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High Frequency of Thyroid Dysfunction in Patients with Vitiligo

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An association between vitiligo and autoimmune thyroid disease has previously been suspected. This study was undertaken to determine the frequency and type of thyroid disease in 35 consecutive patients admitted because of vitiligo compared with a matched control group. One or more signs of thyroid disease was demonstrated in 15 out of 35 patients (43%) with vitiligo, as compared to 7 out of 35 (20%) in the matched control group ($p = 0.04$). Thyroid dysfunction – 6 patients with hyperthyroidism and 2 with hypothyroidism – was found in 8 out of 35 patients, as compared to no patient in the control group ($p = 0.003$). Nine patients had thyroid autoantibodies, compared to 2 controls, and 6 had an enlarged thyroid gland, compared to 5 subjects in the control group. There appears to be an increased frequency of clinical as well as subclinical thyroid disease in patients with vitiligo. Our findings support the theory of vitiligo being an autoimmune disease and indicate a need for screening vitiligo patients for thyroid disease. ***Key words: Thyroid hormones; Goitre; Autoimmunity.***

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Vitiligo is an acquired skin disease caused by a selective destruction of melanocytes. The disease is common, affecting approximately 1% of the world's population (1). Therefore, it is not surprising that a number of diseases have been described in patients with vitiligo. The cause of vitiligo is not known, but the favoured hypothesis at present is that vitiligo is an autoimmune disease (1). This possibility was primarily suggested by the frequent finding of autoimmune diseases or autoantibodies – e.g. autoantibodies to adrenal cortex, thyroid microsomes, parietal cells and mitochondrial and nuclear antigens. A number of studies have demonstrated an increased frequency of thyroid autoantibodies in vitiligo patients (2–6), and vitiligo is commonly seen in patients with clinical thyroid disease, e.g. Graves' disease (7). No doubt vitiligo is frequently seen in patients with overt endocrine disease; however, these patients have generally been highly selected.

The aim of our study was to investigate thyroid function variables in a consecutive number of patients admitted due to vitiligo and not on the grounds of suspicion of endocrine disease. Hereby we hoped to survey whether there is a temporal relationship between vitiligo and thyroid dysfunction and whether a screening for thyroid disease should be recommended in patients with vitiligo.

MATERIAL AND METHODS

Vitiligo lesions

During the period December 1990 through June 1992 (19 months) 35 patients with vitiligo were referred to the Department of Dermatology in order to obtain a series of PUVA treatment. All received written and oral information about the study and accepted to participate. The median age at onset of vitiligo was 27 years (range, 0–63 years). The median duration of the illness was 8 years (range, 9 months–55 years). Of the 35 patients 17 were females and 18 males. Median age was 46 years (range, 17–80 years). Thirty-five healthy subjects selected randomly from a population study and matched with regard to sex, age, body weight and smoking habits served as controls.

A full history was taken from all the patients and controls and a full clinical examination was carried out. Vitiligo was defined as circumscribed lesions characterized by discrete, pale white macules, few or many in number, that tended to enlarge centrifugally. The borders of the lesions were usually convex, as if the depigmenting process were "invading" the normally pigmented skin borders. In some fair-skinned subjects, the lesions were not very apparent but were easily distinguishable with Wood's light examination or after delayed tanning of uninvolved skin. In all patients, the uninvolved skin tanned normally. By definition, patients with chemically induced depigmentation or with depigmentation secondary to various other dermatoses were excluded. The vitiligo lesions were either localized or generalized (Table I).

Typically, vitiligo occurred around the eyes and mouth, the anterior neck, extensor elbows and digits, perineum, palmar wrist and dorsal ankles, anterior tibial regions, and low back. The most commonly involved sites were found to be the lower extremities, particularly the pretibial areas, the upper extremities with maximum involvement of the hands, the face and the neck. Several morphological types of vitiligo were present with hypomelanotical macules in variable size, confetti spots and segmentally distributed lesions. Further details of type and extent of the lesions are given in Table I.

No significant difference in the distributional and morphological pattern of vitiligo was found in regard to sex, age or body weight. Almost 50% of the patients were able to implicate a precipitating cause such as physical injury, sunburn, emotional trauma or illness in relation to the initial awareness of vitiligo.

Thyroid status

In this study thyroid disease was defined as being: 1) known and treated thyroid dysfunction; 2) previous thyroidectomy; 3) untreated hypo- or hyper-thyroidism detected at present investigation; 4) a clinically detectable goitre; (5) the presence of thyroid autoantibodies in serum. The presence of a goitre was defined as a visible and/or palpable thyroid gland. The ultrasonic scanning procedure and the total thyroid volume calculation were performed, as previously described (8), with a compound (static images) scanner (type 1846, Brüel and Kjaer, Naerum, Denmark). The transducer was a 5.5-Mhz type mechanically focused at 1–3 cm. The scanning procedure, volume calculation, accuracy and precision of the method have all been reported previously (8). In short, with the patient supine, transverse scans of the thyroid were obtained at 5-mm intervals from caudal to cranial with hyperextension of the neck. The outline of the gland on the screen was digitized by tracing it with a cursor (light pencil) connected to a computer; the area within each outline and the volume between two successive transverse scans were then calculated. The sum of all partial volumes equals the total thyroid volume. The precision of the ultrasonic method is between 5.1% and

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Table I. *The distributional patterns of vitiligo with estimation of the involved body surface area*

Accurate measurement of the involved skin area, expressed as percentage of body surface area, was performed by using a surface area chart with the "rule of nines": head and neck (9%), arm (9%) right/left, torso (18%) front/back, leg (18%) right/left, genital and perineum (1%). The size of scattered small hypopigmented lesions, e.g. confetti spots, was estimated by comparing them with the size of the patient's hands, which constitutes about 1% of body surface area.

Distributional pattern of vitiligo (Number of patients)	Percentage of the involved body surface area (BSA%) (Number of patients)	
Generalized (4)	1% < BSA ≤ 2%	n = 2
Symmetrical	2% < BSA ≤ 9%	n = 16
	9% < BSA ≤ 18%	n = 7
Localized (13)	18% < BSA ≤ 36%	n = 6
Asymmetrical	36% < BSA ≤ 50%	n = 4
	50% < BSA ≤ 86%	n = 0
Acro-facial (13)	86% < BSA ≤ 100%	n = 0
Segmental (5)		
	Average BSA involved 15.4 (range 1% – 50%)	

7.8% in this range of thyroid volume (9) and is expressed as the coefficient of variation on double determinations. The day-to-day variation was of the same magnitude (9). Only one blood sample was obtained from each person. Serum was stored at −20°C and analyzed in consecutive assays. The serum thyrotropin (TSH, normal range 0.4–4.0 mU/l), thyroxine (T_4, normal range 56–129 nmol/l), triiodothyronine (T_3, normal range 1.6–2.8 nmol/l) and triiodothyronine resin uptake (T_3RU, normal range 0.80–1.20) was determined as previously described (8, 10). Free T_4 index (FT_4I) and free T_3 index (FT_3I) levels were calculated as total hormone concentration x T_3RU and given in arbitrary units. Serum TSH was measured by a third-generation assay (a chem-

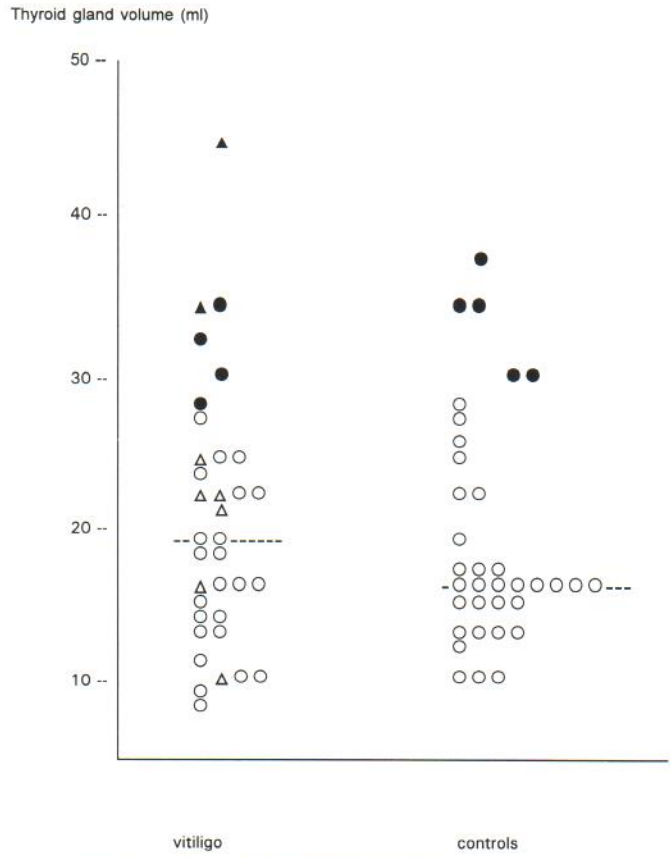

Fig. 1. Thyroid gland volume determined ultrasonically in patients with vitiligo and healthy controls. (---) Median levels. (○) Subjects without goitre and thyroid dysfunction, (△) subjects without goitre but with thyroid dysfunction, (●) subjects with goitre and without thyroid dysfunction and (▲) subjects with goitre and thyroid dysfunction.

Table II. *Median (range) for pertinent clinical and biochemical variables in patients with vitiligo without thyroid dysfunction and a matched control group*

Individual values for patients with vitiligo and thyroid dysfunction are given. NS = not significant; Arb.U = arbitrary units; F = female; M = male.

	Age (years)	Weight (kg)	T_4 (nmol/l)	T_3 (nmol/l)	T_3RU (arb.U)	TSH (mU/l)	FT_4I (arb.U)	FT_3I (arb.U)	Thyroid vol. (ml)
Vitiligo	47 (17–80)	69 (53–84)	101 (73–167)	1.8 (1.0–2.9)	0.93 (0.42–1.33)	1.1 (0.6–2.4)	94.3 (63.0–137.6)	1.68 (0.88–2.08)	19 (8–45)
P–value	NS	NS	NS	NS	NS	NS	NS	P<0.01	NS
Controls	46 (17–85)	68 (54–88)	102 (61–140)	1.9 (1.4–3.0)	0.99 (0.64–1.25)	0.9 (0.1–3.1)	96.3 (68.1–131.6)	1.92 (1.29–3.10)	16 (10–37)
Patients with thyroid dysfunction:									
1. (F)	46	60	300	10.0	1.77	<0.02	531.0	17.7	45
2. (F)	46	53	230	3.8	1.68	<0.02	382.4	6.4	22
3. (F)	55	65	176	3.4	1.75	<0.02	308.0	6.0	24
4. (F)	63	70	143	2.7	1.29	<0.02	184.5	3.5	22
5. (F)	67	68	147	2.1	0.94	0.04	138.2	2.0	16
6. (M)	66	77	152	2.5	1.09	<0.02	165.7	2.7	34
7. (F)	51	75	93	1.4	0.84	8.0	77.1	1.2	21
8. (F)	54	53	86	1.5	0.95	7.3	81.7	1.4	10

iluminometric assay, Berilux hTSH assay, Behringwerke AG, Frankfurt, Germany). The lower detection limit of this assay (defined as mean + 2 SD of the zero standard) was 0.005 mU/l. The working sensitivity (defined as the lowest serum TSH value with an interassay coefficient of variation below 10%) is 0.04 mU/l (10). Hyperthyroidism was diagnosed on the basis of elevated FT_4I (> 129) and/or FT3I (> 2.8) with a serum TSH level < 0.4 mU/l. Hypothyroidism was diagnosed on the basis of an elevated serum TSH level (> 4 mU/l) with a decreased FT_4I level (< 56). Subclinical hypothyroidism was diagnosed on the basis of an elevated serum TSH level with a normal FT_4I level. Anti-thyroid peroxidase antibodies (anti-TPO) were measured by a commercial radioimmunological method (DYNO-test, Firma Henning, Berlin). The anti-TPO method was based on a principle described by Ruf et al. (11). The within assay precision (coefficient of variation) was 4–6% and the between assay precision was 6–8% at a level of 1600 U/ml, and 12.5–19% at a level of 170 U/ml. Serum anti-TPO values > 200 U/ml were considered positive (12).

Statistical analyses were performed using Mann-Whitney's U-test and the chi-squared test. A significance level of 5% was chosen.

RESULTS

Fifteen of the patients (43%) had one or more signs of thyroid disease. Eight patients had biochemical evidence of thyroid dysfunction; 6 had hyperthyroidism and 2 had subclinical hypothyroidism with elevated serum TSH levels (7.3 and 8.0 mU/l) but normal FT_4I and FT_3I levels. All 6 patients with hyperthyroidism had a diffuse uptake on a thyroid scintiscan and were considered to have Graves' disease. Both patients with subclinical hypothyroidism had positive anti-TPO antibody levels (2921 and > 10.000 U/ml) but no goitre and were therefore classified as having atrophic autoimmune thyroiditis. In all, 9 patients had anti-TPO antibody levels above 200 U/ml. The median level was 2921 U/ml (range, 230 – > 10.000). Only 2 of the controls had slightly elevated anti-TPO antibody levels ($p < 0.05$). Six patients, of whom 4 were smokers, had a clinically detectable goitre while this could be found in 5 of the control subjects, of whom 4 were smokers (NS). Consequently a significant difference in the frequency of thyroid disease was demonstrated between patients with vitiligo (15/35, 43%) and healthy controls (7/35, 20%, $p = 0.04$). This was even more pronounced if one contemplates only subjects with thyroid dysfunction – (8/35, 23%) versus (0/35, 0%, $p = 0.003$).

The clinical data and thyroid function tests are given in Table II and Fig. 1. Except for a significantly reduced FT_3I level in patients with vitiligo, no significant differences in thyroid function variables could be demonstrated between patients and controls. However, patients with thyroid dysfunction (hyper- and hypothyroid subjects) were excluded from some of the comparisons (Table II). No significant difference could be demonstrated between median thyroid volume in patients with thyroid dysfunction: 22 ml (range, 10–45 ml) and in subjects without thyroid dysfunction 19 ml (range, 8–34 ml) (NS). The median duration of vitiligo in patients with thyroid dysfunction 9 years (range, 1–55), did not differ significantly from that of patients without thyroid dysfunction 8 years (range, 1–50). No relation between extent or type of vitiligo and thyroid function could be demonstrated.

DISCUSSION

The present study supports the already suggested association between vitiligo and thyroid disease. The fact that 8 out of 35 patients (23%) compared to none in the control group had biochemical thyroid dysfunction – 6 patients with Graves' disease and 2 with atrophic thyroiditis – is in keeping with the presently favoured hypothesis of vitiligo being an autoimmune disease. This theory is also strengthened by the finding of a significantly higher incidence of thyroid antibodies in patients as compared to controls. Others have demonstrated significantly higher incidences of thyroglobulin and microsomal autoantibodies in vitiligo (2–4) as compared to controls. We have substantiated this by demonstrating a higher incidence of thyroid-peroxidase autoantibodies (anti-TPO), that is autoantibodies to the specific antigen of microsomal antibodies (13). The level of positivity for anti-TPO used in this study (> 200 U/ml) has previously been demonstrated to distinguish almost completely between controls and chronic thyroiditis (12).

A reliable evaluation of the possible association between vitiligo and thyroid disease and a quantitative measure of the incidence of thyroid disease in vitiligo have probably not been achieved. Our population, although comprising consecutive patients, is probably highly selected and may well comprise patients that have more pronounced symptoms than the average vitiligo patient. This could in fact be the very reason for referral for evaluation. This is indirectly suggested by the often long duration of vitiligo before referral to our Department of Dermatology and the in our view high incidence of thyroid dysfunction. The possible bias inflicted by this cannot be quantified. When this is said, it should be emphasized that our patients were consecutively evaluated vitiligo patients and none had previously known thyroid dysfunction. Thereby our study differs from that of others where generally the way of selecting patients and/or control groups has been inadequately accounted for (2–7).

Thyroid function parameters were not significantly different between the two groups after exclusion of the 8 patients with autoimmune thyroid disease. The low FT_3I level in patients with vitiligo is compatible with the euthyroid sick syndrome as seen in patients with non-thyroidal illnesses (14).

Goitre was not more frequent and thyroid volume not increased in patients with vitiligo. Numerous factors influence thyroid function and size, e.g. sex, age, bodyweight, time of menstrual cycle, smoking habits, the use of several drugs and numerous other factors (15). Therefore, it is necessary that the control group – as in the present study – is matched with regard to these variables. The relatively high frequency of goitre in the control group as well as in the vitiligo patients could be explained by their smoking habits (16), as 4 out of 6 vitiligo patients and 4 out of 5 controls with goitre were smokers.

The fact that vitiligo is often seen in patients with autoimmune thyroid disease is well accepted (7). The present study suggests that patients with vitiligo seem to run an increased risk of developing autoimmune thyroid disease. Although no difference in duration of vitiligo between patients with or without thyroid dysfunction could be demonstrated, the fact that none of our patients had known thyroid dysfunction at time of investigation for vitiligo suggests that vitiligo often precedes thyroid dysfunction. Therefore, we suggest that patients with vitiligo should be screened for thyroid dysfunction.

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