

Skin findings in autoimmune and nonautoimmune thyroid disease with respect to thyroid functional status and healthy controls

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Received: 08.10.2015 • Accepted/Published Online: 14.01.2017 • Final Version: 12.06.2017

Background/aim: Thyroid disorders are associated with a wide variety of skin disorders that respond to treatment of hormone imbalance in most cases and thus are of vital importance to dermatologists. This study aimed to evaluate skin findings associated with autoimmune and nonautoimmune thyroid disease with respect to thyroid functional status and healthy controls.

Materials and methods: A total of 300 consecutive patients with either autoimmune (n = 173) or nonautoimmune (n = 127) thyroid disease and 100 healthy control subjects were included in this cross-sectional study. Data on patient demographics, thyroid function tests, and skin findings were recorded for patient and control groups.

Results: Compared to control subjects, patients had higher proportions in populations with alopecia (P < 0.001), nail thinning (P = 0.02), brittle nails (P = 0.001), pruritus (P < 0.001), diffuse hyperhidrosis (P = 0.01), flushing (P = 0.001), and xerosis (P < 0.001). Onycholysis (P = 0.02), yellow skin (P = 0.04), periorbital edema (P = 0.03), psoriasis (P = 0.001), and palmoplantar hyperkeratosis (P = 0.007) were significantly more common in patients with autoimmune than nonautoimmune thyroid disease. A significantly higher percentage of patients with autoimmune rather than nonautoimmune thyroid disease had overall skin findings (P = 0.03) among the hyperthyroid patients.

Conclusions: Our findings indicate that the presence of skin findings in a majority of thyroid patients significantly differs for certain cutaneous manifestations with respect to controls, autoimmune etiology, and thyroid functional status.

Key words: Skin findings, thyroid disease, autoimmune, thyroid status

1. Introduction

Thyroid hormone has an integral role in sustaining normal epidermal functions including oxygen consumption, protein synthesis, mitosis, differentiation, and determination of layer thickness (1,2). Given that the skin is often the first organ where a wide range of clinical manifestations of thyroid hormone imbalance arises, thyroid disease can often first be diagnosed by recognizing cutaneous manifestations related to thyroid hormone imbalance (2).

Hence, cutaneous manifestations of thyroid diseases are of vital importance to dermatologists as they not only signal the need of investigating and thus diagnosing an underlying thyroid disorder but also they improve in most cases with the treatment of thyroid disease (2,3).

Autoimmune thyroid diseases are also of special importance given that they are associated with other organ-specific or systemic autoimmune disorders (4–6).

The present study was designed to evaluate skin manifestations associated with autoimmune and nonautoimmune thyroid disease with respect to thyroid functional status and healthy controls.

2. Materials and methods

2.1. Study population

A total of 300 consecutive patients with either autoimmune (n = 173, mean (SD) age: 42.0 (14.0) years; 93.6% were female) or nonautoimmune (n = 127, mean (SD) age: 44.0 (10.0) years; 88.2% were females) thyroid disease and 100 healthy control subjects (mean (SD) age: 40.0 (13.0) years;

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90.0% were females) were included in this cross-sectional study conducted at our outpatient clinic. Patients who were diagnosed with only thyroid diseases and had not received any treatment previously were included. The control group consisted of healthy adults. Patients under 18 years of age, patients with other known systemic and endocrine diseases, and pregnant and lactating women were excluded from the study.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the institutional ethics committee.

2.2. Assessments

Data on patient demographics, thyroid function tests [serum levels for free triiodothyronine (T3), free thyroxine (T4), thyroid stimulating hormone (TSH), antithyroglobulin antibody, and antithyroid peroxidase antibody], and examination of the integumentary system (alopecia, hair dryness, nail thinning, onycholysis, pitting, brittle nails, xerosis, pruritus, diffuse hyperhidrosis, palmoplantar hyperhidrosis, facial erythema, flushing, yellow skin, carotenemia, periorbital edema, diffuse edema, palmoplantar hyperkeratosis, moist skin, vitiligo, alopecia areata, psoriasis, urticarial, acne rosacea, contact dermatitis, acanthosis nigricans, localized hyperpigmentation) were recorded for patient and control groups as well as among thyroid patients with respect to thyroid functional status. Physical examinations of the patients were performed by an endocrinologist. All subjects were examined for skin findings or dermatoses by the same dermatologist.

2.3. Thyroid functional status

Patients were categorized as hyperthyroid, hypothyroid, or euthyroid based on normal ranges defined for serum levels for free T3 (1.71–3.71 pg/mL), free T4 (0.70–1.48 ng/mL), TSH (0.35–4.94 IU/mL), antithyroglobulin antibody (0–34 IU/mL), and antithyroid peroxidase antibody (0–115 IU/mL).

2.4. statistical analysis

Statistical analysis was conducted using computer software (SPSS version 13.0, SPSS Inc., Chicago, IL, USA). The chi-square test for the comparison of categorical data and ANOVA and post hoc Tukey test were used for the parametric variables. Data were expressed as “mean (standard deviation; SD)” and percent (%) where appropriate. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics

Our study group included 300 patients (274 females, 26 males) with thyroid disease, including 173 (58%) patients with autoimmune thyroid disease and 127 (42.0%) with

nonautoimmune thyroid disease, and 100 control subjects (90 females, 10 males). Patient and control groups were homogeneous in terms of sex distribution, while patients with nonautoimmune thyroid disease (mean (SD) age: 44.0 ± 10.0 years) were older than patients with autoimmune thyroid disease (42.0 ± 14.0 years) and control subjects (40.0 ± 13.0 years) ($P < 0.001$ for each) (Table 1).

3.2. Skin findings with respect to autoimmunity

Skin findings were positive in 243 of 300 thyroid disease patients (81.0%) and in 57 of 100 (57.0%) control subjects. The most frequently observed skin findings were xerosis in 135 patients (45.0%), alopecia in 97 (32.3%), pruritus in 82 (27.3%), brittle nails in 66 (22.0%), nail thinning in 39 (13.0%), flushing in 43 (14.3%), and hair dryness in 27 patients (9.0%) (Table 1).

Among the population with at least one skin finding (243 patients and 57 control subjects), 45.0% were patients with autoimmune thyroid disease, 36.0% were patients with nonautoimmune thyroid disease, and only 19.0% were control subjects ($P < 0.001$). Specifically, patients rather than control subjects had higher proportions in populations with alopecia (54.2%, 36.4%, and 9.3%, respectively, $P < 0.001$), nail thinning (61.7%, 21.3%, and 17.0%, respectively, $P = 0.02$), brittle nails (60.8%, 28.4%, and 10.8%, respectively, $P = 0.001$), pruritus (52.4%, 45.2%, and 2.4%, respectively, $P < 0.001$), diffuse hyperhidrosis (58.1%, 34.9%, and 7.0%, respectively, $P = 0.01$), flushing (54.5%, 43.2%, and 2.3%, respectively, $P = 0.001$), and xerosis (43.7%, 45.7%, and 10.6%, respectively, $P < 0.001$) along with a higher likelihood of autoimmune than nonautoimmune thyroid patients to have these skin findings except for xerosis (Table 1).

Onycholysis (80.0% vs. 20.0%, $P = 0.02$), yellow skin (64.7% vs. 35.3%, $P = 0.04$), periorbital edema (75.0% vs. 25.0%, $P = 0.03$), and psoriasis (91.7% vs. 8.3%, $P = 0.001$) were significantly more common in patients with autoimmune than nonautoimmune thyroid disease, while they were not observed in any of the control subjects. All palmoplantar hyperkeratosis cases were observed in patients with autoimmune thyroid disease ($P = 0.007$) (Table 1).

3.3. Skin findings with respect to thyroid status

A total of 56 (18.7%) patients had hyperthyroidism, 158 (52.7%) patients had hypothyroidism, and 86 (28.7%) patients had euthyroidism. Skin findings were observed in 54 (96.4%), 135 (85.4%), and 77 (89.5%) patients with hyperthyroid, hypothyroid, and euthyroid status, respectively (Table 2).

A significantly higher percentage of patients with autoimmune than nonautoimmune thyroid disease had overall skin findings (70.3% vs. 29.7%, $P = 0.03$), alopecia (84.6% vs. 15.4%, $P = 0.01$), and brittle nails (88.9% vs. 11.1%, $P = 0.02$) among hyperthyroid patients and had nail thinning (90.9% vs. 9.1%, $P = 0.01$) and periorbital

Table 1. Demographic and clinical characteristics and skin findings in study groups.

	Control (n = 100)	Autoimmune disease (n = 173)	Nonautoimmune disease (n = 127)	P-value
Age, years, mean (SD)	40.0 (13.0)	42.0 (14.0)	44.0 (10.0)	<0.001
Sex, n (%)				
Female	90 (90.0)	162 (93.6)	112 (88.2)	0.24
Male	10 (10)	11 (6.4)	15 (11.8)	
Skin findings, n (%)				
At least one skin finding	57 (19.0)	135 (45.0)	108 (36.0)	<0.001
Alopecia	10 (9.3)	58 (54.2)	39 (36.4)	<0.001
Hair dryness	8 (22.9)	19 (54.3)	8 (22.9)	0.34
Nail thinning	8 (17.0)	29 (61.7)	10 (21.3)	0.02
Onycholysis	-	8 (80.0)	2 (20.0)	0.02
Pitting	-	2 (25.0)	6 (75.0)	0.47
Brittle nails	8 (10.8)	45 (60.8)	21 (28.4)	0.001
Xerosis	16 (10.6)	66 (43.7)	69 (45.7)	<0.001
Pruritus	2 (2.4)	44 (52.4)	38 (45.2)	<0.001
Diffuse hyperhidrosis	3 (7.0)	25 (58.1)	15 (34.9)	0.01
Palmoplantar hyperhidrosis	-	5 (41.7)	7 (58.3)	0.99
Facial erythema	5 (21.7)	10 (43.5)	8 (34.8)	0.91
Flushing	1 (2.3)	24 (54.5)	19 (43.2)	0.001
Yellow skin	-	11 (64.7)	6 (35.3)	0.04
Carotenemia	-	3 (27.5)	5 (62.5)	0.58
Periorbital edema	-	9 (75.0)	3 (25.0)	0.03
Diffuse edema	-	2 (28.6)	5 (71.4)	0.47
Palmoplantar hyperkeratosis	-	6 (100)	-	0.007
Moist skin	-	8 (66.7)	4 (33.3)	0.14
Vitiligo	-	2 (50)	2 (50)	0.99
Alopecia areata	-	1 (100)	-	0.44
Psoriasis	-	11 (91.7)	1 (8.3)	0.001
Urticaria	3 (75.0)	1 (25.0)	-	0.63
Acne rosacea	5 (55.6)	3 (33.3)	1 (11.1)	0.73
Contact dermatitis	2 (11.8)	10 (58.8)	5 (29.4)	0.32
Acanthosis nigricans	-	-	2 (100)	0.51
Localized hyperpigmentation	-	-	2 (100)	0.51

edema (100.0% vs. 0.0%, $P = 0.04$) among hypothyroid patients. A significantly lower percentage of patients with autoimmune than nonautoimmune thyroid disease had xerosis (20.9% vs. 79.1%, $P = 0.006$) in the case of euthyroid status (Table 2).

4. Discussion

Our findings in a cohort of patients with thyroid disease and healthy control subjects revealed positive skin

findings in 81.0% of thyroid disease patients and in 57.0% of control subjects. The presence of autoimmune thyroid disease was associated with a higher likelihood of skin findings including alopecia, nail thinning, brittle nails, diffuse hyperhidrosis, and flushing as compared with nonautoimmune thyroid disease and normal thyroid functions. There was a significantly higher percentage of patients with autoimmune than nonautoimmune thyroid disease among patients with onycholysis, yellow skin,

Table 2. Skin findings in patients with autoimmune or nonautoimmune thyroid disease with respect to thyroid status.

Skin findings (+) n (%)	Hyperthyroid status (n = 56)				Hypothyroid status (n = 158)				Euthyroid status (n = 86)			
	Autoimmune	Nonautoimmune	P-value		Autoimmune	Nonautoimmune	P-value		Autoimmune	Nonautoimmune	P-value	
Overall	38 (70.3)	16 (29.7)	0.03		91 (67.4)	44 (32.6)	0.83		25 (32.4)	52 (67.6)	0.95	
Alopecia	22 (84.6)	4 (15.4)	0.01		29 (69)	13 (31)	0.83		7 (24.1)	22 (75.9)	0.14	
Hair dryness	5 (100)	-	0.16		11 (91.7)	1 (8.3)	0.10		3 (37.5)	5 (62.5)	0.56	
Nail thinning	8 (80)	2 (20)	0.31		20 (90.9)	2 (9.1)	0.01		1 (16.7)	5 (83.3)	0.65	
Onycholysis	2 (100)	-	0.45		6 (85.7)	1 (14.3)	0.43		-	1 (100)	0.65	
Pitting	-	2 (100)	0.09		2 (50)	2 (50)	0.59		-	2 (100)	0.54	
Brittle nails	16 (88.9)	2 (11.1)	0.02		24 (75)	8 (25)	0.32		5 (33.3)	10 (66.7)	0.91	
Xerosis	12 (57.1)	9 (42.9)	0.18		45 (66.2)	23 (33.8)	0.71		9 (20.9)	37 (79.1)	0.006	
Pruritus	10 (66.7)	5 (33.3)	0.90		25 (75.8)	8 (24.2)	0.26		9 (28.1)	23 (71.9)	0.32	
Diffuse hyperhidrosis	15 (75)	5 (25)	0.39		8 (80)	2 (20)	0.50		2 (22.2)	7 (77.8)	0.48	
Palmoplantar hyperhidrosis	2 (66.7)	1 (33.3)	0.96		3 (100)	-	0.55		-	6 (100)	0.08	
Facial erythema	2 (66.7)	1 (33.3)	0.96		7 (100)	-	0.09		1 (12.5)	7 (87.5)	0.25	
Flushing	8 (66.7)	4 (33.3)	0.92		11 (84.6)	2 (15.4)	0.17		5 (27.8)	13 (72.2)	0.58	
Yellow skin	-	-	-		9 (81.8)	2 (18.2)	0.50		2 (40)	3 (60)	0.79	
Carotenemia	-	-	-		3 (60)	2 (40)	0.65		-	3 (100)	0.54	
Periorbital edema	1 (100)	-	0.99		8 (100)	-	0.04		-	3 (100)	0.54	
Diffuse edema	-	1 (100)	0.32		1 (50)	1 (50)	0.54		1 (25)	3 (75)	0.99	
Palmoplantar hyperkeratosis	-	-	-		6 (100)	-	0.17		-	-	-	
Moist skin	6 (66.7)	3 (33.3)	0.99		2 (100)	-	0.99		-	1 (100)	0.99	
Vitiligo	-	-	-		1 (100)	-	0.99		1 (33.3)	2 (66.7)	0.99	
Alopecia areata	-	-	-		1 (100)	-	0.99		-	-	-	
Psoriasis	1 (100)	-	0.99		8 (88.9)	1 (11.1)	0.27		2 (100)	-	0.11	
Urticaria	-	-	-		1 (100)	-	0.99		-	-	-	
Acne rosacea	-	-	-		1 (100)	-	0.99		2 (66.7)	1 (33.3)	0.27	
Contact dermatitis	3 (100)	-	-		4 (57.1)	3 (42.9)	0.68		3 (60)	2 (40)	0.33	
Acanthosis nigricans	-	-	-		-	-	-		-	-	-	
Localized hyperpigmentation	-	2 (100)	0.09		-	-	-		-	-	-	

periorbital edema, psoriasis, and palmoplantar keratosis in the overall study population; among hyperthyroid patients with overall skin findings, alopecia, and brittle nails; and among hypothyroid patients with nail thinning and periorbital edema.

In a past study conducted with Turkish patients with thyroid disease ($n = 220$), skin findings were reported to be detected in 56.8% of patients with chronic urticaria (6.8%), vitiligo (6.8%), diffuse alopecia (6%), acne vulgaris (5%), and acne rosacea (3.6%) as the most common findings (7).

In our study population 81.0% of patients had skin findings with xerosis (45.0%), alopecia (32.3%), pruritus (27.3%), brittle nails (22.0%), nail thinning (13.0%), flushing (14.3%), and hair dryness (9.0%) as the most commonly observed ones. When compared to controls, the likelihood of alopecia, nail thinning, brittle nails, diffuse hyperhidrosis, flushing, and xerosis was higher in thyroid patients. Hence, our findings support the likelihood of thyroid diseases to manifest with a wide range of changes in the hair, skin, and nails depending on the thyroid status and are in agreement with the positivity of skin findings such as diffuse alopecia, xerosis, hyperhidrosis, soft and friable nails, onycholysis, and pruritus reported in past studies (3,5,7–11).

Xerosis is one of the characteristic cutaneous symptoms in adults with hypothyroidism that has been considered to occur as a result of peripheral cutaneous vasoconstriction, hypohidrosis, and decline in epidermal sterol biosynthesis and sebaceous gland secretion (2). Moreover, a potential role for topical thyroid hormone has also been suggested in the management of xerosis, even in patients with euthyroidism (12). Hence, identification of xerosis as the most common skin finding in our cohort of patients seems consistent with the fact that 52.7% of overall patients were hypothyroid and 28.7% were euthyroid.

None of our patients had thyroid acropachy, pretibial myxedema, xanthoma, generalized myxedema, bullous pemphigoid, or lupus erythematosus, along with identification of vitiligo, alopecia areata, urticaria, acne rosacea, acanthosis nigricans, and localized hyperpigmentation in less than 1% of our patients.

Among the skin manifestations observed more commonly in patient than in control groups in our cohort, diffuse alopecia, nail thinning, and brittle nails are more commonly associated with hypothyroidism (1,2), while diffuse hyperhidrosis and flushing are among the typical skin findings in hyperthyroid patients, attributed to increased cutaneous blood flow and peripheral vasodilation (13).

Diffuse alopecia and thyroid diseases have been suggested to be associated in 60% of cases, mainly of autoimmune origin (9–11). In a past study from Turkey diffuse alopecia was noted in 6% of overall patients

with thyroid disease, being higher in both autoimmune hyperthyroidism and hypothyroidism patients when compared to healthy controls (7). In our study population, alopecia was the second most common skin finding in overall patients, while among hyperthyroid patients with alopecia, autoimmune rather than nonautoimmune origin was more likely. This seems interesting given that alopecia areata rather than diffuse alopecia was in fact associated particularly with a history of atopy and autoimmune disease (14–16).

Aside from alopecia areata, vitiligo and chronic urticaria have also been considered among the dermatological diseases associated with autoimmune thyroid disorders (15,16). In a past study from Turkey, chronic urticaria, vitiligo, and pruritus were reported to be significantly more common among thyroid patients, while urticaria, vitiligo, and diffuse alopecia were more common among patients with autoimmune thyroid diseases as compared with healthy control subjects (7). However, none of these skin findings were more common in autoimmune than in nonautoimmune disease in our cohort, and they were observed in less than 1% of patients.

Nail changes are frequently encountered in thyroid diseases with thin, striated, and brittle nails in hypothyroidism and yellow nails in hyperthyroidism as well as onycholysis in both conditions (3,5,8,9,17). Accordingly, brittle nails were the most common thyroid disease-related change in nails among our patients, and like diffuse alopecia, among hyperthyroid patients with brittle nails, autoimmune rather than nonautoimmune origin of thyroid disease was more likely.

Being among the typical cutaneous manifestations of autoimmune hypothyroidism and/or hyperthyroidism (2), onycholysis, yellow skin, periorbital edema, psoriasis, and palmoplantar keratosis were not observed among control subjects, while they were more likely in the case of autoimmune than nonautoimmune origin of thyroid disease in our cohort. Based on the clinical and biochemical overlap between Hashimoto's thyroiditis and Graves' hyperthyroidism, the occurrence of the same dermatologic and ophthalmologic manifestations has been considered likely (8,10,18–21). Hence, our findings seem to indicate that special emphasis should be placed on skin manifestations of autoimmune etiologies of hypothyroidism (i.e. Hashimoto's thyroiditis) and hyperthyroidism (i.e. Graves' disease) (2,5,22).

Skin findings were observed in 96.4%, 85.4%, and 89.5% of our patients with hyperthyroid, hypothyroid, and euthyroid status, respectively. Notably, there were significantly higher percentages of patients with autoimmune than nonautoimmune thyroid disease among hyperthyroid patients with overall skin findings, alopecia, and brittle nails and among hypothyroid patients with nail thinning and periorbital edema.

In contrast to our findings no statistical difference was reported between “autoimmune vs. nonautoimmune” hyperthyroidism, hypothyroidism, and euthyroidism in a past study, while vitiligo and diffuse alopecia in patients with autoimmune hyperthyroidism and vitiligo in patients with autoimmune hypothyroidism were reported to be higher as compared with the control group (7).

In this regard, our findings emphasize the higher likelihood of certain cutaneous manifestations among patients with autoimmune thyroid disease as compared not only with controls but also with nonautoimmune thyroid disease even in hyperthyroid and hypothyroid states.

Autoimmune thyroid diseases are frequently associated with other organ-specific or systemic autoimmune disorders (4), while both thyroid autoimmunity and increased TSH were reported to represent independent risk factors for thyroid malignancy (6). Hence, upon the diagnosis of autoimmune thyroid disease, clinicians are suggested to be vigilant for any of the potential associated disorders for which the patient may be at risk throughout the patient's entire life (5,23).

Hyperthyroid patients had significantly higher likelihoods of overall skin manifestations in the case of autoimmune than nonautoimmune origin of thyroid disease, while hypothyroid and euthyroid patients with autoimmune thyroid disease showed higher prevalences of only certain skin findings. Hence, our findings emphasize the importance of recognizing cutaneous manifestations and thus screening for thyroid autoimmunity and function for early identification of thyroid dysfunction and potential comorbidities when the thyroid disease is to be classified as autoimmune, particularly among hyperthyroid patients.

In conclusion, our findings indicate the presence of skin findings in a majority of thyroid patients, the prevalence of which significantly differs for certain cutaneous manifestations with respect to controls, autoimmune etiology, and thyroid functional status. Early recognition of cutaneous manifestations in thyroid patients, particularly among patients with autoimmune hyperthyroidism, seems to enhance timely screening for thyroid autoimmunity and function and thus early identification of thyroid dysfunction and potential comorbidities.

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