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LETTER TO THE EDITOR

Letter to the Editor: SNAS and thyroid autoimmunity risk

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To the Editor,

We commend Andrioli et al. for highlighting the higher prevalence of chronic autoimmune thyroiditis (CAT) in Systemic Nickel Allergy Syndrome (SNAS) patients (26.5%) compared to patients with other autoimmune inflammatory disorders (12.7%) including type 1 diabetes, celiac disease, Sjogren's disease, rheumatoid arthritis, and systemic lupus erythematosus [1], as this calls for re-evaluation of the outdated paradigm of categorizing autoimmune diseases strictly into Th1 and Th2 axes.

SNAS is a chronic inflammatory disorder that is reportedly characterized by a constellation of symptoms which can involve cutaneous, respiratory, gastrointestinal, and/or neurologic manifestations following systemic exposure to nickel (e.g., ingestion, implantation, inhalation) in individuals with prior sensitization. However, despite multi-system involvement, there is currently no literature regarding the management of SNAS patients for endocrine abnormalities. While the mechanism for SNAS is poorly understood, elevated levels of interleukin-4 (IL-4) have been reported [2]. Like SNAS, CAT pathogenesis also involves both Th1/IFNγ and Th2/IL-4 pathways [1, 2]. Given that IL-4 stimulates Th2 cell proliferation in a self-perpetuating cycle, it is plausible that the corresponding disproportionate and elevated Th2 axes may become further potentiated by repetitive nickel exposure, creating an immunologic milieu that further increases the susceptibility towards the development of CAT through its Th2/IL-4 mediated component. The elevation in IL-4 supports a positive feedback loop for Th2 lymphocyte activation and promotes B lymphocyte differentiation, maturation, and autoimmune antibody production.

Although Th1/IFNγ and Th17 proinflammatory pathways in CAT are primarily associated with cytotoxic cell-mediated thyroid destruction, the Th2/IL-4 pathway is associated with the production of anti-TG/TPO antibodies during the early stages of CAT prior to the development of subclinical or overt hypothyroidism [2]. Notably, the SNAS group was also associated with higher anti-TPO antibody titers, which are found in 90–95% of CAT patients, compared to the non-SNAS group (19.9% vs. 7.8) [1, 2].

A recent study by Zaletel et al.'s on the polymorphisms of transforming growth factor (TGF-β), a critical anti-inflammatory cytokine and enhancer of Th1 cell activation in CAT, may explain the dysregulated Th1/Th2 balance underlying both diseases [2]. TGF-β polymorphisms, such as the T allele of +369 T/C SNP, were associated with lower TGF-β secretion and severe clinical hypothyroidism [2]. Given the counterbalancing effect between TGF-β and Th2-mediated IL-4, TGF-β polymorphisms theoretically promote a shift towards the Th2/IL-4 axis thereby stimulating the production of antibodies by B lymphocytes [2]. Of further interest, induction of the Th2-IL-4 axis by nickel also supports the observations reported by Andrioli et al. [1] Systemic exposure to nickel in SNAS patients may promote increased production of autoantibodies and increase susceptibility of developing multi-system diseases (e.g., CAT) [1].

There is supporting evidence for the improvement of SNAS following a low nickel diet, raising the question of the potential role of a low nickel diet in managing the progression of multi-system autoimmune disorders, such as CAT. However, low nickel diet is difficult, and often unsustainable by most patients who may not be ready to significantly impact their quality of life. A recent study by Machler et al. identified that patients with nickel contact allergies have responded to dupilumab, an IL-4 inhibitor, which suggests that contact allergies to nickel may have both an underlying Th1 and Th2-mediated component [3]. Considering the immunological relationship underlying

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nickel allergic contact dermatitis and SNAS, it may be a worthwhile avenue to explore the relationship between targeted immunomodulators, such as dupilumab, and their efficacy for treating SNAS. This would set the stage for future studies to retrospectively determine whether the treatment of SNAS may lead to a reduction in the incidence of associated systemic autoimmune disorders among this cohort, and also provide us with a better understanding of the Th2-IL-4 immune response underlying SNAS and CAT.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors

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