

Chronic fatigue syndrome and nickel allergy

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50 patients with chronic fatigue syndrome (CFS) and 73 controls were patch tested with 8 metal allergens. We found an overrepresentation of allergies among the CFS patients, which was not significant. However, allergy to nickel occurred in 36% of patients in the CFS group and in 19% of subjects in the control group ($p < 0.05$). The high frequency of nickel allergy was more noteworthy in females in the CFS group than among female controls (52% and 24%, respectively, $p < 0.05$). Similarly, in the males the figures were 14% and 9%. We suggest that in vivo immunoactivation by ions of nickel, or metal cross-reacting with nickel, could be an etiological factor in CFS.

Key words: metals; nickel; chronic fatigue syndrome; contact allergy; psychoimmunology.
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Recently, we reported a significantly increased frequency of nickel, gold and palladium delayed-type allergy in patients with subjective symptoms having a temporal relationship with the fixation of dental metal constructions (1). We found that 62% of such patients complained of fatigue (1). In another clinical study, in which patients were subjected to low patch-test doses of metallic mercury and phenyl mercuric acetate, using a double-blind design, a relationship was detected between exposure to low doses of mercury on the one hand, and psychological and subjective somatic symptoms, on the other. Sleep disturbances were also a factor in this subgroup of patients (2). A minority of the patients with symptoms were allergic to mercury. Thus, sometimes allergy to metals, and sometimes not, seems to be associated with various generalized symptoms, including fatigue. Patients with the chronic fatigue syndrome (CFS) have been shown to have a high frequency of atopic or allergic conditions, as well as other immunological abnormalities (3, 4). We therefore wished to study whether allergies to various metals (delayed-type T-cell-mediated allergy) might play a rôle in the pathogenesis of CFS.

Materials and Methods

50 patients with CFS (14 men, 36 women, mean age 34 years, range 24–61 years), classified according to the Center for Disease Control (CDC) cri-

teria (5), were included in the study. 84% of the patients had an acute flu-like onset, and when included, the mean duration of illness was 5.5 years (range 8 months–19 years). 73 subjects (23 men and 50 women, mean age 31, range 19–68), with no history of metal allergy or symptoms of fatigue were controls. Of these, 32 were recruited by the patients (sex- and age-matched, unrelated, but living in the same surroundings) and 41 were on the hospital staff.

Test reagents and test chambers (IQ chamber™, polyethylene plastic chambers) were from Chemo-technique Diagnostics AB, Malmö, Sweden. Metal salts and vehicles used, as well as their concentrations, are shown in Table 1. Test substances were

Table 1. The frequency of metal allergies in 50 patients with CFS and 73 healthy controls

Metal salts	Test concentrations and vehicle	Positive patch test	
		CFS no. (%)	Controls no. (%)
potassium dichromate	0.5% pet.	7 (14)	6 (8)
metallic mercury	0.5% pet.	4 (8)	5 (7)
cobalt chloride	1% pet.	3 (6)	6 (8)
nickel sulphate	5% pet.	18 (36)	14 (19)*
gold sodium thiosulfate	1% pet.	9 (18)	12 (16)
palladium dichloride	1% pet.	3 (6)	10 (14)
tin powder	50% pet.	0	0
silver nitrate	1% aq.	0	0

CFS: chronic fatigue syndrome. pet.: petrolatum. aq.: aqua.

* $p < 0.05$.

Table 2. The frequency of metal allergies in females and males

Metal salts	Positive patch test			
	females		males	
	CFS no. (%) (total 36)	control no. (%) (total 50)	CFS no. (%) (total 14)	control no. (%) (total 50)
potassium dichromate	7 (20)	4 (8)	0	2 (9)
metallic mercury	4 (11)	2 (4)	0	3 (13)
cobalt chloride	2 (6)	5 (10)	1 (7)	1 (4)
nickel sulphate	16 (52)	12 (24)*	2 (14)	2 (9)
gold sodium thiosulfate	7 (20)	10 (20)	2 (14)	2 (9)
palladium dichloride	3 (8)	10 (20)	0	0
tin powder	0	0	0	0
silver nitrate	0	0	0	0

CFS: chronic fatigue syndrome.

* $p < 0.05$.

Table 3. Overall metal allergy in 50 patients and 73 controls, specified regarding presence of 1 or more metal allergies

	Overall allergy: no. allergic patients (%)	1 allergen: no. allergic patients (%)	2 allergens: no. allergic patients (%)	3 or more allergens: no. allergic patients (%)	No allergy: no. non-allergic patients (%)
patients	23 (46)	10 (20)	8 (16)	5 (10)	27 (54)
controls	26 (36)	11 (15)	10 (14)	5 (7)	47 (64)
	ns	ns	ns	ns	ns

ns: not significant.

placed on the upper back, removed after 2 days and read after 4 days (2). The following criteria were used to evaluate the reactions: +, weak (non-vesicular); ++, moderate (oedematous or vesicular); +++, severe reaction. Only ++ and +++ reactions were accepted as positive. The χ^2 -test and the Fisher exact test were used for the statistical analysis. Significance was set at $p < 0.05$.

Results

The frequency of contact allergies to metals among the patients and healthy controls is shown in Table 1. Nickel (sulfate) allergy was found in 36% of the CFS group compared to 19% of the control group ($p < 0.05$). With further subdivision of the material into male and female groups (Table 2), the differences in the frequency of nickel allergy became more marked. Thus, nickel allergy occurred in 52% of female patients and in 24% of female controls ($p < 0.05$). Corresponding figures in male patients and male controls were 14% and 9%, respectively. Allergy to (potassium) dichromate was present in 14% of the patient group and in 8% of the control group. As for palladium (chloride), the trend was reversed, i.e., a higher frequency in the control group (14%) than in the patient group (6%). However, neither of these differences, nor any of the others, were significant.

46% of the patients in the CFS group and 36% in the control group had contact allergy to 1 or

more metals (Table 3). The control group had a few more patients with no such allergies. Allergic subjects subdivided into groups with 1, 2 or more metal allergies showed a slightly greater non-significant increase in the patient group. Only a few patients suffered from eczema.

Discussion

Dermatologists have found nickel to play an important rôle in various types of eczema. With regard to hand eczema, presence of nickel allergy has been described as a bad prognostic factor (6, 7). Since nickel and other metals are ubiquitous, we should like to review some studies concerning their systemic effects. Oral provocation with various metal salts (nickel, cobalt and chromium) and their influence on the skin have been extensively investigated, e.g., activation of hand eczema, maculopapular rash, flare-up of previous patch tests, contact dermatitis and urticarial reactions (8–10) have been observed. In some subjects, orthopaedic implants containing nickel may cause rejection, dermatitis or even impair wound healing in a sensitized person (11, 12). Gold may also cause systemic reactions (13, 14). Other metals, such as platinum, indium and iridium salts, have also been shown to induce various reactions involving the skin that are associated with contact allergy (15–17). Even low doses of mercury cause many subjective symptoms which, however, are not related to

delayed-type hypersensitivity. The oxidative metabolism of neutrophils in such patients has been shown to respond differently to in vitro challenge with mercury compounds (18). Thus, there is evidence that various metals or metal ions may have biological effects not only confined to the skin.

In the present material of chronic fatigue patients, we have found a significantly increased frequency of nickel allergy in the patient group (36%) compared to the control population (Table 1) ($p < 0.05$). This increased frequency was more noticeable between the female patient and control groups but not so marked between the corresponding male groups. Since overall metal allergy is not significantly increased in contrast to nickel allergy, we believe that nickel itself, and/or metals cross-reacting with nickel, might play a specific rôle in the pathogenesis of CFS. These findings suggest an extension of the rôle of nickel to induce disease complexes other than purely dermatological ones.

The concept of psychoimmunology is growing (19). Lymphocytes and nerve cells share receptors for many common mediators, and cytokines are common to both. In 1991, Landay et al. (4) reported that the activation markers of the lymphocytes in CFS were increased and concluded that CFS might be caused by chronic stimulation of the immune system. Nickel could be one such stimulator. Various investigations of the in vitro lymphocyte transformation test with nickel have shown that nickel ions also stimulate lymphocytes from non-allergic controls (mitogenic effect) (20). The clinical effects of this phenomenon are not understood.

A prerequisite for cutaneous contact allergy is the presence of sensitised T-lymphocytes and an allergic response also involves in vivo activation of T-lymphocytes. It therefore seems plausible that metals or metal ions from various sources, such as odontological restoration alloys (released by wear and corrosion) and metal contamination of food and water, may activate lymphocytes in vivo in certain subjects, and then induce the release of various cytokines that cause generalized symptoms (13, 21).

Nickel allergy may merely be a "marker" symptom, which can help us to understand the pathogenic mechanisms involved in CFS. It is also possible that the transition group of metals (to which nickel belongs) may cross-react, i.e., may cause similar cell activation. This concept suggests that metal ions play a more important rôle than previously believed (22, 23). A method has recently been described for further exploration of this theory. It permits detailed analysis of the content of dental metal alloys, without damage to the construction. This method seems promising, because

it can be used to verify the relationship between contact allergy and the metal allergens in odontological constructions (14). Whether nickel alone or together with other causes is involved in CFS, remains an open question.

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