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INCREASED PREVALENCE OF ANTITHYROID ANTIBODIES AND THYROID DISEASES IN PUSTULOSIS PALMOPLANTARIS

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Abstract. A statistically significant increased prevalence of antithyroid antibodies was found by an indirect immunofluorescence technique in 37 patients with pustulosis palmoplantaris, as compared with an approximately age- and sex-matched group of healthy controls. A history of thyroid disease was also more frequent in patients with PPP than in the population at large. The increased risk of thyroid dysfunction should be kept in mind in the long-term care of PPP cases. The prevalence of non-cutaneous autoantibodies was not increased in psoriatic subjects. The results accord with the concept that PPP and psoriasis may be separate entities.

Pustulosis palmoplantaris (PPP) is a chronic disease of still undetermined etiology (17). Functional abnormalities of circulating granulocytes have been reported (15, 16) but it is not known whether such factors or immunological mechanisms contribute to the development of skin lesions. The presence of autoantibodies in the blood may reflect a disturbed regulation of the immune system.

The purpose of this study was to determine the occurrence of circulating non-cutaneous autoantibodies and the incidence of thyroid disease in patients with PPP. Since the association of PPP with psoriasis is controversial (17), another aim was to compare the prevalence of such autoantibodies in PPP with that in a group of patients with psoriasis.

MATERIAL AND METHODS

Patients. Thirty-seven consecutive outpatients (31 females and 6 males) with lesions typical of PPP and no signs of psoriasis on the rest of the body were included in the study. Our clinical definition of PPP is given elsewhere (12). The mean age was 51 years (range 23–70). The mean duration of the disease was 8.3 years (range 0.5–30). All patients had actively pustulating lesions at the time of the study.

Sera obtained from 44 consecutive female patients with psoriasis vulgaris were tested with regard to the presence of autoantibodies. The mean age was 48 years (range 16–68) and the mean duration of the disease was 20 years (range 0.6–54). The patients were hospitalized or admitted to the day-care centre at the time of the study. None of the patients with PPP or psoriasis were being treated systemically with corticosteroids or immunosuppressive drugs at the time of blood sampling.

Clinically obvious polyarthritis did not occur in the patients with PPP and psoriasis.

Controls. Twenty-seven female and 2 male healthy persons were used as a reference group for the autoantibody study. The mean age was 45 years (range 35–57).

History of thyroid disease. All patients with PPP, 34 psoriatics and all the healthy controls were questioned about a history of thyroid disease (goitre, operations on the neck, treatment for abnormal body metabolism, etc.) and symptoms of hyper- och hypothyroidism.

Autoantibodies. Sera were screened for antinuclear factor (ANF) as well as for autoantibodies against thyroid antigens (thyroglobulin and thyroid microsomal antigen) and parietal cells, by means of the indirect immunofluorescence technique. Cryostat sections, 4 μm thick, of rat liver, human thyroid and rat stomach were used as substrates. The sections were air-dried and used unfixed. Polyspecific anti-human immunoglobulin from sheep, conjugated with fluorescein–isothiocyanate, was purchased from the National Bacteriological Laboratory, Stockholm, Sweden. The conjugate contained 1.7 mg anti-IgG protein/ml and had a molar fluorescein to protein ratio (F/P) of 2.9. A Leitz Orthoplan fluorescence microscope equipped with incident illumination as described by Ploem (19) was used. The light source was a halogen lamp (Osram 12 V, 100 W); 3 mm colour filters BG 12 and BG 38 were used as primary filters and K 490 as secondary filter. A standard procedure (5) was used for processing the slides. Slides were read blind as a part of routine testing of patient sera and without knowledge of the origin of the individual sera. Sera positive in dilution 1/10 were tested further in two-fold serial dilutions.

Antithyroglobulin antibodies were also determined by the passive hemagglutination technique (HA), using a commercially available kit (Wellcome Reagents Ltd., Beckenham, Kent, England). HA tests were performed according to the manufacturer's directions as earlier described (14). Titres of positive sera are given as the reciprocal of the highest dilution of the serum with a positive reaction. Only titre values ≥10 were regarded as positive.

Statistical methods. The prevalence values of individuals with a history of thyroid disease or demonstrable au-

Table I A. *Occurrence of thyroid diseases in 9 patients with pustulosis palmoplantaris*

Patient	Sex	Age at study (y.)	Onset of skin disease	Onset of thyroid disease	Thyroid disease	Thyroxine orally at study
1	F	54	1963	1940	Goitre + hypothyroidism	+
2	F	66	1973	1921	Goitre + hyperthyroidism (operated)	+
3	F	65	1948	1971	Hypothyroidism	–
4	F	55	1975	1970	Goitre	–
5	M	60	1973	1962	Goitre (operated)	+
6	F	66	1965	1942	Goitre + hyperthyroidism (operated)	+
7	F	66	1967	1977	Goitre + hyperthyroidism (J^{125} treated)	–
8	F	53	1963	1964	Hypothyroidism	+
9	F	23	1976	1974	Goitre + hypothyroidism	+

Table I B. *Occurrence of thyroid diseases in 2 patients with psoriasis and in one control subject*

Patient	Sex	Age at study (y.)	Onset of skin disease	Onset of thyroid disease	Thyroid disease	Thyroxine orally at study
1	F	32	1957	1962	Goitre + hyperthyroidism (J^{125} treated)	–
2	F	37	1958	1963	Goitre (operated)	–
3[a]	F	39	–	1974	Hypothyroidism	+

[a] = Healthy control individual.

toantibodies in the patient groups were compared by means of Fisher's exact test. A double-sided p-value was used (6).

RESULTS

History of thyroid disease. Nine of the 37 patients with PPP had a history of thyroid disease (Table I A). The thyroid disease preceded PPP in 6 patients (mean interval: 19 years), and the cutaneous symptoms appeared first in 3 patients (mean interval: 11 years). Seven patients had had goitre, which had been treated surgically in 3 cases. Initially 3 of the 7 patients were hyperthyrotic and 4 were hypothyrotic. Six of the 9 patients were treated with thyroxine at the time of the study.

Thirty-four of the psoriatics were available for interview, and 2 of them were aware of a pre-existent thyroid disorder (Table I B). One of the 29 control subjects had had a thyroid disorder (Table I B).

Autoantibodies. The prevalence of ANF, thyroid and parietal cell autoantibodies in the three groups are presented in Table II. The prevalences of autoantibodies do not differ statistically between patients with psoriasis and healthy controls. Almost half of the patients with PPP had demonstrable autoantibodies against one or more of the substrates used. This is a significantly higher frequency than in psoriatic patients ($p<0.01$) and controls ($p<0.05$). The most pronounced increase in prevalence of autoantibodies was exhibited by the two types of thyroid autoantibodies. Only low titre values were recorded. Two of the 9 PPP patients with a history of thyroid disease had autoantibodies against thyroid antigens. The prevalence of parietal cell antibodies or ANF was not significantly higher in PPP patients than in psoriatic patients or healthy controls.

DISCUSSION

In the present study circulating antithyroid antibodies were found more frequently in the sera from patients with PPP than in either patients with psoriasis or healthy controls. Antibodies against gastric parietal cells also occurred more frequently

Table II. *Prevalence of autoantibodies in patients with pustulosis palmoplantaris, psoriasis and in healthy control individuals*

Tissue antibody	I PPP ($n=37$)	II Psoriasis ($n=44$)	III Healthy control individuals ($n=29$)	Levels of significance Groups I–III	Groups I–II
Thyroglobulin	10 (27%)	4 (9%)	3 (10%)	NS	$p<0.05$
Thyr. microsomal antigen	8 (22%)	2 (4%)	2 (7%)	NS	$p<0.05$
Any thyroid antibody	15 (40%)	6 (14%)	4 (14%)	$p<0.05$	$p<0.05$
Parietal cell antibody	4 (11%)	2 (4%)	1 (3%)	NS	NS
Antinuclear antibody	0 (0%)	1 (2%)	1 (3%)	NS	NS
Any autoantibody	17 (46%)	8 (18%)	5 (17%)	$p<0.05$	$p<0.01$
Two antibodies or more	4 (11%)	1 (2%)	2 (7%)	NS	NS

NS=not statistically significant.
There is no statistically significant difference between psoriatic patients and healthy controls.

in PPP than in controls, but the differences were not statistically significant, possibly owing to the small number of individuals. In a follow-up study of PPP patients, Enfors & Molin (9) briefly mention the finding of an unspecified abnormality in the occurrence of autoantibodies in PPP. High titres of thyroglobulin and microsomal antigen antibodies are found in Hashimoto's and Grave's disease (21). Evaluation of the significance of thyroid autoantibodies in *low titres* must, however, be done with caution, since they may occur in non-thyroid autoimmune diseases and in healthy or asymptomatic individuals (10, 21). The prevalence of thyroid autoantibodies is higher in women than in men and increases with age (7, 8). For apparently normal women, middle-aged as in the present study, the prevalence of autoantibodies has been reported to be 15–25% (7, 8). The corresponding figures from the psoriatic subjects and the control group in this study fall between these levels. It should be noted that the age range and female predominance is about the same in the two last-mentioned groups as in the PPP subjects.

While the role of antithyroid antibodies in inducing thyroid disease is not clearly established (21), it has been suggested that such antibodies may be of pathogenetic significance by directing the activity of "killer" K cells to antibody-coated target cells (for a review, see 21). The existence of thyroid autoantibodies in individuals without clinical signs of thyroid disease is associated with a high frequency of asymptomatic focal or diffuse thyroiditis (2). In a small number of such patients observed over many years, the occurrence of thyroid antibodies seemed to precede symptomatic thyroid disease (2). In the present study, 9 of the 37 cases with PPP had a history of thyroid disease. As a suitable control group of "normal" people, a large sample of women representative of the total population in our city was chosen (4). Out of 1 009 females aged 46–54 years, 10.5% reported having had a confirmed or suspect thyroid disease (3). Although this figure probably exaggerates the frequency of thyroid disease in the population at large, the occurrence of thyroid disorders in the group of PPP patients studied here was significantly higher ($p<0.05$). There was no significant difference in the prevalences of thyroid disease between the psoriatics or the healthy controls, and the above control group.

The pattern of thyroid disorder in the patients with PPP was not uniform; both hyper- and hypothyroidism occurred. It seems unlikely that increased occurrence of thyroid disease and antithyroid antibodies in patients with PPP might be coincidental. The prevalence of thyroid autoantibodies is higher even in those patients who have not manifested clinical thyroid disease. Therefore some patients with PPP may run an increased risk of developing thyroid disease (cf. 2). Further studies are required to elucidate the thyroid function in patients with PPP. It should be borne in mind that the early symptoms of hypo- or hyperthyroidism may be difficult to diagnose clinically and are easily overlooked (11).

The occurrence of thyroid autoantibodies may indicate a defect in the T lymphocyte mediated control of the immune system. A hypothesis postulating that immunological mechanisms may be

of importance for the development of PPP has been published recently (20).

The relation of PPP to psoriasis has been discussed lately: some authors suggest that PPP is a variant of psoriasis (cf. 17) while others consider that the differences—including that PPP has a reversed sex ratio, infrequent occurrence of psoriasis among relatives, and absence of the increase in the particular HLA antigens observed in psoriasis—support the suggestion that the two diseases are separate entities (1, 12, 13, 18, 22, 23). The present findings of increased prevalence of thyroid autoantibodies and thyroid disorders in PPP, in contrast to psoriasis, is another piece of evidence in favour of the latter suggestion.

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