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Review article

Allergies in orthopaedic and trauma surgery

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ABSTRACT

Hypersensitivity reactions to implants in orthopaedic and trauma surgery are a rare but devastating complication. They are considered as a delayed-type of hypersensitivity reaction (type IV), characterized by an antigen activation of sensitized T-lymphocytes releasing various cytokines and may result in osteoclast activation and bone resorption. Potential haptens are originated from metal alloys or bone-cement. A meta-analysis has confirmed a higher probability of developing a metal hypersensitivity postoperatively and noted a greater risk of failed replacements compared to stable implants. Hypersensitivity to implants may present with a variety of symptoms such as pain, joint effusion, delayed wound/bone healing, persistent secretion, allergic dermatitis (localized or systemic), clicking noises, loss of joint function, instability and failure of the implant. Various diagnostic options have been offered, including patch testing, metal alloy patch testing, histology, lymphocyte transformation test (LTT), memory lymphocyte immunostimulation assay (MELISA), leukocyte migration inhibition test (LIF) and lymphocyte activation test (LAT). No significant differences between in vivo and in vitro methods have been found. Due to unconvincing evidence for screening methods, predictive tests are not recommended for routine performance. Infectious aetiology always needs to be excluded. As there is a lack of evidence on large-scale studies with regards to the optimal treatment option, management currently relies on individual case-by-case decisions. Several options for patients with (suspected) metal-related hypersensitivity exist and may include materials based on ceramic, titanium or oxinium or modified surfaces. Promising results have been reported, but long-term experience is lacking. More large-scaled studies are needed in this context. In patients with bone-cement hypersensitivity, the component suspected for hypersensitivity should be avoided. The development of (predictive) biomarkers is considered as a major contribution for the future.

1. Introduction

Total joint replacement is the standard treatment of care for end-stage osteoarthritis and is known for excellent clinical results. In general, materials implanted are well tolerated by the body. However, the host response to implants in orthopaedic and trauma surgery is essential for their clinical performance.

Hypersensitivity reactions in general are known as a state of altered reactivity in which the body reacts with an exaggerated immune response to a foreign agent. Hypersensitivity can be classified as an immediate humoral response driven by antibodies or antibody-antigen complexes or as a delayed cell-mediated response. Implant-associated hypersensitivity reactions are considered as a delayed-type of hypersensitivity (type IV) reaction and are characterized by activation of sensitized T-lymphocytes releasing various cytokines which results in the recruitment and activation of macrophages. A variety of inflammatory mediators may be involved, such as cytokines (IL-1ß, Il-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17, IFNγ, IP10), chemokines (MIP-1α and MIP-1ß) and growth factors (GM-CSF and PDGF). Although the exact pathways remain unclear at present, the common endpoint is osteoclast activation and bone resorption, leading to destabilization of the implant and may even result in revision surgery due to aseptic loosening. Implant loosening caused by hypersensitivity has first been presented in the mid 1970s. Increased attention has been given to high failure rates in second-generation metal-on-metal hip replacements.

Implants currently available in orthopaedic and trauma surgery are made of various materials and may contain stainless steel, cobalt-chromium-molybdenum alloys, nickel, titanium, Vitallium, beryllium, vanadium and tantalum as well as plastic and ceramic components. Released metal components in periprosthetic tissue

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have been reported to exist in different forms, including wear debris, metallo-protein complexes, metal ions in solution and/or by-products of synergistic corrosion and wear processes. Potential haptens causing implant-related hypersensitivity are also known to be originated from bone-cement.

Various terms have been used to describe periprosthetic tissue reactions. Characteristic alterations may include vasculitis with diffuse and/or perivascular lymphocytic infiltration, high endothelium venules, recurrent localized bleeding and/or necrosis. In general, tissue reactions are described according to their predominant cellular response as either (i) macrophage-dominated type without immunological memory, which is mostly seen in foreign-body type reactions, or as (ii) lymphocyte-dominated type of tissue response, describing a T-cell mediated reaction, comprising diffuse and perivascular lymphocytic infiltrates and characterized by an adaptive, immunological memory. The authors prefer the semi-quantitative score proposed by Willert et al. to evaluate histological features and the dominant type of tissue response [1]. We demonstrated in one of our previous studies that the combined surface area comprising number and size of all particles, named as "biologically active area" rather than the size or number of particles alone predicts the type of tissue response [2].

2. Do implant-related allergies exist?

Several study groups aimed to investigate the cause-and-effect relationship between hypersensitivity reactions and implant failure in orthopaedic and trauma surgery. Recently, a systematic review and meta-analysis by Granchi et al. comprising 3634 patients has combined the results of the current literature showing that the prevalence of hypersensitivity was influenced by the following factors: presence and status of the implant, the type of coupling, and the number of haptens tested. According to these authors, metal sensitization manifests more often in patients undergoing joint replacement when compared to the normal population (odds ratio (OR) 1.52 (95% confidence interval [CI] 1.06 to 2.31). The probability of hypersensitivity was higher in particular in patients with failed implants compared to those with stable joint replacements (OR 2.76 [95% CI 1.14 to 6.70]) [3]. Based on seven reports, the average prevalence of metal hypersensitivity (nickel, cobalt or chromium) was compared among the normal population (approximately 10–15%), patients with a well functioning implant (25%) and patients with a poorly functioning implant (60%) [4]. However, these numbers should be interpreted carefully, since it was recently shown that the proportion of positive tests is almost twice compared to that four decades ago. This finding has been interpreted as a consequence of the increased number of haptens tested [3].

The risk for hypersensitivity is thought to be largely depending on the individual's exposure and risk factors including age, gender (female > male), occupation and a positive history of metal hypersensitivity have been reported [5].

Hypersensitivity reactions to implants may present with a variety of symptoms such as pain, joint effusion, delayed wound/bone healing, persistent secretion, allergic dermatitis (localized or systemic), clicking noises, loss of joint function, implant instability and failure. Symptoms mainly exhibit within the first postoperative year after primary implantation. Radiologic findings are typically non-specific and may include radiolucent lines and progressive osteolysis without any bone atrophy. The presence of pseudotumors has been reported in literature.

Objective criteria supporting a causative association between implant-related metal ions and metal hypersensitivity have been proposed by Thyssen et al. including "(i) chronic dermatitis beginning weeks to months after metallic implantation, (ii) eruption overlying the metal implant, (iii) morphology consistent with dermatitis (erythema, induration, papules, vesicles), (iv) in rare instances, systemic allergic dermatitis reactions (characterized by universal dermatitis reactions, typically localized in body flexures), (v) histology consistent with allergic contact dermatitis, (vi) positive patch test reaction to a metal used in the implant (often strong reaction), (vii) serial dilution patch testing give positive reactions to low concentrations of the metal under suspicion, (viii) positive in vitro test to metals, (ix) dermatitis reaction is therapy resistant and (x) complete recovery following removal of the offending implant" [6].

Though joint registers become more and more established nowadays, reliable epidemiologic data on implant-related hypersensitivity are still lacking; often hypersensitivity-related complications are not systematically collected. In Germany, there is an increasing attempt to overcome this lack of information. Under the supervision of the German reference dermatologist for orthopaedic and trauma surgery, an implant hypersensitivity registry collecting detailed patients' characteristics and documenting the long-term results after revision surgery for implant-related hypersensitivity has been initiated.

In conclusion, given the clinical and temporal evidence, the authors support the theory of hypersensitivity-related complications in orthopaedic and trauma surgery. However, the underlying mechanisms still remain to be fully elucidated. The prevalence presented is inconsistent, and due to diagnostic difficulties, the reported numbers may be not realistic. Because of potential serious clinical implications for the patient, hypersensitivity following implantation of a foreign-body is considered as an important topic for the surgical community.

3. How to diagnose hypersensitivity to implants?

The diagnosis of implant-related hypersensitivity in orthopaedic and trauma surgery is challenging. Although various diagnostic algorithms have been proposed, there is no generally established guideline so far. An overview of in vivo and in vitro diagnostic options for metal hypersensitivity including their objectives and potential drawbacks are given in Table 1.

Patch testing, though controversial, is still the most commonly used diagnostic method and remains considered as gold standard for in vivo assessment. However, it has to be noticed that the FDA approved thin-layer rapid use epicutaneous patch test (TRUE test; Mekos Laboratories A/S Hillerød, Denmark) only contains the most common sensitizers, namely nickel, cobalt and chromium [7]. It does not include the whole variety of antigens relevant for hypersensitivity in orthopaedic and trauma surgery. Extending the patch test to other known triggering substances should be considered, but may lack validation. Critics point out differences in epicutaneous environment compared to deep tissue layers. Antigen-presenting mechanisms may be therefore of limited reflection. Moreover, the actual form of released metal components may not reflect the preparations used in the patch testing panels and be unable to penetrate the skin [8].

Due to the lack of additional benefits through metal alloy disk patch testing, this modified patch testing has not been recommended by the German contact allergy group (Deutsche Kontaktallergie Gruppe, DKG) [9]. For the patient reported history of allergy, a sensitivity of 85.5% and a specificity of 83.5% have been reported in a prospective study by Frigerio et al. [10], and is therefore considered inferior compared to the standard patch test. Evaluating histological features requires an invasive action, but provides the opportunity of investigating the true periprosthetic tissue response. Formalin fixation of tissue samples is required. In

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