

Case Control Study

Skin disease and thyroid autoimmunity in atopic South Italian children

Marcella Pedullà, Vincenzo Fierro, Pierluigi Marzuillo, Francesco Capuano, Emanuele Miraglia del Giudice, Eleonora Ruocco

Marcella Pedullà, Vincenzo Fierro, Pierluigi Marzuillo, Francesco Capuano, Emanuele Miraglia del Giudice, Department of Woman, Child and General and Specialized Surgery, Seconda Università degli Studi di Napoli, 80138 Napoli, Italy

Eleonora Ruocco, Department of Dermatology, Seconda Università degli Studi di Napoli, 80138 Napoli, Italy

Author contributions: Pedullà M drafted the manuscript; Pedullà M, Fierro V and Marzuillo P participated in the conception and the design of the study; Pedullà M and Capuano F examined the patients, collected anthropometric data; Miraglia del Giudice E and Ruocco E supervised the design and execution of the study.

Institutional review board statement: An informed consent was obtained from the parents and the children all enrolled after the nature of the investigation was explained and in accordance with the approved protocol from the Institutional Review Board at the Second University of Naples.

Informed consent statement: An informed consent was obtained from the parents and the children all enrolled after the nature of the investigation was explained.

Conflict-of-interest statement: Nothing to declare.

Data sharing statement: We agree with data sharing.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Pierluigi Marzuillo, MD, Department of

Woman, Child and General and Specialized Surgery, Seconda Università degli Studi di Napoli, Via L. De Crecchio n° 2, 80138 Napoli, Italy. pierluigi.marzuillo@gmail.com
Telephone: +39-081-5665420

Received: January 26, 2016

Peer-review started: January 26, 2016

First decision: March 23, 2016

Revised: April 8, 2016

Accepted: May 7, 2016

Article in press: May 9, 2016

Published online: August 8, 2016

Abstract

AIM: To verify the prevalence of thyroid autoimmunity (TA) and the possible association between atopy and TA in children affected by skin disease.

METHODS: Three hundred and twenty-four children consecutively referred due to skin disease symptoms to our Pediatric Department were enrolled. One hundred and eighty-seven were diagnosed with atopic dermatitis (AD), 95 with acute urticaria, 40 with chronic urticaria (CU), and 2 with alopecia areata (AA). According to the work-up for atopy, the children were divided into two groups: Atopics and non-atopics. TA was diagnosed by serum thyroid peroxidase autoantibodies and/or thyroglobulin autoantibodies levels more than twice normal values over a period of two months by immunoassay.

RESULTS: In all children with skin disease, a significant prevalence of TA in atopics compared with non-atopics (13.67% vs 2.67%, $P = 0.0016$) and a significant association between TA and atopy (OR = 5.76, 95%CI: 1.71-19.35) were observed. These findings were confirmed as significant in children with AD: TA in atopics was 11.5%, while TA in non-atopics was

2.7% ($P = 0.03$, OR = 4.68, 95%CI: 1.02-21.38). In addition, atopics with CU showed a significantly higher prevalence of TA (26.9%), but none of the non-atopics showed CU ($P = 0.0326$). On the other hand, atopics with AA showed a 100% (2 out of 2) prevalence of TA, compared with none of the non-atopics.

CONCLUSION: In children with skin disease, atopy seems to be associated with an increased risk of TA.

Key words: Skin disease; Thyroid autoimmunity; Atopic dermatitis; Children

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: We observed a significant association between atopy and thyroid autoimmunity (TA) in atopic children with skin disease. This association was confirmed in atopic children affected by atopic dermatitis. The key message from our study for pediatricians is that clinicians should always evaluate thyroid peroxidase and thyroglobulin autoantibodies in atopic children with skin disease, as these children could also have TA.

Pedullà M, Fierro V, Marzuillo P, Capuano F, Miraglia del Giudice E, Ruocco E. Skin disease and thyroid autoimmunity in atopic South Italian children. *World J Clin Pediatr* 2016; 5(3): 288-292 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v5/i3/288.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v5.i3.288>

INTRODUCTION

Recent observations have challenged the validity of the Th1/Th2 paradigm^[1] and considerable effort has been focused on understanding the relationship between atopic inflammation and developing autoimmunity both in experimental models and in human populations^[2].

Thyroid autoimmunity (TA) has been regularly associated with chronic urticaria (CU) both in adults^[3] and in children^[4] and less frequently with several dermatological diseases such as vitiligo^[5], alopecia areata (AA)^[6], post-adolescent acne^[7] and atopic dermatitis (AD)^[8]. On the other hand, even if less frequent, atopy is considered a cause of both AD and acute urticaria (AU) or CU presenting with intermittent symptoms^[9] and has been associated with increased risk and severity of AA^[10].

The aim of the present study is to verify the prevalence of TA and the possible association between atopy and TA in South Italian children affected by skin disease.

MATERIALS AND METHODS

From January 2013 to July 2015, 324 children consecutively referred to the Pediatric Department of the Second University of Naples for evaluation of

dermatological symptoms such as erythema, pruritus, eczematous rash, xerosis, hair loss, wheals and/or angioedema were enrolled. None of the children suffered from endocrine or systemic diseases and did not show signs of genetic syndromes.

The work-up for dermatological disease included complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum levels of complement C3, C4 and C1 inhibitor, serum immunoglobulins, antinuclear antibody and anti-DNA antibody (if needed), immunoglobulin A (IgA) and IgG anti-transglutaminase, FT3, FT4, TSH, thyroid peroxidase antibodies (TPO Ab) and thyroglobulin antibodies (TG Ab), urine analysis and culture, nasal and throat swabs, and microscopic investigation of stool for *Helicobacter pylori* antigens and parasite ova. No urticarial vasculitis, physical or other types of eliciting urticaria were diagnosed. In addition, cold provocation and threshold test (ice cube and cold water) were also performed in patients to exclude physical urticaria.

None of the patients had IgA deficiency, but two patients with urticaria were diagnosed with celiac disease and excluded. Therefore, 324 children were enrolled.

The same dermatologist from the Dermatology Department of the Second University of Naples defined the dermatological diseases. On the basis of the dermatologist's diagnosis, the cohort was then divided into 4 subgroups: 187 children were affected by AD, 95 by AU, 40 by CU, and 2 by AA.

TA was diagnosed by TPO Ab and /or TG Ab (immunoassay: High-specific solid-phase technique-chemiluminescence immune-assays PerkinElmer, Turku, Finland) serum levels more than twice normal values (TPO Ab n.v. < 30 UI/mL; TG Ab n.v. < 100 UI/mL) over a period of two months.

Atopy, defined as serum-specific IgE positivity against inhalant allergens was suspected on the basis of clinical history and diagnosed by skin prick tests (SPTs) and by a specific IgE assay (> 0.36 kUA/L - ImmunoCap 0-100 Phadia AB, Uppsala, Sweden). SPTs were performed using a standard battery of aeroallergens and food allergens: House dust mite (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), *Parietaria officinalis*, grasses (*Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*), mold (*Alternaria*, *Aspergillus*, *Cladosporium*), dog fur, cat fur, egg, cow milk, casein, wheat, soyabean, codfish, peanut and tree-nuts (Epernox, Cedex, France). Allergens were applied to a stencil stamped on the forearm with ink and pricked with a lancet (Bayer DHS Diagnostic). Histamine chloride (10 mg/mL) was used as a positive control and the allergen diluent served as the negative control. The results were read after 15 and 30 min and the test was considered positive if the wheal was at least 3 mm in diameter compared with the negative control. Thus, on the basis of the work-up for atopy, the children affected by skin disease were divided into atopics ($n = 212$) and non-atopics ($n = 112$). None of the children received steroids or immuno-suppressive therapy for at least 3

Table 1 Differences between clinical characteristics in children with skin disease divided into atopics and non-atopics

	Atopics (n = 212)	Non-atopics (n = 112)	Statistical analysis
Age in years (mean ± SD)	6.3 ± 4.18	5.55 ± 3.67	P = 0.1
Sex (male %)	111/212 (52.8%)	48/112 (42.8%)	P = 0.26
Family history of atopy (%)	188/212 (88.67%)	93/112 (83.03%)	P = 0.91
Family history of thyroid diseases (%)	93/212 (43.86%)	43/112 (38.39%)	P = 0.6

Table 2 Thyroid autoimmunity in children with skin disease divided into atopics and non-atopics

	Thyroid autoimmunity (%)	Atopics (%)	Non-atopics (%)	Statistical analysis
All skin diseases	9.6	29/212 (13.67)	3/112 (2.67)	P = 0.0016 OR = 5.76 (1.71-19.35)
Atopic dermatitis	8.02	13/113 (11.5)	2/74 (2.7)	P = 0.03 OR = 4.68 (1.02-21.38)
Alopecia areata	100	2/2	0	NA
Chronic urticaria	17.5	7/26 (26.9)	0/14	P = 0.0326
Acute urticaria	8.42	7/71 (9.85)	1/24 (4.1)	P = 0.38

mo before the investigation. Antihistamine therapy was stopped at least 2 wk before the investigation.

An informed consent was obtained from the parents and the children all enrolled after the nature of the investigation was explained and in accordance with the approved protocol from the Institutional Review Board at the Second University of Naples.

Statistical analysis

In this observational study the *t* test was used to compare the difference between the mean values and a χ^2 test was used to analyze the differences between the frequencies among categorical variables assessed by Kurtosis. A *P* value < 0.05 was considered significant.

An odds ratio (OR) was calculated to evaluate the association between atopy and TA. This was considered significant when showing a 95%CI and excluding unity.

Statistical analyses were performed using Stat-Graph 3.0 for Windows.

RESULTS

Table 1 shows the differences between the characteristics of the 324 children with skin diseases divided into atopics and non-atopics.

Significant differences regarding age in years, sex, and family history of atopic and thyroidal disease were not observed between the two groups (Table 1).

It is worth noting that in all children with skin disease a significant prevalence of TA in atopics compared with non-atopics (13.67% vs 2.67%, *P* = 0.0016) and a significant association between TA and atopy (OR = 5.76, 95%CI: 1.71-19.35) were observed (Table 2). These findings were confirmed as significant in AD affected children: TA prevalence in atopics was 11.5%, while TA prevalence in non-atopics was 2.7% (*P* = 0.03, OR = 4.68, 95%CI: 1.02-21.38) (Table 2). In addition, atopics affected by CU showed a significantly higher

prevalence of TA (26.9%) compared with non-atopics (*P* = 0.0326), but none of the non-atopics had CU (Table 2). On the other hand, AA atopics showed a 100% (2 out of 2) prevalence of TA compared with none of the non-atopics (Table 2).

AU atopics did not show a significant difference compared with non-atopics in terms of a significant risk for TA.

DISCUSSION

There is currently great interest in defining the link between atopy and autoimmunity.

T regulatory (T reg) cells seem to play a pivotal role in this relationship, as they are essential for the maintenance of immune homeostasis and prevention of autoimmunity^[11]. There is also evidence that the number or function of T reg cells may be deficient in patients with atopy^[12].

Furthermore, decoy receptor 3 (DcR3), a member of the tumor necrosis factor receptor superfamily, can promote M2 macrophage differentiation *via* epigenetic regulation, with a pleiotropic immunomodulatory effect^[13]. Indeed, elevated levels of DcR3 have been found in the serum of atopic patients^[14]. DcR3 can also promote tumorigenesis *via* the induction of tumor-associated macrophages^[15]. It has also been proposed that atopy may have effects on the risk of cancer, but studies of thyroid cancer^[16] and non-melanoma skin cancer^[17] have shown no association or conflicting results related to atopy.

To date, few papers in the literature address the relationship between atopy and TA. In our study, TA prevalence in children with skin disease was 8.9% and atopics had a significant higher prevalence of TA compared with non-atopics. Moreover, they showed a significant risk for TA. We would underline a possible selection bias in our patient sample, which was selected

from children referred to a University Pediatric Center for the diagnosis and treatment of allergic disease. The prevalence of TA reported for age-matched healthy children in different geographic areas ranges from 0.3%^[18] to 1.6%^[19]. In a recent study conducted in a Mediterranean area similar to South Italy with regard to iodine status (Almeria, Spain), the prevalence of TA was higher and reached 3.7% in healthy children and adolescents^[20].

In the four subgroups selected on the basis of different dermatological diagnoses, a significant association between TA and atopy was found only in children with AD, similar to the findings in our previously published paper^[8].

We also identified 2 cases of AA, both atopics. In the literature, AA is regularly associated both with TA and atopy. This was not confirmed in our cohort as only two patients were diagnosed with AA. Barahmani *et al*^[21] suggested that AA has features of both atopic and autoimmune-mediated skin disease.

Leznoff *et al*^[22], for the first time, demonstrated a TA prevalence of 16% in a large population of adults with CU. Rumblyrt *et al*^[23] described a TA prevalence ranging from 10% to 35% in adults with CU.

TA prevalence in our CU children was 17.5%, slightly higher than the reported prevalence in healthy children, which ranged from 4.3%^[4] to 14.8%^[24]. On the other hand, in our CU atopics we found a TA prevalence of 26.9%, significantly higher compared to our non-atopics (0%, $P = 0.0326$) and higher than that reported in healthy children in the literature. In addition, TA prevalence in our AU patients was 8.42% and no significant association between TA and atopy was found. It is possible that an acute atopic inflammation could contribute to the occurrence of TA in patients with AU. To date, only Gangemi *et al*^[25] have identified TA positivity in 3 out of 6 adult patients affected by idiopathic acute urticaria.

To our knowledge, this is the first report to show a significant prevalence of TA in a population of atopic children affected by skin disease and a significant risk of TA in these atopics.

The key message from our study for pediatricians is that clinicians should always evaluate TPO and TG autoantibodies in atopic children affected by skin disease, as these children could have concomitant TA.

COMMENTS

Background

Thyroid autoimmunity (TA) is regularly associated with chronic urticaria both in adults and in children and less frequently with several dermatological diseases such as vitiligo, alopecia areata, post-adolescent acne and atopic dermatitis. The aim of the present study was to verify the prevalence of TA and the possible association between atopy and TA in children affected by skin disease.

Research frontiers

Important areas of research related to this study are represented by the field of pediatric dermatology and allergology. This study aimed to verify the association between TA and skin diseases in a population of atopic children.

Innovations and breakthroughs

To our knowledge, this is the first report to show a significant prevalence of TA in a population of atopic children affected by skin disease and a significant risk of TA in these atopics.

Applications

Future research is necessary to confirm the authors' findings and to understand the pathophysiological basis underlying the association between TA and skin diseases in atopic children.

Terminology

Atopy is defined as serum-specific IgE positivity against inhalant allergens suspected on the basis of clinical history and diagnosed by skin prick tests and by a specific IgE assay (> 0.36 kU/L - ImmunoCap 0-100).

Peer-review

This is a very interesting manuscript with the aim to verify the prevalence of thyroid autoimmunity and the possible association with atopy in a restricted population showing skin disease.

REFERENCES

- 1 Nowak EC, Noelle RJ. Interleukin-9 as a T helper type 17 cytokine. *Immunology* 2010; **131**: 169-173 [PMID: 20673237 DOI: 10.1111/j.1365-2567.2010.03332.x]
- 2 Shah A. The pathologic and clinical intersection of atopic and autoimmune disease. *Curr Allergy Asthma Rep* 2012; **12**: 520-529 [PMID: 22898881 DOI: 10.1007/s11882-012-0293-0]
- 3 Pan XF, Gu JQ, Shan ZY. The prevalence of thyroid autoimmunity in patients with urticaria: a systematic review and meta-analysis. *Endocrine* 2015; **48**: 804-810 [PMID: 25064381 DOI: 10.1007/s12020-014-0367-y]
- 4 Levy Y, Segal N, Weintrob N, Danon YL. Chronic urticaria: association with thyroid autoimmunity. *Arch Dis Child* 2003; **88**: 517-519 [PMID: 12765919]
- 5 Kroon MW, Vrijman C, Chandeck C, Wind BS, Wolkerstorfer A, Luiten RM, Bos JD, Geskus RB, van Trotsenburg P, van der Veen JP. High prevalence of autoimmune thyroiditis in children and adolescents with vitiligo. *Horm Res Paediatr* 2013; **79**: 137-144 [PMID: 23548513 DOI: 10.1159/000348388]
- 6 Huang KP, Mullangi S, Guo Y, Qureshi AA. Autoimmune, atopic, and mental health comorbid conditions associated with alopecia areata in the United States. *JAMA Dermatol* 2013; **149**: 789-794 [PMID: 23700152 DOI: 10.1001/jamadermatol.2013.3049]
- 7 Vergou T, Mantzou E, Tseke P, Moustou AE, Katsambas A, Alevizaki M, Antoniou C. Association of thyroid autoimmunity with acne in adult women. *J Eur Acad Dermatol Venereol* 2012; **26**: 413-416 [PMID: 21521376 DOI: 10.1111/j.1468-3083.2011.04084.x]
- 8 Pedullà M, Fierro V, Papacuiuolo V, Alfano R, Ruocco E. Atopy as a risk factor for thyroid autoimmunity in children affected with atopic dermatitis. *J Eur Acad Dermatol Venereol* 2014; **28**: 1057-1060 [PMID: 24118567 DOI: 10.1111/jdv.12281]
- 9 Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau A, Grattan CE, Kapp A, Merk HF, Rogala B, Saini S, Sánchez-Borges M, Schmid-Grendelmeier P, Schünemann H, Staubach P, Vena GA, Wedi B, Maurer M. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy* 2009; **64**: 1417-1426 [PMID: 19772512 DOI: 10.1111/j.1398-9995.2009.02179.x]
- 10 Li SF, Zhang XT, Qi SL, Ye YT, Cao H, Yang YQ, McElwee KJ, Zhang X. Allergy to dust mites may contribute to early onset and severity of alopecia areata. *Clin Exp Dermatol* 2015; **40**: 171-176 [PMID: 25252126 DOI: 10.1111/ced.12471]
- 11 Wing JB, Sakaguchi S. Foxp3⁺ T(reg) cells in humoral immunity. *Int Immunol* 2014; **26**: 61-69 [PMID: 24324208 DOI: 10.1093/intimm/dxt060]
- 12 Josefowicz SZ, Niec RE, Kim HY, Treuting P, Chinen T, Zheng Y, Umetsu DT, Rudensky AY. Extrathymically generated regulatory

- T cells control mucosal TH2 inflammation. *Nature* 2012; **482**: 395-399 [PMID: 22318520 DOI: 10.1038/nature10772]
- 13 **Lin WW**, Hsieh SL. Decoy receptor 3: a pleiotropic immunomodulator and biomarker for inflammatory diseases, autoimmune diseases and cancer. *Biochem Pharmacol* 2011; **81**: 838-847 [PMID: 21295012 DOI: 10.1016/j.bcp.2011.01.011]
 - 14 **Chen CC**, Yang YH, Lin YT, Hsieh SL, Chiang BL. Soluble decoy receptor 3: increased levels in atopic patients. *J Allergy Clin Immunol* 2004; **114**: 195-197 [PMID: 15282937]
 - 15 **Tai SK**, Chang HC, Lan KL, Lee CT, Yang CY, Chen NJ, Chou TY, Tarng DC, Hsieh SL. Decoy receptor 3 enhances tumor progression via induction of tumor-associated macrophages. *J Immunol* 2012; **188**: 2464-2471 [PMID: 22287720 DOI: 10.4049/jimmunol.1101101]
 - 16 **Merrill RM**, Isakson RT, Beck RE. The association between allergies and cancer: what is currently known? *Ann Allergy Asthma Immunol* 2007; **99**: 102-116; quiz 117-119, 150 [PMID: 17718097]
 - 17 **Skaaby T**, Nystrup Husemoen LL, Roswall N, Thuesen BH, Linneberg A. Atopy and development of cancer: a population-based prospective study. *J Allergy Clin Immunol Pract* 2014; **2**: 779-785 [PMID: 25439371 DOI: 10.1016/j.jaip.2014.06.010]
 - 18 **Jaksić J**, Dumić M, Filipović B, Ille J, Cvijetić M, Gjurić G. Thyroid diseases in a school population with thyromegaly. *Arch Dis Child* 1994; **70**: 103-106 [PMID: 8129428]
 - 19 **Marwaha RK**, Tandon N, Karak AK, Gupta N, Verma K, Kochupillai N. Hashimoto's thyroiditis: countrywide screening of goitrous healthy young girls in postiodization phase in India. *J Clin Endocrinol Metab* 2000; **85**: 3798-3802 [PMID: 11061541]
 - 20 **García-García E**, Vázquez-López MÁ, García-Fuentes E, Rodríguez-Sánchez FI, Muñoz FJ, Bonillo-Perales A, Soriguer F. Iodine intake and prevalence of thyroid autoimmunity and autoimmune thyroiditis in children and adolescents aged between 1 and 16 years. *Eur J Endocrinol* 2012; **167**: 387-392 [PMID: 22728345 DOI: 10.1530/EJE-12-0267]
 - 21 **Barahmani N**, Schabath MB, Duvic M. History of atopy or autoimmunity increases risk of alopecia areata. *J Am Acad Dermatol* 2009; **61**: 581-591 [PMID: 19608295 DOI: 10.1016/j.jaad.2009.04.031]
 - 22 **Leznoff A**, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol* 1989; **84**: 66-71 [PMID: 2754146]
 - 23 **Rumbyrt JS**, Schocket AL. Chronic urticaria and thyroid disease. *Immunol Allergy Clin North Am* 2004; **24**: 215-223, vi [PMID: 15120148]
 - 24 **Kilic G**, Guler N, Suleyman A, Tamay Z. Chronic urticaria and autoimmunity in children. *Pediatr Allergy Immunol* 2010; **21**: 837-842 [PMID: 20609133 DOI: 10.1111/j.1399-3038.2010.00986.x]
 - 25 **Gangemi S**, Saitta S, Lombardo G, Patafi M, Benvenga S. Serum thyroid autoantibodies in patients with idiopathic either acute or chronic urticaria. *J Endocrinol Invest* 2009; **32**: 107-110 [PMID: 19411805]

P- Reviewer: Aksoy B, Cuevas-Covarrubias SA, Sergi CM
S- Editor: Gong XM **L- Editor:** Webster JR **E- Editor:** Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

