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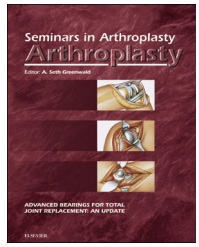

Arthroplasty patients and nickel sensitization: What do patch test and lymphocyte transformation test tell us

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ABSTRACT

Immunological sensitization to metals is a potential elicitor of arthroplasty failure. Since nickel (Ni) allergy is the most frequent contact allergen for cutaneous contact allergic reactions, we assessed the relation between patch test reactivity and LTT reactivity to Ni in 2 groups of patients: eczema patients without implants (30 without and 38 with cutaneous metal intolerance, CMI, e.g., eczema to jewelry, jeans button) and arthroplasty patients (100 without and 200 with complications). After establishing the appropriate in vitro Ni test concentrations, a good correlation between patch test and LTT reaction was seen in the first patient group. It was also found that "self-reported Ni allergy," e.g., CMI was only in one-third of the patients verified to be Ni allergy. In arthroplasty patients with complications, higher patch test reactivity and LTT reactivity was found—but to some extent was also found in symptom-free arthroplasty patients. Thus identification of further characteristics is needed to reveal metal implant allergy.

1. Introduction

About 13% of the general population in Germany is sensitized to nickel (Ni) and correspondingly allergic contact dermatitis is most frequently elicited by Ni [1]. The typical medical history suggestive of Ni allergy is the occurrence of itching, eczematous dermatitis to jeans button, wrist watch, or jewelry. From an allergological point of view, the standardized testing to prove Ni allergy is the patch test. It offers evaluated patch test preparations and a standardized reading procedure of the reactions [2]. By using the model of patch test, a specific tissue response to allergens, e.g., Ni could be studied. Histological characteristics included the predominance of T-lymphocytic inflammation. By use of the

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lymphocyte transformation test (LTT), Ni-reactive T-cell response in vitro could be assessed by enhanced proliferation. Early reports also showed similarities between tissue-derived and blood-derived Ni-specific T cells—but also indicated that varying cytokine profiles of such T-cells might be found [3]. The concept of allergen-specific T-cell response—at least in Ni allergy—was supported by the clonality of such reactive T cells [4]. Furthermore, a TH1-type reactivity, e.g., with IFN-γ production was described [5,6]. In 1997, Cederbrant et al. wondered if monitoring sensitization to Ni, palladium, and gold preparations by LTT would be comparable to patch testing. At that time, however, the authors stated that such in vitro assay was not useful for diagnosis of contact allergy to those metals due to low specificity and risk of large number of false-positive results [7]. Since that time various modifications of LTT have been developed—but very rarely controls are included to define significant, discriminative conditions. As we are seeing large numbers of both contact allergic patients and arthroplasty patients with suspected metal implant allergy, we investigated patch test reactivity and LTT reactivity to Ni in individuals without metal implant and patients with/without symptoms/complications to CoCrMo-based arthroplasty.

2. Materials and methods

2.1. Patients

We assessed different patient groups with regard to patch test reactivity and LTT reactivity to Ni:

A total of *68 patients* who had to get patch testing (at least standard series) as allergological diagnostic procedure due to eczema. All of them were without metal implant. Of 68, 38 reported cutaneous metal intolerance reactions (CMI, e.g., eczema/itching to jeans button, ear-ring, and wrist watch) and 30/68 had no history of CMI.

A total of *100 patients with well-performing*, symptom-free CoCrMo-based arthroplasty and *200 patients with symptoms/complications* to CoCrMo arthroplasty (including pain, effusions, loosening—however no malpositioning or infection). Part of the findings and detailed characterization of these 300 patients has been published previously [8]. The study was approved by the ethics committee. Patient characteristics are given in Tables 1 and 2.

Patch testing was performed according to the guidelines of the German Contact Dermatitis Research Group on the patient's upper back. We tested the following series: standard series, which includes Ni, Cr, Co; additional series if adapted to exposure history (e.g., work place related, in the 68 patients) and in case of cemented arthroplasty a bone cement series with acrylates and additives including gentamicin. Evaluation of the reactions was after 2, 3 days (and 7 days in case of bone cement components testing).

The LTT with Ni, Cr, and Co was done by stimulating peripheral blood mononuclear cells (PBMC) in quadruplicate over 6 days with the following substances: as controls T-cell mitogen phytohemagglutinine (PHA, Biochrom, Berlin, Germany) 2.4 μg/ml, tetanus toxoid (TT, Chiron Behring, Berlin, Germany) 5 μg/ml, and culture medium alone; $NiSO_4$, $CoCl_2$, $CrCl_3$ (1×10^{-6} M – 1×10^{-3} M, 7 different concentrations, Sigma, Germany). After 5 days, cells were pulsed with ^3H thymidine overnight and proliferation was measured by incorporated radioactivity. The proliferative response was given as stimulation index (SI), which was calculated by the ratio of mean counts per minute (cpm) of stimulated to unstimulated cultures. SI >3 was regarded as positive. The LTT was performed according to Summer et al. [9].

3. Results

3.1. Patch testing (here focussing on Ni-reactivity)

Group of 68 patients without implant, but allergological diagnostics due to eczema were included.

In the 30 patients without history of CMI, no patch test reaction to Ni was found. Out of the 38 patients with history of CMI, 13/38 showed contact allergic reaction to Ni.

With regard to the *arthroplasty patients*, in the *100 patients with well-performing*, symptom-free CoCrMo-based arthroplasty, there were 9/100 patients with patch test reaction to Ni, and within the *200 patients with symptoms/complications* to CoCrMo arthroplasty, 35/200 patients with patch test reactivity to Ni were found.

3.2. LTT reactivity (here focussing on Ni-reactivity)

By assessing the *group of 68 patients* without implant, we first defined the Ni-stimulation concentration that did not give enhanced LTT reactivity in the 30 patients without CMI and without patch test reactivity to Ni: this concentration was (for our laboratory conditions) 1×10^{-5} M. At such stimulation conditions, within the 38 patients, 14/38 had an enhanced (SI > 3) LTT reactivity to Ni. There was also a high correlation ($p < 0.01$) between patch test and LTT reactivity.

Table 1

	Characteristics of Patients Without Metal Implant	
	Eczema, But No CMI[a] ($n = 30$)	Eczema and CMI ($n = 38$)
Sex	8 Females, 22 males	34 Females, 4 males
Age	52.43 Years (18–75 years)	61.63 Years (44–75 years)
Atopy	12/30	23/38
Patch test reactivity to Ni	0/30	13/38

[a] CMI, cutaneous metal intolerance (e.g., eczema, itching to jeans button, jewelry, and wrist watch).