

Systemic nickel allergic syndrome as an immune-mediated disease with an increased risk for thyroid autoimmunity

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Introduction

Chronic autoimmune thyroiditis (CAT) represents the most prevalent cause of hypothyroidism in areas with sufficient iodine intake. CAT is characterized by high serum levels of antibodies against thyroid antigens, and lymphocytic infiltration of the gland causing the typical hypoechoic ultrasonographic pattern, and a gradual thyroid dysfunction [1, 2]. A combination of genetic susceptibility and environmental factors is thought to be at the basis of CAT [2, 3]. As a result of the involvement of genes modulating the immune system, CAT can be associated to other autoimmune diseases or can occur as a part of a polyglandular autoimmune syndrome [4]. Viral infections, stress, sex steroid hormones, pollution, and/or allergenic antigens, instead, represent the environmental factors most probably involved [5].

Systemic nickel allergic syndrome (SNAS) is an emergent chronic inflammatory disorder that has been defined as a definite condition only recently [6–11]. It occurs in roughly 20 % of patients with delayed allergy to nickel sulfate and it is characterized by eczema, systemic contact dermatitis and extra-cutaneous respiratory, gastrointestinal, and neurological symptoms induced by the dietary intake of nickel [6]. A mixed Th1-type, Th2-type, and regulatory cytokines response are involved in SNAS pathogenesis [10]. Therefore, immune dysfunction and environmental factors seem to be involved also in this inflammatory disorder [6, 7, 9, 10]. Due to these similarities a certain susceptibility to the development of CAT in patients with SNAS can be assumed. However, data on association between CAT and SNAS are completely lacking. The aim of the present retrospective study was to estimate the risk of CAT in patients with SNAS.

Materials and methods

Between January 2010 and January 2011, a consecutive series of 260 subjects (199 females and 61 males) clinically suspected to be affected by immune-mediated inflammatory diseases were recorded at Department of Immune-Mediated Inflammatory Diseases of the Padre Pio Hospital, of Campi Salentina, Lecce (Italy). Susceptibility to immune-mediated inflammatory diseases was examined by several clinical symptoms and/or signs (i.e., fatigue, skin, and/or respiratory allergic diseases, diseases of the mucosal barrier with immunoallergic genesis) and biochemical evaluation. All these patients gave informed consent and were included in the present study that was approved by the ethics committee of the institute.

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Serum evaluation of c-reactive protein (CRP), thyroid-stimulating hormone (TSH), free thyroxine (FT4), thyroperoxidase antibodies (TPOAb), thyroglobulin antibodies (TGAb), and thyroid gland ultrasonography were performed in all enrolled patients.

CAT was defined by elevated serum TPOAb and/or TGAb, and/or ultrasonographic pattern compatible with chronic thyroiditis, i.e., hypoechoic and heterogenous thyroid gland (US thyroiditis) [1].

SNAS was defined, according to the diagnostic criteria more commonly reported by literature [6, 11], by the coexistence of the following criteria: (a) typical cutaneous and systemic manifestations suggesting SNAS; (b) patch test positivity to nickel sulfate; (c) oral challenge test positivity to nickel vs placebo; (d) clinical improvement after low nickel-content diet for 4 weeks [6, 11]. Systemic allergic diseases potentially mimicking SNAS and inflammatory disorders of the upper intestinal tract causing a non-specific “allergy” including that nickel related were accurately excluded.

FT4 and TSH were measured by an automated commercial luminescence immunoassay system (Elecsys, Roche Diagnostic Corporation, Indianapolis, USA). Serum TPOAb and TGAb values were determined by commercial immunometric assays (Elecsys, Roche Diagnostic Corporation, Indianapolis, USA) and considered positive when above 10–20 UI/ml, respectively. CRP was measured by an automated commercial assay system (Flex Reagent Cartridge Dimension, Siemens Healthcare Diagnostic, Frimley, Camberley, UK).

Thyroid ultrasounds were performed using a 7.5–10 MHz linear transducer with a Logiq P5 machine, General Electric (General Electric Company, USA). The thyroid was considered hypoechogenic when its signal was equal or below the echogenicity of the surrounding neck muscles.

Statistical analysis

Comparison of means and standard errors was made by Student's *t* test. Frequencies of positivity of antibodies and chronic autoimmune disease reported in the two groups were compared by χ^2 test or Fisher exact test, when appropriate. Statistical significance was set at $p < 0.05$. All statistical analysis was performed using Graph Pad Prism (Graph Pad Software Inc., USA).

Results

Twenty-one subjects without any immune-mediated inflammatory disorder were excluded by the study. Among the remaining 239 patients (184 females, 55 males), SNAS was diagnosed in 136 (SNAS group), whereas the

remaining 103 subjects were included in the no-SNAS group (40 with non-celiac gluten hypersensitivity, 32 with idiopathic dermatitis, 16 with lactose intolerance, and 15 with allergic sensitivity to aeroantigens). These two series were compared. The main characteristics of the two groups are summarized in Table 1.

Euthyroidism could be recorded in all 239 patients, but 4 who showed mild subclinical hypothyroidism (3/4 presenting SNAS). A number of 48 (20.1 %) out of 239 patients had positive serum thyroid antibodies ($n = 45$) or hypoechoic thyroid ultrasound pattern ($n = 37$), diagnostic for overt CAT. High titer of TPO antibodies was detected in 19.9 % of SNAS patients and in 7.8 % of the no-SNAS subjects. In 9 out of 48 subjects with thyroiditis, CAT was previously diagnosed (6/9 with concomitant SNAS). Six patients (4/6 having SNAS) were under thyroxine replacement because of overt previously diagnosed hypothyroidism. No case of polyglandular autoimmune disease was found in the two groups.

Discussion

CAT, a very common disease in areas with sufficient iodine intake, is considered as the most frequent and archetypal type of organ-specific autoimmune disorder and can be associated with other autoimmune endocrine or non-endocrine diseases. Here we describe the existence of a significant risk for autoimmune thyroid disease in SNAS patients (26.5 % of these patients had CAT).

SNAS is a non-endocrine immune-mediated disorder, such as other allergic manifestations, that has been characterized and well defined as a nosologic disease only recently. It is characterized by eczema, systemic contact dermatitis and extra-cutaneous respiratory, gastrointestinal, and neurological symptoms caused by the dietary intake of nickel sulfate [6–11].

Data on possible association between CAT and SNAS are completely lacking, and the prevalence of CAT in SNAS is unknown [12]. To the best of our knowledge, this is the first study reporting the association between these two conditions.

Data on prevalence of CAT in the general population are discordant, depending on the iodine intake, ethnic origin, and the geographical characteristics of the areas in which the studies were conducted [13–15]. A comprehensive study performed in the general population of a southern Italian village, shows occurrence of CAT in 4.9 % of females and 1.9 % of men [15]. Globally, data coming from the literature indicate that, prevalence of CAT in general population is in the 1–2 % range in white women, with a 5–10 time preference over men [16, 17].

Table 1 Percentage distribution of cases according to positivity for TGAb or TPOAbs, thyroiditis consistent ultrasonographic pattern or chronic autoimmune thyroiditis diagnosis

	SNAS (<i>n</i> = 136)	No-SNAS (<i>n</i> = 103)	<i>p</i>
Age	41.5 ± 12.2	43.3 ± 16.6	0.33
Gender (females/males)	100/36	84/19	0.19
CRP (mg/dl)	0.3 ± 0.6	0.4 ± 1.1	0.36
FT4 (pg/ml)	1.1 ± 0.2	1.1 ± 0.4	0.98
TSH (mU/l)	1.6 ± 1.6	1.6 ± 0.8	0.97
Positivity of TGAb (<i>n</i> ; %)	18; 13.2	4; 3.9	0.013
Positivity of TPOAb (<i>n</i> ; %)	33; 24.3	9; 8.7	0.003
CAT at US (<i>n</i> ; %)	29; 21.3	8; 7.8	0.007
CAT (<i>n</i> ; %)	36; 26.5	12; 12.7	0.007

CRP c-reactive protein, TGAb thyroglobulin antibodies, TPOAb thyroperoxidase antibodies, US thyroid gland ultrasonography, CAT subjects with chronic autoimmune thyroiditis diagnosed on the basis of the biochemical profile and/or thyroid ultrasound, *n* number of cases

Unlike the above mentioned studies on general population, our study was performed on the selected category of subjects affected by immune-mediated inflammatory disorders. In the immune-affected population, the prevalence of CAT is higher than that in general population [18–21]. Indeed, as expected in patients affected by immune disorders, we found a high prevalence of CAT (12.7 %) in the no-SNAS group. The prevalence of CAT found in the no-SNAS subjects is in line with data coming from literature that indicates an increased risk of CAT in selected patients affected by immune diseases, such as type 1 diabetes (14.4 %), coeliac disease (10.3 %), Sjogren's syndrome (7.0 %), rheumatoid arthritis (6.0 %), and systemic lupus erythematosus (17.6 %) [18–21].

Interestingly, we documented a twofold prevalence of CAT in SNAS subjects compared to that observed in patients with no-SNAS immune diseases (26.5 vs. 12.7 %, $p < 0.01$). This result is remarkable but remains unclear due to the different immunopathogenetic mechanisms underlying the two diseases. Past studies suggested that environmental factors, such as high iodine intake, selenium deficiency, drugs, and pollutants may be implicated in the development of CAT [2]. Moreover, metals had been reported to be implicated in the immune process and in inflammation [2]. Therefore, nickel, a potent allergen, plays a crucial role in SNAS and it may be potentially involved in the development of CAT, perhaps by increasing thyroid antigenicity and promoting the progression of the autoimmune response in susceptible individuals. Focused studies are mandatory to support these speculative hypotheses and a possible shared genetic background. In fact, CAT is supposed to be related to variants in the HLA and CTLA-4 genes [3], whereas data on the genetic predisposition of SNAS are scanty, being the association with DR7-DQ2.2 haplotype, the most frequent finding [7].

In conclusion, this retrospective study shows a twofold higher prevalence of CAT in patients with SNAS compared

to patients affected by other immune-mediated disorders. Therefore, our results prompt further studies in SNAS and CAT patients in order to confirm the significant association and eventually advise the screening of autoimmune thyroid disease in patients with SNAS and/or investigate the potential role of nickel in the development of the autoimmune process in the thyroid gland.

Conflicting interest The authors have no conflicts of interest to disclose.

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