

1-1-2016

Rigorous evaluation of the patterns of nickel sensitization in children with atopic dermatitis is needed

NIKOLETA BRANKOV

SHARON E. JACOB

Follow this and additional works at: <https://journals.tubitak.gov.tr/medical>



Part of the [Medical Sciences Commons](#)

Recommended Citation

BRANKOV, NIKOLETA and JACOB, SHARON E. (2016) "Rigorous evaluation of the patterns of nickel sensitization in children with atopic dermatitis is needed," *Turkish Journal of Medical Sciences*: Vol. 46: No. 5, Article 49. <https://doi.org/10.3906/sag-1606-101>
Available at: <https://journals.tubitak.gov.tr/medical/vol46/iss5/49>

This Article is brought to you for free and open access by TÜBİTAK Academic Journals. It has been accepted for inclusion in Turkish Journal of Medical Sciences by an authorized editor of TÜBİTAK Academic Journals. For more information, please contact academic.publications@tubitak.gov.tr.

Rigorous evaluation of the patterns of nickel sensitization in children with atopic dermatitis is needed

Nikoleta BRANKOV¹, Sharon E. JACOB^{2,*}

¹Loma Linda University, Loma Linda, CA, USA

²Contact Dermatitis Clinic, Department of Dermatology, Loma Linda University, Loma Linda, CA, USA

Received: 17.06.2016 • Accepted/Published Online: 29.07.2016 • Final Version: 17.11.2016

To the Editor,

We applaud Akan et al. for astutely drawing attention to the association of nickel sulfate (NS) sensitization in children with moderate to severe atopic dermatitis (AD) and increased eczema involvement area, including trunk involvement (1). Widespread dermatitis, a key feature of systemic contact dermatitis (SCD) to nickel and its association with sustained nickel exposures (through diet, inhalation, or implantation), has remained largely controversial in the literature and its occurrence in association with AD is poorly described (2). Rigorous investigation of SCD and nickel in AD is very much needed.

There is a complex relationship between *Staphylococcus aureus* AD and nickel allergy (3). For one, the biofilm formation by AD-associated staphylococci plays a major role in the occlusion of sweat ducts that leads to inflammation and pruritus (4). Furthermore, elevated secretion of IL-2 under NS stimulation in vitro was exclusively found in atopic patients with nickel allergy infected by *S. aureus*, suggesting a link between nickel allergy, *S. aureus* infection, and AD (3). This is further supported by the findings that *S. aureus* releases its virulence factor alpha-toxin, and it preferentially destroys the filaggrin-deficient keratinocytes in AD, leading to poor keratinocyte adhesion and the increased potential for haptens to penetrate the epidermal barrier and induce sensitization (5).

Akan et al. highlighted the need to recognize NS sensitization in the management of moderate to severe AD (1) and utilized epicutaneous patch testing to make this determination; however, they did not discuss the use of intradermal nickel prick testing. Patch testing can lead to potential false-negative reactions, and therefore, for negative or equivocal patch test results, an intradermal test may be indicated to confirm clinical suspicion of nickel

allergy in patients (6), because intradermal testing (skin prick test [SPT]) may unveil false negative metal reactions and can shed light on doubtful patch test reactions (7). We suggest that the intradermal testing paired with epicutaneous testing could have identified more accurately the moderate to severe AD patients who had nickel sensitization, who may have benefited from nickel-allergic contact dermatitis (Ni-ACD) avoidance measures.

According to the methods of Akan et al., a SPT was performed for food and aeroallergens on all patients as well as determination of total serum IgE and percentage of peripheral blood eosinophilia.

In their results, the authors mentioned that 53% of the study population had positivity to the SPT and allergen-specific IgE (1), but the authors did not delineate which allergen-specific IgEs were evaluated (e.g., nickel), nor the total IgE level. Of interest, Akan et al. had the subjects discontinue antihistamines 7 days before patch testing. Evidence suggests that antihistamines have no effect on delayed-type hypersensitivity confirmation through patch testing. That said, antihistamines may in fact subdue a concurrent TH2 response. This is important because decreased expressions of immune, TH1-subset, and TH2-subset genes in nickel-related AD responses, with increased TH17/IL-23 skewing and inconsistent upregulation in levels of TH2 products, have been reported in association with AD (8). These baseline immune abnormalities seen in nickel-associated SCD in AD underscore the inconsistencies in the literature and highlight the need for rigorous systematic evaluation of SCD to nickel in patients with AD.

Understanding the significance of nickel sensitization in mild, moderate, and severe atopic dermatitis patients and the pathophysiologic mechanisms at play will hopefully lead to more targeted patient care in the future.

* Correspondence: sjacob@contactderm.net

References

1. Akan A, Toyran M, Vezir E, Azkur D, Kaya A, Erkoçoğlu M, Civelek E, Dibek Misirlioğlu E, Kocabaş CN. The patterns and clinical relevance of contact allergen sensitization in a pediatric population with atopic dermatitis. *Turk J Med Sci* 2015; 45: 1207-1213.
2. Pizzutelli S. Systemic nickel hypersensitivity and diet: myth or reality? *Eur Ann Allergy Clin Immunol* 2011; 43: 5-18.
3. Anna BM, Grazyna A, Wojciech D, Aleksander O, Anna B, Andrzej K, Zofia M, Krystyna O. Nickel allergy and relationship with *Staphylococcus aureus* in atopic dermatitis. *J Trace Elem Med Biol* 2016; 33: 1-7.
4. Allen HB, Vaze ND, Choi C, Hailu T, Tulbert BH, Cusack CA, Joshi SG. The presence and impact of biofilm-producing staphylococci in atopic dermatitis. *JAMA Dermatol* 2014; 150: 260-265.
5. Novak N, Baurecht H, Schäfer T, Rodriguez E, Wagenpfeil S, Klopp N, Heinrich J, Behrendt H, Ring J, Wichmann E et al. Loss-of-function mutations in the filaggrin gene and allergic contact sensitization to nickel. *J Invest Dermatol* 2008; 128: 1430-1435.
6. Torres F, das Gracas M, Melo M, Tosti A. Management of contact dermatitis due to nickel allergy: an update. *Clin Cosmet Investig Dermatol* 2009; 17: 39-48.
7. Moller H. Intradermal testing in doubtful cases of contact allergy to metals. *Contact Dermatitis* 1989; 20: 120-123.
8. Correa da Rosa J, Malajian D, Shemer A, Rozenblit M, Dhingra N, Czarnowicki T, Khattri S, Ungar B, Finney R, Xu H et al. Patients with atopic dermatitis have attenuated and distinct contact hypersensitivity responses to common allergens in skin. *J Allergy Clin Immunol* 2015; 135: 712-720.

Reply to Letter to the Editor:

Author response to “Letter to the editor: Rigorous evaluation of the patterns of nickel sensitization in children with atopic dermatitis is needed”

Ayşegül AKAN*, Müge TOYRAN, Emine VEZİR, Dilek AZKUR, Aşenur KAYA, Mustafa ERKOÇOĞLU, Ersoy CİVELEK, Emine DİBEK MISIRLIOĞLU, Can Naci KOCABAŞ

Department of Pediatric Allergy and Immunology, Ankara Children's Hematology Oncology Education and Research Hospital, Ankara, Turkey

We read the letter to the editor by Brankov and Jacob with great interest and thank them for appreciating our study. The main suggestion of our study was to be suspicious of contact sensitization in children with moderate to severe atopic dermatitis (AD), particularly widespread dermatitis (1).

As they remarked, we performed specific immunoglobulin E (IgE) tests for the patients with a suggestive history of allergy to the proposed foods or common inhaled allergens, or who had positive skin prick tests (SPT) to foods such as cow's milk or hen's eggs and inhaled allergens such as house dust mites. Totally, 53% of the patients had positive SPT results and/or a specific IgE above the cut-off value of 0.35 kU/L, so they were classified as having allergen sensitization. Mean serum total IgE (tIgE) was 42 IU/mL (ranging between 16 and 392). There was no significant difference for serum tIgE between the patients with and without any positive patch test reaction, nor between those with and without positive nickel (Ni) sensitization defined by patch test. SPT or specific IgE tests for Ni were not used in the study.

Brankov and Jacob suggested to perform the SPT and patch tests together to reveal the patients with potential false-negative results on patch tests. There are a very few old studies about intradermal testing (SPT), probably before the standardization of patch tests (2-4), and there are no studies about this subject in children. In a recent review about management of contact dermatitis due to Ni allergy, the authors recommended SPT for Ni in patients with contact urticaria (5). To our knowledge, the most recent study about different test methods for Ni allergy in adult patients with AD or contact dermatitis was published in 2003 (6). In that study, the authors could find the benefit of using neither specific IgE to Ni nor SPT with different dilutions of Ni sulfate in diagnosing Ni allergy.

As Brankov and Jacob highlighted, patients treated with oral antihistamines or oral and topical steroids in the last 7 days before patch testing were excluded from our study. The interference of antihistamines on patch test results is challenging. There are very few studies investigating this subject. In one study, the patch test results were shown to be reduced by oral loratadine (7). In spite

* Correspondence: aysegul.akan@hotmail.com

of the controversy, most clinicians prefer to discontinue antihistamine treatment before patch testing, in order to get rid of the feeling of uncertainty about results (8,9). We also made our preference in this direction.

The term “systemic contact dermatitis” (SCD) was defined as widespread dermatitis including baboon syndrome and other dermatitis types caused by systemically administered substances, regardless of the presence of previous topical exposure (10). This term is preferably used when a person sensitized to a contact allergen is exposed to the same allergen through a systemic route. Systemic administration of allergens includes percutaneous, transmucosal, transrectal, oral, intravenous, intramuscular, inhalational, and implant routes (11). In order to distinguish contact dermatitis induced by prior cutaneous sensitization, the term “allergic contact dermatitis syndrome” (ACDS) was introduced later (9,11). For Ni, it is not easy to distinguish whether the first sensitization route was systemic or cutaneous, because Ni is a potent allergen found in most of the foods that are universally consumed throughout the world and dental alloys. Ni is also a common contact allergen with exposure

occurring via several sources such as ear piercing, watches, wrist straps, snaps, belt buckles, and most cosmetics (1). Thus, the main situation in which to consider SCD is when a patient with refractory widespread dermatitis has a positive patch test to a known cause of SCD such as Ni and does not heal with the avoidance of cutaneous exposure (12). According to this, double-blind placebo-controlled Ni challenge testing and avoidance of foods including Ni should have been accepted as the gold-standard diagnosis and treatment of SCD due to Ni. However, the relationship between dietary Ni and SCD remains controversial, despite experimental studies in patients with ACD demonstrating that systemically ingested Ni can be real cause of outspread aggravation of skin lesions that cannot be explained by simple cutaneous exposure (13). The main cause of the uncertainty seems to be related to the inconsistencies of diagnostic procedures, diet, and doses of challenges used in different studies (13,14). Unless a consensus is achieved in adult studies that could be used in clinical practice with certainty, it would not seem to be possible to clarify the systemic role of Ni in childhood dermatitis.

References

1. Akan A, Toyran M, Vezir E, Azkur D, Kaya A, Erkoçoğlu M, Civelek E, Dibek Mısırlıoğlu E, Kocabaş DN. The patterns and clinical relevance of contact allergen sensitization in a pediatric population with atopic dermatitis. *Turk J Med Sci* 2015; 45: 1207-1213.
2. Moller H. Intradermal testing in doubtful cases of contact allergy to metals. *Contact Dermatitis* 1989; 20: 120-123.
3. Christensen OB, Wall LM. Open, closed and intradermal testing in nickel allergy. *Contact Dermatitis* 1987; 16: 21-26.
4. Meneghini C, Angelini G. Intradermal test in contact allergy to metals. *Acta Derm Venereol Suppl (Stockh)* 1979; 59: 123-124.
5. Torres F, das Gracas M, Melo M, Tosti A. Management of contact dermatitis due to nickel allergy: an update. *Clin Cosmet Investig Dermatol* 2009; 2: 39-48.
6. Antoszczyk G, Obtulowicz K, Wojas-Pelc A, Szmigiel-Michalak K, Bogdaszewska-Czabanowska J, Obtulowicz A. Nickel allergy in contact and atopic dermatitis. *Przegl Lek* 2003; 60: 334-337 (in Polish with abstract in English).
7. Motolese A, Ferdani G, Manzini BM, Seidenari S. Echographic evaluation of patch test inhibition by oral antihistamine. *Contact Dermatitis* 1995; 32: 250-251.
8. Elston D, Licata A, Rudner E, Trotter K. Pitfalls in patch testing. *Am J Contact Dermat* 2000; 11: 184-188.
9. Lachapelle JM, Maibach HI. Patch testing methodology. In: Lachapelle KM, Maibach HI, editors. *Patch Testing and Prick Testing. A Practical Guide*. Berlin, Germany: Springer Verlag; 2009. pp. 33-70.
10. Menne T, Veien NK, Maibach HI. Systemic contact-type dermatitis due to drugs. *Semin Dermatol* 1989; 8: 144-148.
11. Kulberg A, Schliemann S, Elsner P. Contact dermatitis as a systemic disease. *Clin Dermatol* 2014; 32: 414-419.
12. Fabbro SK, Zirwas MJ. Systemic contact dermatitis to foods: nickel, BOP, and more. *Curr Allergy Asthma Rep* 2014; 14: 463.
13. Antico A, Soana R. Nickel sensitization and dietary nickel are a substantial cause of symptoms provocation in patients with chronic allergic-like dermatitis syndromes. *Allergy Rhinol (Providence)* 2015; 6: 56-63.
14. Pizzutelli S. Systemic nickel hypersensitivity and diet: myth or reality? *Eur Ann Allergy Clin Immunol* 2011; 43: 5-18.