients. Reduction of inflammation by removal of these specific triggers could present a new way to treat not only FM but also other chronic inflammatory diseases.

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