

Metal-induced inflammation triggers fibromyalgia in metal-allergic patients

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

Tab. 1. Metal exposure, positive lymphocyte responses and health outcome in fibromyalgia patients.

Patient code	Age	Duration of symptoms (years)	Reported metal exposure	Smoker	Dental exposure ¹	Lymphocyte responses to metals <i>in vitro</i> ²	Health status 5 years after treatment
P5	50	21	Vaccines	Yes	16A, 3G, 3RF	Hg, PhHg, Pd , MeHg, EtHg, Thim, Ni	cured
P2	63	3	Orthodontics, environment	Yes	9A, 4G, 5RF	PhHg, Au , Pd, Pb, Ti, Ni	cured
P14	51	20	Vaccines	No	12A, 1G, 2RF	Sn, Ni	cured
P6	50	15	Not reported	Yes	16A, 1G, 1RF	Hg , PhHg, Au, Ti, EtHg, Thim, Ni	cured
P7	44	8	Not reported	Yes	12A, 4RF	Hg, Cd	cured
P15	39	19	Anti-D globulin injection	Yes	15A	Hg	cured
P13	66	2	Occupational	No	13A	Hg, PhHg , Pb, Cd, Ni	cured
P9	50	3	Orthodontics, environment	No	11A, 1G	Cd	possible FM
P10	42	21	Vaccines	Yes	15A, 3G, 2RFB	Pd, Cd, MeHg, Thim, Ni	possible FM
P12	34	10	Not reported	Yes	18A	Ti, Ni	possible FM
P1 ³	53	29	Husband works at car factory	No	1A, 6G, 2RFB	Hg , PhHg, Sn, Au , Pd, Pb, Ti, Ni	FM
P3 ⁴	49	10	Lived near chemical factory	Yes	7A, 3G, 1RF	Hg, Sn, Pb, Ni	FM
P8	40	5	Father welder, vaccines, environment	No	13A, 1G, 4RFB	Hg, PhHg, Au, Pd, Pb, Cd, Ti, MeHg, EtHg, Thim, Ni	FM
P11 ⁵	54	7	Anti-D globulin injection	Yes	4A, 6G, 2RF, Ti	Sn, Cd, Ni	FM
P4	53	7	Contact lenses	No	6A, 4G, 2RFB, 2Ti	Hg, PhHg , Sn, Pb, Cd, Ti, Ni	not available

1. Number of amalgam fillings (A), gold restorations (G), root fillings (RF), root fillings with gold-plated brass pins (RFB), titanium crown and screw (Ti)

2. Positive lymphocyte responses to metals are shown; strongly positive responses are in bold

3. Onset of FM following placement of root filling containing lead and phenyl mercury

4. Worsening of FM after placement of gold bridge

5. Worsening of FM after placement of titanium crown; patient refused to replace the crown

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

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

Code ¹	Inorganic mercury	Phenyl mercury	Tin	Copper	Silver	Gold	Palladium	Platinum	Lead	Cadmium	Titanium dioxide	Methyl mercury	Ethyl mercury	Thimerosal	Nickel
P1	15.2²	3.6	5.3	0.9	2.1	11.0	3.2	2.0	6.6	1.7	3.0	1.3	ND	2.6	4.5
P2	2.6	3.3	1.4	1.0	1.1	14.0	3.0	2.5	4.0	2.3	3.1	1.6	1.4	1.3	11
P3	6.1	2.9	5.4	1.6	0.7	1.4	2.7	1.1	3.6	1.6	1.5	1.4	1.9	1.5	12
P4	20	12.9	8.1	1.0	1.0	2.5	1.5	1.1	8.6	4.3	9.6	2.2	2.8	1.9	3.1
P5	6.1	6.2	0.8	0.5	0.5	2.0	13.2	0.6	2.8	2.4	2.6	5.1	6.1	6.3	18
P6	19	4.3	0.8	1.3	1.0	4.4	2.3	1.6	1.6	2.9	4.8	1.3	4.9	6.7	17
P7	9.4	ND	2.0	ND	ND	ND	ND	ND	ND	3.8	ND	1.9	ND	ND	2.6
P8	9.2	3.6	0.8	1.7	2.1	8.0	4.0	2.3	3.4	3.8	4.5	6.2	6.0	4.9	17
P9	2.0	1.5	1.2	0.8	1.9	1.9	1.6	1.2	0.9	5.9	1.3	1.2	0.9	1.4	2.3
P10	1.4	1.0	1.0	2.5	0.9	1.4	5.6	1.2	0.9	3.3	1.5	4.5	0.5	4.5	90
P11	1.9	1.2	3.6	1.1	1.0	1.8	1.9	1.5	1.4	4.0	2.3	2.7	0.3	1.3	7.4
P12	1.6	1.2	1.2	1.0	1.0	1.2	1.7	1.0	1.0	2.7	3.2	2.9	1.6	2.1	19
P13	10	11	1.0	0.3	0.5	2.9	0.8	0.4	3.6	3.6	2.1	2.1	0.9	1.1	3.6
P14	1.7	1.4	5.4	0.4	0.7	1.0	1.9	1.0	0.8	1.3	1.0	1.9	1.1	1.5	29
P15	3.6	1.0	1.4	0.4	0.6	1.4	1.3	1.2	1.5	2.1	1.5	2.4	0.5	0.7	2.5
C1	1.6	2.2	1.4	0.8	0.9	0.7	1.0	0.9	1.4	1.5	1.4	1.4	1.1	0.3	0.9
C2	1.9	ND	0.1	0.5	0.7	2.2	ND	0.7	0.4	1.1	1.0	1.4	0.1	0.9	2.5
C3	0.5	0.3	1.2	0.7	0.6	0.8	1.3	0.8	0.8	1.0	0.9	1.1	0.9	0.9	0.9
C4	4.0	ND	1.3	0.6	0.9	0.8	0.8	0.7	1.1	1.5	2.1	ND	ND	0.7	1.3
C5	0.7	0.7	2.3	1.0	1.0	1.0	1.2	0.9	1.0	1.2	1.1	1.0	1.1	1.0	2.6
C6	4.4	3.1	1.4	0.9	0.7	1.0	1.1	0.9	1.7	1.8	1.5	1.2	1.0	0.8	2.6
C7	1.8	3.9	1.1	0.7	0.5	2.0	2.0	0.6	1.4	1.6	1.2	2.5	1.5	1.3	1.0
C8	1.7	2.4	1.2	0.7	1.3	1.7	1.6	0.5	1.5	1.1	1.7	1.4	1.2	0.9	2.0
C9	4.4	2.9	1.2	0.5	1.1	2.8	2.5	1.2	1.1	1.2	3.7	1.7	0.2	1.5	1.6
C10	0.7	0.8	0.5	ND	ND	0.5	0.8	0.5	0.8	1.2	0.6	ND	ND	0.3	ND

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

to healthy subjects (De Luca *et al.* 2010). 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).

Marcusson *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 (Marcusson 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 profound fatigue disappeared. Regland *et al.* (2001) investigated 204 women that fulfilled the criteria for both 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 conversion of metallic mercury through oral and gastrointestinal bacteria (Liang & Brooks 1995). It 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.

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

Metal	Before treatment ^{1,2}	%	After treatment	%
Mercury	6/9	67%	0/9	0%
Phenyl mercury	2/4	50%	0/4	0%
Tin	3/3	100%	1/3	33%
Gold	3/5	60%	1/5	20%
Palladium	3/7	43%	1/7	14%
Lead	2/5	40%	1/5	20%
Cadmium	4/5	80%	0/5	0%
Titanium dioxide	4/6	67%	0/6	0%
Methyl mercury	2/7	29%	0/7	0%
Thimerosal	2/5	40%	0/5	0%
Nickel	8/11	73%	3/11	27%
Total	39/67	58%	7/67	10%

¹⁾ Number of positive tests/total tests

²⁾ The treatment consisted of reduction of metal exposure by replacement of dental metals with ceramic or composite restorations as well as removal of other known sources of metal exposure

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 (Marcusson 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 Valentine-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).

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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