The lymphocyte response to nickel salt in patients with orthopedic implants

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In this pilot study, 14 patients with different symptoms and signs in relation to orthopedic implants were compared with 12 asymptomatic patients to determine the in vitro lymphocyte response to nickel sulfate. We conclude that nickel allergy may explain some, but not most, of the local and generalized symptoms associated with orthopedic implants.

Metallic orthopedic implants leak measurable concentrations of corrosive products (Cohen 1962, Ferguson et al. 1962, Brown and Merrit 1981). No full investigation has been made yet into the impact that this may have had on various reported local and generalized symptoms, such as pain and inflammation, as well as dermatitis (Foussereau and Laugier 1966, Barranco and Solomon 1972, Samitz and Klein 1973, Pegum 1974). Because nickel allergy frequently occurs and is often not diagnosed (Peltonen 1979), one would expect a certain proportion of postoperative complications to be due to latent allergy, i.e., the absence of skin symptoms on challenge with nickel-containing alloys, but a positive in vitro lymphocyte transformation test.

The purpose of this pilot study was to ascertain whether diverse symptoms and signs in patients with various metal implants might be correlated with the in vitro lymphocyte response to nickel sulfate.

Patients and methods

Twenty-six patients with various types of metallic implants for fracture (Table 1) were subdivided into two groups (A and B) depending on the presence of symptoms and signs. The mean age was 60 (25–80) years.

No case was included in which the fractures were compressed and the pain could be assumed to be caused by the end of a nail penetrating into the surrounding soft tissue or joint cavity.

Group A: Fourteen patients (12 females, 2 males) who suffered from local and/or widespread eczematous lesions and/or symptoms of pain at rest in the operated on area. All the symptoms and signs had a temporal relationship to the operation.

Group B: Twelve patients (9 females, 3 males) who were asymptomatic from the orthopedic and dermatologic points of view.

Table 1. Fracture types and nickel content in various osteosynthesis material used in Group A (symptomatic) and B (nonsymptomatic) patients, respectively

Type of implant	Nickel (%)	Group A (n)	Group B (n)
A-O, Pugh, Rydell, Richards	14	12[a]	9[b]
Rush-pin, Ender, von Bahr	13	1[c]	2[d]
Jewett	2	1[e]	1[f]

Fractures

[a] 2 femoral shaft
5 pertrochanteric
5 femoral neck

[b] 1 lower arm
5 pertrochanteric
3 femoral neck

[c] 1 ankle

[d] 1 femoral neck
1 subtrochanteric

[e] 1 pertrochanteric

[f] 1 pertrochanteric

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Patients in Group A had had their implants on an average for 24 months, whereas patients in Group B had had theirs for 43 months. Local or widespread eczematous skin reactions were found in 7 of 14 patients in Group A. Of the latter patients, 9 complained of local pain at rest or on movement. In 7 the osteosynthesis material was removed because of the prevailing symptoms; 5 patients became asymptomatic thereafter.

In vitro testing

In vitro experiments were performed as described elsewhere (Al-Tawil et al. 1981); a brief description is given here. Lymphocytes from 12 healthy nonimplanted and non nickel allergic blood donors served as controls for the in vitro test—*Group C*.

Metal salts: Solutions of $NiSO_4$ were prepared to give concentrations in culture of 6.25, 12.5, and 25 µg/mL.

Assay of DNA synthesis: Mononuclear cells were separated from heparinized blood, washed and resuspended in modified Eagle's minimum essential medium (Flow Laboratories, Irvine, Scotland) to which 1 percent HEPES buffer, 1 percent glutamine, and 20 percent pooled human AB serum were added. Cultures were set up in triplicate in microtiter plates (Nunc, Denmark), with each well containing 5×10^4 cells in a total volume of 0.2 mL medium. Solutions of the metal salts were added to the final concentrations. Cells cultured in medium served as background controls.

The plates were then incubated, and to each well 1 µCi of methyl (^3H) thymidine (Radiochemical Centre, Amersham, England; Spec. Activity 5 Ci/mmol) was added 24 hours before harvesting on fiberglass filters on Days 5 and 6. The filters were dried and assayed in a liquid scintillation counter.

The results were expressed as stimulation indices (SI; test values in counts per minute divided by background values).

To establish in vitro allergy, the following previously defined criteria were applied (Al-Tawil et al. 1981).

On Day 5 of culture, the SIs should be twice the SIs (or more) of the healthy control cells simultaneously tested, using 12.5 or 25 µg $NiSO_4$/mL. On Day 6, the experimental SIs should be at least twice the SIs of the controls that were simultaneously tested using 6.25 µg $NiSO_4$, and the SIs of the patients should be more than 3 using 6.25 µg and more than 6 using 12.5 µg/mL.

The Kruskal-Wallis Test 2 was used to evaluate the results.

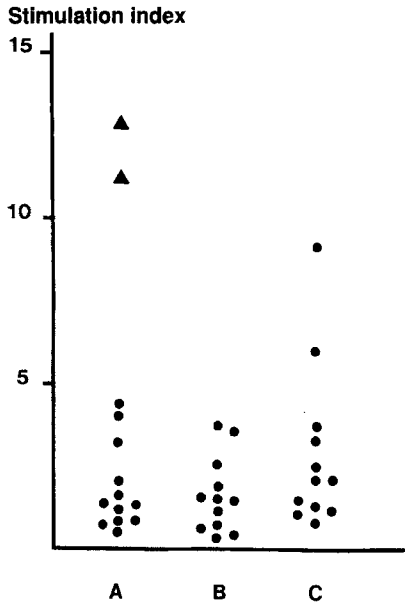

Figure 1. The magnitude of the lymphocyte responses when challenged with 12.5 µg $NiSO_4$ are given as stimulation indices (SI) on the y-axis in the three groups.
A is the group with various local and generalized symptoms related to the implant, B the symptomfree group, and C the control group.
▲ denotes in vitro nickel allergy.
● in vitro nonallergic subjects.
Those in Groups B and C with high SIs did not fulfill all the criteria for in vitro allergy.

Results

No differences were found in a comparison of the lymphocyte responses of Groups A, B, and C for any of the concentrations of the nickel salt used.

Two patients fulfilled the in vitro criteria for nickel allergy, and both were in Group A (Figure 1). The clinical course in these 2 patients did not deviate from that in the rest of the group. None in Group B or in the control group was in vitro nickel allergic when the result of all the experiments were examined. Some SIs in Figure 1 seem to be high, but do not suggest allergy when all the laboratory data obtained on Days 5 and 6 were taken into consideration and the previously defined criteria were applied.

Discussion

In the present study, we have investigated 2 groups of orthopedic patients with metal implants; 1 with various symptoms and signs and the other asympto-

matic. The mononuclear cells of these patients were challenged in vitro with solutions of nickel sulfate in various concentrations. No difference could be found in the proliferative lymphocyte responses between the groups. Two of the symptomatic patients were definitely in vitro nickel allergic, as assessed by our in vitro criteria, and 12 were in vitro negative. Are these findings compatible with our dermatologic experience of patch testing and the in vitro lymphocyte response?

In our investigation of the correlation between the positive cutaneous patch-test response and the in vitro, positive skin tests outnumberd those with positive in vitro tests (Al-Tawil et al. 1981). This also applies to dermatitis around the pierced earlobe caused by wearing earrings containing nickel in direct contact with the skin (Gilboa et al. 1988). Thus, nickel in the metal alloy used in inexpensive jewelry and nickel as a test substance can provoke a cutaneous inflammation that, to some extent, is associated with nickel allergy, as diagnosed by the lymphocyte transformation test.

Moreover, it is known that implants release corrosion products into the surrounding tissue (Merrit et al. 1981). By analogy with the dermatologic experience, it is conceivable that the metal ions would produce local symptoms due to an inflammatory reaction in some, but not all, patients. In case of allergy, i.e., the presence of sensitized mononuclear cells in the peripheral blood, the clinical picture is expected to be more marked. However, a larger patient material is needed to prove the validity of this theory.

As regards the discrepancies between in vivo and in vitro testing for metal allergy, it is difficult to compare the results of previous studies (Deutman et al. 1977, Carlsson et al. 1980, Waterman and Schrik 1985). On the other hand, in laboratory animals in which planned and controlled sensitization with nickel has been carried out, a more pronounced inflammatory reaction distinct from that in nonallergic animals has been described in connection with implants containing nickel (Merrit and Brown 1981, Lewin et al. 1982). This is also related in some degree to other patient materials employing different in vitro test systems (Merrit et al. 1980).

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