Nickel Allergy Is Found in a Majority of Women with Chronic Fatigue Syndrome and Muscle Pain– And May Be Triggered by Cigarette Smoke and Dietary Nickel Intake

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ABSTRACT. Two hundred and four women with chronic fatigue and muscle pain, with no signs of autoimmune disorder, received immune stimulation injections with a *Staphylococcus* vaccine at monthly intervals over 6 months. Good response was defined as a decrease by at least 50% of the total score on an observer's rating scale. Nickel allergy was evaluated as probable if the patient had a positive history of skin hypersensitivity from cutaneous exposure to metal objects. The patient's smoking habits were recorded. Fifty-two percent of the patients had a

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positive history of nickel contact dermatitis. There were significantly more good responders among the non-allergic non-smokers (39%) than among the allergic smokers (6%). We also present case reports on nickel-allergic patients who apparently improved after cessation of cigarette smoking and reducing their dietary nickel intake. Our observations indicate that exposure to nickel, by dietary intake or inhalation of cigarette smoke, may trigger systemic nickel allergy and contribute to syndromes of chronic fatigue and muscle pain.

KEYWORDS. Nickel allergy, cigarette smoking, dietary nickel, fatigue, muscle pain

INTRODUCTION

Nickel is a common sensitizing agent responsible for the high prevalence of allergic contact dermatitis. However, the health hazards of nickel allergy with regard to diffuse and general symptomatology, such as chronic fatigue and muscle pain, appear not to be fully understood and are probably underestimated.

The prevalence of nickel contact dermatitis among women has increased remarkably and there is a clear relationship between ear piercing and induction of nickel allergy (1). In two Norwegian unselected populations, the prevalence figures for women were reported to be 27.5 and 31.1%, respectively (2). Although in the same study the prevalence for men was 5%, the modern fashion of piercing also anticipates an increasing prevalence among men (3). Nickel allergy is associated with fatigue syndromes with or without autoimmunity (4). In women with chronic fatigue syndrome the prevalence of nickel contact dermatitis has been reported to be as high as 52% (5).

Recently we chanced upon findings regarding nickel allergy in a study set up with quite another purpose. Immune stimulation with a *Staphylococcus* vaccine was tested in clinical trials of female patients with chronic fatigue and muscle pain (see 6 for a preliminary report). The patients received subcutaneous injections at monthly intervals. The results are interesting, showing clinical improvement in a substantial number of patients. Moreover, we unexpectedly found that nickel allergy influenced the efficiency of the treatment and that nickel allergy was interrelated with cigarette smoking.

The primary incidental finding of nickel sensitization came out of a Memory Lymphocyte Immuno Stimulation Assay (MELISA®) in 16 patients who did not improve or had reacted adversely to the vaccine treatment (7). MELISA® is an optimized lymphocyte proliferation test (8). The purpose of using MELISA® in the study was to check whether the unresponsiveness to the vaccine could be due to hypersensitivity to the preservative thiomersal (*syn*. merthiolate, thimerosal). In addition, reactivity was tested to various metals such as nickel, although the vaccine compound does not contain nickel. The main finding was that 13 of the 16 tested patients (81%) reacted strongly against nickel *in vitro* (7). Moreover, we found a substantial number of cigarette smokers among the non-responding and MELISA®-positive nickel-allergic patients, whereas the combination of smoking and contact allergy was hardly seen at all in the group of patients rated as good responders. Thus, we were made attentive to the intriguing possibility that a connection might exist between nickel allergy and cigarette smoking. As nickel and a variety of other metals occur in trace amounts in mainstream cigarette smoke (9), it would be a plausible suggestion that exposure to cigarette smoke may be nickel-sensitizing or, at least, a potential trigger of hyperreactivity in a person already sensitized to nickel.

The aim of this study was to further explore the impact of nickel allergy and its interrelation with cigarette smoking in a large number of women with chronic fatigue and muscle pain included in clinical trials of immune stimulation therapy.

PATIENTS AND METHODS

Two hundred and four women with chronic fatigue and muscle pain, aged between 21 and 73 years (mean ± SD, 48 ± 11), had been included in clinical trials and treated for at least 6 months with subcutaneous injections of a staphylococcus vaccine (Staphypan Berna®) at monthly intervals. Each woman had a disorder that fulfilled the criteria for both fibromyalgia (10) and chronic fatigue syndrome (11), with no obvious sign of autoimmune disorder. The trials were approved by the Ethics Committee of Göteborg University.

Treatment outcome was rated using the Comprehensive Psychopathological Rating Scale (CPRS), an observer's rating scale previously described (6).

A good responder was defined as a person in whom the symptomatology evaluated by the CPRS, i.e., the CPRS total score, was decreased by at least 50% 6 months after the initiation of the treatment.

Nickel allergy was evaluated as possible/probable if the patient had a positive history of skin hypersensitivity from cutaneous exposure to metal objects such as ear rings (most common), other jewelry, wrist watches and/or clothing fasteners, e.g., jeans buttons.

RESULTS

Table 1 shows the numbers and percentages of good responders in subgroups of patients divided according to smoking habits and histories of contact allergy.

There were no significant differences in baseline CPRS score between the nickel-allergic smokers and the others.

Among the patients, 52% had a history of possible/probable nickel contact dermatitis and 28% were habitual cigarette smokers.

Thirty-seven percent (36/98) of the non-allergic and 16% (17/106) of the allergic patients were good responders, which is a statistically significant difference according to Fischer's exact 2-tailed test ($p < 0.0009$).

According to the Chi-square test, there were significant differences ($p = 0.02$) regarding the number of good responders in the subgroups (Table 1). The most obvious difference was found between non-allergic non-smokers and allergic smokers, which reached statistical sig-

TABLE 1. Numbers and percentages of good responders in subgroups of patients divided according to smoking habits and histories of contact allergy

Subgroups of patients	Number	Good responders	
		Yes	No
Non-allergic non-smokers	75	29 (39%)	46
Non-allergic smokers	23	7 (30%)	16
Allergic non-smokers	72	15 (21%)	57
Allergic smokers	34	2 (6%)	32
Total	204	53 (26%)	151

nificance according to Fischer's exact 2-tailed test ($p < 0.0005$) even after adjusting for multiple testing (Bon-Ferroni method).

Case Reports

We present two case reports on patients who responded favourably after cessation of cigarette smoking (case 1) and reduced intake of nickel-rich food items (case 2):

Case 1: At baseline, a formerly healthy 36-year-old woman had a troublesome sinusitis with headaches, blurred visual sharpness and a left hand that readily went numb. One month later, she experienced fatigue and diffuse muscle pain. Her mother has fibromyalgia. Routine laboratory check-outs, including thyroid hormones, were normal. One year after the onset, she was placed on treatment with Staphypan Berna® and received monthly injections that caused no side effects. However, she was not improving and after 7 months of treatment she was as fatigued as before. At that time we had learned (see above) that the combination of nickel allergy and cigarette smoking may predict a poor outcome of vaccine treatment. She was known to be nickel-sensitive and used to smoke 15 cigarettes per day. When she heard of our experience she became motivated to give up smoking with the aid of nicotine chewing gums. She used to have a high intake of chocolate and liquorice and regularly had oatmeal porridge for breakfast; all of which she dismissed from that time and on. Two months later, she reported that she was healthy and no longer had any of the symptoms she had experienced for more than a year. She no longer had use of analgesics and the improvement held on for more than 6 months. However, after taking up smoking again she relapsed into fatigue and muscle pain symptoms.

Case 2: A 54-year-old non-smoking woman who had had fibromyalgia and chronic fatigue syndrome for many years was treated with Staphypan Berna®. After the injections, she became worse and was bed-ridden with headaches and severe fatigue and pain for a week. MELISA® was negative for the preservative thiomersal but strongly positive for nickel. She was not aware of any contact allergy. She had symptoms of irritable bowel syndrome (IBS) but knew of no specific food intolerance. Advised to try a diet she started to avoid food items known to be high in nickel content such as crustaceans, chocolate, oatmeal products and certain vegetables (mainly broccoli and spinach). This made her experience improved well-being. After 3 months

on this type of diet she reported that she had not been in such good condition for many years. After 6 months she is still improving. However, when eating nickel-rich food items she experiences an increased fatigue within two hours and the fatigue may not vanish until 3-4 days later.

DISCUSSION

Metal contact allergy is mostly due to nickel which is ubiquitous in the environment. Sources of human exposure are air, water, food, and tobacco. Food is the main route of uptake followed by cigarette smoke. The dietary intake of nickel is highly variable; the most reported averages are 200-300 micrograms/person/day (12). Consumption of nickel-rich food items may increase the nickel intake from 150 to 900 micrograms/person/day or more (13). Certain food items have very high nickel contents: high levels have been found in legumes, spinach, lettuce, soya beans, oatmeal, and nuts. Certain products, such as baking-powder and cocoa powder, contain excessive amounts of nickel, perhaps because of leaching of nickel during the manufacturing process. Soft drinking-water and acid beverages may dissolve nickel from pipes and containers. Leaching and corrosion processes may contribute significantly to the oral nickel intake (13).

Immune stimulation with a *Staphylococcus* vaccine represents a new treatment principle for patients suffering from chronic fatigue and muscle pain. Our studies have focused on women and the reason is that chronic pain defined as fibromyalgia is a syndrome that almost exclusively affects women. The efficiency of the treatment is evaluated separately (manuscript in preparation). In this paper we report that immune stimulation differentiated patients who were nickel-allergic smokers from those who were neither nickel-allergic nor smokers. This interesting outcome was thus an incidental observation in a study set up with another purpose.

Skin patch testing or an *in vitro* test such as MELISA® was not possible to perform in the large number of patients included in the clinical trials. Therefore we evaluted nickel contact allergy from a positive patient history of metal hypersensitivity. It has been claimed that there is high correlation between patient histories and patch testing results (14). The estimated prevalence of nickel contact dermatitis

in our study is equivalent to that in women with chronic fatigue syndrome and a positive skin patch test (5).

Patch testing is the standard for evaluating nickel contact dermatitis. A number of patients, however, have a positive patch test without a history of dermatitis (15) and there appears to be considerable intraindividual variation in nickel patch test reactivity (16). With a patch test as reference, dermatologists may consider the sensitivity and specificity of an *in vitro* lymphocyte proliferation test to be low (17). However, both sensitivity and specificity must be related to the purpose of the assessment. If the main purpose is to assess nickel hyperreactivity with general symptomatology of ill-being, such as chronic fatigue and muscle pain, an *in vitro* test of lymphocyte reactivity may prove to be a better reference than a skin test.

It might be expected that nickel contact allergy was misdiagnosed in some patients of our study. On the other hand, nickel hyperreactivity along the gastrointestinal route might have been underestimated in patients with no obvious skin contact allergy, as in case report 2. This notion is supported by several reports indicating that nickel activates T cells from individuals with no history or clinical manifestation of skin diseases (18).

Dietary nickel has the potential for triggering hyperreactivity (19). Consequently, one study found that reduction of the dietary intake of nickel may induce long-term improvement of dermatitis in nickel-sensitive patients (20). In another study a low nickel diet was effective in controlling the symptoms in 39% of nickel-sensitive patients with chronic allergic-like dermatopathies (21).

Presumed nickel allergy was a more obvious adverse factor than cigarette smoking with regard to the treatment outcome of the clinical trials in this study, and there was no obvious overrepresentation of habitual smokers in our patient group (28%) in comparison with general populations of adult women (26-31%) in Western societies (22). In a synergistic way, however, cigarette smoking may add to the effects of nickel allergy since mainstream cigarette smoke contains trace amounts of nickel. In this context smoking may be a trigger of nickel hyperreactivity in patients who already have been nickel-sensitized for other reasons (piercing, etc.). We know of no previous study investigating the possible interaction between cigarette smoking and nickel allergy (or metal allergy in general).

CONCLUSIONS

The conclusion of this study is that exposure to nickel by dietary intake or by inhalation of cigarette smoke may trigger systemic nickel allergy and result in general symptoms of ill-being. In this way, nickel allergy may contribute to syndromes of chronic fatigue and muscle pain. Considering the increasing prevalence of women with nickel contact allergy and the increasing rate of female smokers (23), the consequences of the possible interaction between nickel allergy and cigarette smoking may turn out to be a disorder of distinguished selection–a gender trap with vast health hazards.

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