

PREVALENCE OF THYROID AUTOIMMUNITY IN PATIENTS WITH PEMPHIGUS VULGARIS

FABIAN PITOIA¹, DANIEL MONCET¹, ROBERTO GLORIO², ADRIANA GRACIELA DIAZ¹,
GRACIELA RODRIGUEZ COSTA², SERGIO CARBIA², HUGO CABRERA², HUGO NIEPOMNISZCZE¹

¹División Endocrinología y ²División Dermatología, Hospital de Clínicas José de San Martín,
Facultad de Medicina, Universidad de Buenos Aires

Abstract Among bullous diseases, *pemphigus vulgaris* (PV) is a classical variety of this type of skin disorders.

To establish the real prevalence of thyroid abnormalities in such a disease, a prospective study was developed. For this reason, thyroid evaluation was performed in 15 consecutive patients who attended the Dermatology Clinic for PV and in a group of 15 healthy volunteers (Control Group) matched by age and gender. Thyroid function was evaluated by measuring T3, T4 and TSH. The presence or absence of goiter was searched by palpation, while thyroid autoimmunity was investigated through the assay of thyroperoxidase antibodies (TPO-Ab). In each group there were 9 women and 6 men, aging 25-65 years (mean = 48.3 y) in the PV Group, and 25-69 years (mean = 45.4 y) in the Control Group. It was found that 7 patients (46.6%) of the PV Group and 1 subject (6.7%) of the Control Group ($p < 0.015$) disclosed thyroidal alterations. Positive titers of TPO-Ab were observed in 6 patients with PV and in one volunteer. Goiter and subclinical hypothyroidism were found in one PV patient with negative TPO-Ab. Out of the total 7 cases with positive TPO-Ab, only a PV patient had an overt Hashimoto's thyroiditis. All other cases had only the presence of thyroid auto-antibodies without clinical evidences of chronic thyroiditis. It is concluded that PV is highly associated with primary thyroid disorders, mainly with positive titers of TPO-Ab, although most patients do not present overt clinical thyroid disease.

Key words: pemphigus vulgaris, thyroid, autoimmunity, TPO-Ab

Resumen *Prevalencia de autoinmunidad tiroidea en pacientes con pénfigo vulgar.* El pénfigo vulgar (PV) es una enfermedad ampollar clásica de etiología autoinmune que se caracteriza por la presencia de lesiones intraepiteliales. Para establecer la prevalencia de anomalías tiroideas en el PV, realizamos un estudio prospectivo en 15 pacientes consecutivos que consultaron a la División Dermatología debido a PV y en un grupo de 15 voluntarios sanos (Grupo Control). La función tiroidea se evaluó a través de la medición de T3, T4 y TSH y la presencia de bocio se determinó por medio de la palpación tiroidea. La autoinmunidad se investigó usando un ensayo IRMA para la medición de anticuerpos antitiroperoxidasa (ATPO). En cada grupo había 9 mujeres y 6 hombres que fueron apareados por edad y sexo, con edades comprendidas entre 25 y 65 años (promedio 48.2 años) en el grupo PV, y entre 25 y 69 años (promedio 45.4 años) en el grupo control. Se encontró que 7 pacientes (46.6%) del grupo PV y uno (6.6%) del grupo control presentaron alteraciones tiroideas, ($p < 0.015$). La presencia de ATPO positivos se observó en 6 pacientes con PV y en un voluntario del grupo control. Un paciente con PV presentó un bocio difuso asociado a un hipotiroidismo subclínico con ATPO negativos. De los 7 casos con ATPO positivos, solo un paciente del grupo PV presentó una tiroiditis de Hashimoto manifiesta. Todos los demás casos solo tuvieron ATPO positivos sin evidencias clínicas de tiroiditis crónica. El PV se asocia frecuentemente con ATPO positivos, aunque la mayoría de los pacientes no presentan enfermedades tiroideas que se expresen clínicamente.

Palabras clave: pénfigo vulgar, tiroides, autoinmunidad, ATPO

Pemphigus is a life-threatening autoimmune disease characterized by intraepidermal blister and acantholysis. The hallmark of pemphigus is the finding of IgG auto-antibodies against the cell surface of keratinocytes¹. Pemphigus is divided into three major types, pemphigus

vulgaris (PV), pemphigus foliaceus and paraneoplastic pemphigus.

The clinical difference between them is defined by the profile of anti-desmoglein antibodies. In PV patients with mucosal-dominant type, autoantibodies are mainly directed against desmoglein 3 and in mucocutaneous type, both anti-desmoglein 3 and 1 are found².

The pemphigus autoantibodies found in patients' sera play a primary pathogenic role in inducing the loss of cell adhesion of keratinocytes with resultant blister formation. These antibodies bind to calcium dependent adhesion

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Postal address: Dr. Fabián Pitoia, División de Endocrinología, Hospital de Clínicas José de San Martín, Universidad de Buenos Aires, Córdoba 2351, 1120 Buenos Aires, Argentina
Fax: (5411) 5950-8830 e-mail: fpitoia@intramed.net

molecules in cell surface desmosomes³. PV patients also have significantly increased frequencies of HLA DR4 and HLA DR14⁴.

On the other hand, thyroid disorders have a high prevalence in medical practice and they are associated with a wide range of skin disorders with which they may or may not share etiological factors⁵⁻⁷. There are only seldom reports on the association of thyroid disorders and PV^{5,8,9}. For this reason, in this prospective study, we were able to assess the real prevalence of primary thyroid disorders (PTD) in patients with PV.

Patients and Methods

Our study included 15 patients with PV (PV Group) and 15 healthy volunteers (Control Group). The diagnosis of PV was established on the base of clinical, histological and immunological (direct and indirect immunofluorescence) examinations.

Thyroid evaluation was performed in 15 consecutive patients who attended the Dermatology Clinic for PV and in 15 healthy volunteers matched by age and gender. Thyroid function was evaluated by measuring T3, T4 and TSH levels. Serum TSH was measured using an ultrasensitive commercial immunometric assay.

The presence or absence of goiter was searched by palpation, and thyroid autoimmunity was investigated through the assay of anti-thyroperoxidase autoantibodies (TPO-Ab) by an immunoradiometric assay method.

A patient was defined as having PTD by one or more of the following diagnostic criteria: i) goiter; ii) positive antithyroid antibodies (TPO-Ab); and iii) primary thyroid function abnormalities.

The Control Group consisted of 15 healthy individuals who attended the blood bank of our hospital. An aliquot of their donated blood was employed for measuring TPO-Ab, and serum T3, T4 and TSH. Thyroid gland palpation was also performed in these subjects. All subjects (PV group and Control group) denied having known thyroid diseases or relatives with any kind of thyroid disorders. It should be pointed out that all patients and controls were living in iodine sufficient areas of Argentina. In each group, there were 9 women and 6 men; mean age PV Group 48.3 ± 11.3 y (range 25-65 years) and mean age Control Group 45.4 ± 12.2 y (range 25-69 years)

All patients in PV Group had received immunosuppressive glucocorticoids doses at the moment of PV diagnosis. Mean duration of glucocorticoid treatment in this group was 13 ± 10 months (range 1-41 months). Twelve out of the 15 patients in the PV Group were receiving oral metilprednisolone; mean dose 30.5 ± 34 mg (range 4 to 120 mg) at the moment of measuring serum thyroid hormones, TSH and TPO-Ab (Table 1).

Informed consent was obtained from the patients and from the control group to perform these studies.

Statistical analysis

Data were expressed as mean ± SEM. Statistical analysis was performed by SPSS for Windows 11.0 (Cary, NC, USA). Comparison between groups was performed by *chi* square test and significance was set at 5%.

Results

The overall rate of primary thyroid disorders diagnosed in PV Group was 46.6% (7/15 patients) and 6.7% (1/15 subjects) in the Control Group ($p < 0.015$) (Fig 1).

TABLE 1.- Age, gender, prednisolone dose, thyroid laboratories and thyroid palpation in 15 patients with PV

Patient	Gender	Age (years)	Prednisolone dose (mg/day)	TSH (mU/l)	T4 (ug/dl)	T3 (ng/dl)	TPO-Ab (U/ml)	Goiter
1	F	65	no	7.20	9.0	160	< 0.5	yes
2	F	48	8	0.98	10	120	28	no
3	F	28	60	2.30	8.0	110	< 0.5	no
4	F	55	20	1.00	8.1	112	< 0.5	no
5	F	50	4	1.60	9.4	124	116	no
6	F	51	no	1.40	6.3	158	< 0.5	no
7	F	40	10	0.99	9.0	122	15	no
8	F	25	60	3.60	8.0	112	22	yes
9	F	65	30	0.90	9.0	155	< 0.5	no
10	M	47	10	0.32	7.0	109	< 0.5	no
11	M	48	120	1.20	9.4	59	< 0.5	no
12	M	41	8	2.00	7.0	53	< 0.5	no
13	M	56	20	2.30	6.3	81	102	no
14	M	54	16	2.45	9.1	108	14	no
15	M	51	no	1.30	9.5	159	< 0.5	no

PV: pemphigus vulgaris, TSH: serum thyrotropin, T3: triiodothyronine, T4: thyroxine, TPO-Ab: thyroperoxidase antibodies. Normal values: TSH= 0.3-4.5 mU/l, T3=80-190 ng/dl, T4=4.5-12.5 ug/dl, TPO-Ab < 0.5 U/ml

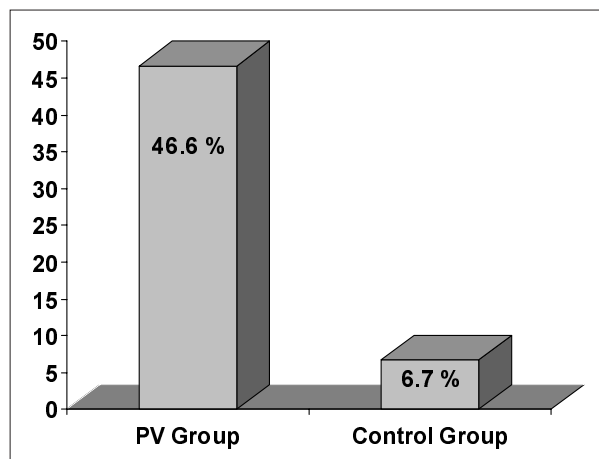


Fig. 1.— Frequency of primary thyroid disorders in patients with pemphigus vulgaris (PV) compared with a Control Group.

Positive titers of TPO-Ab were observed in 6 patients with PV and in one volunteer. Goiter and subclinical hypothyroidism (TSH = 7.2 mUI/L) was found in one PV patient with negative TPO-Ab. Out of the 7 cases with positive TPO-Ab, only a PV patient had an overt Hashimoto's thyroiditis with normal thyroid function and goiter. All other cases had only the presence of positive titers of TPO-Ab without clinical and laboratory evidences of chronic thyroiditis (Table 1).

Discussion

PV is the most common form of pemphigus. Its incidence varies from 0.1-0.5 cases every 100 000 inhabitants in the US population, but it is higher among Jewish people¹⁰. Men and women are equally affected. On the other hand, PTD occur more frequently in the general population. Prevalence in studies varies with the criteria for diagnosis, the decade when the study was performed, and the patients studied¹¹. Titers of antithyroid microsomal antibodies higher than 1:100 were found in 10 to 13 percent of women and 3 percent of men in community surveys in Whickham, United Kingdom, and New South Wales, Australia^{12,13} but only 1 percent of the subjects had titers higher than 1:6400.

Corticosteroids are the most useful drugs in the treatment of PV and continue to be the mainstay of therapy for this disorder. Their use, rapidly induces remission in the majority of patients^{14,15}. Remarkably, most of the subjects (12/15) in the PV Group were receiving glucocorticoids at the moment of thyroid evaluations. Glucocorticoids are known to suppress autoimmune reactions through the reduction of T cell proliferation¹⁶ and they have been used to treat patients with Hashimoto's thyroiditis¹⁷. In such patients, glucocorticoids may decrease antithyroid antibody titers and normalize

thyroid function¹⁷. Although we found a high frequency of positive TPO-Ab in the PV Group, it is possible that this prevalence may be underestimated, at least in those patients receiving immunosuppressive doses of glucocorticoids.

The apparent contradiction whereby thyroid autoimmune disease appears during therapy with methylprednisolone may be related to the dose of steroids. It is possible that high doses of glucocorticoids, commonly employed in the treatment of severe PV, might indeed suppress thyroid disease, whereas the low doses might precipitate thyroid abnormalities⁴. Interestingly, five out of the 6 patients with positive TPO-Ab in the PV Group were receiving methylprednisolone with doses inferior to 20 mg/day (Table 1). In the only patient with goiter, subclinical hypothyroidism and negative TPO-Ab, glucocorticoid treatment had been withdrawn 4 months previously.

It has been shown that endogenous Cushing's syndrome exhibits a remarkably high prevalence of primary thyroid diseases and that resolution of hypercortisolism seems to trigger the development of autoimmune thyroid disorders in presumably predisposed subjects¹⁸. Perhaps this situation may be reproduced in predisposed PV subjects after withdrawal or dose decreasing of exogenous glucocorticoid treatment⁴. However, thyroid autoimmunity and PV are both autoimmune disorders which might share some etiopathogenic factors still unknown. It is concluded that PV is highly associated with primary thyroid disorders with a high prevalence of positive TPO-Ab, although most patients do not present overt clinical thyroid disease.

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Famines are, in fact, extremely easy to prevent. It is amazing that they actually take place, because they require a severe indifference on the part of the government. Here political asymmetry joins hands with social and cultural alienation. The sense of distance between the ruler and the ruled –between "us" and "them"– is a crucial feature of famines. It is true in Sudan and Somalia today as it was in Ireland and India in the last century.

Las hambrunas son, de hecho, extremadamente fáciles de prevenir. Es sorprendente que realmente ocurran, porque se requiere una grave indiferencia por parte del gobierno. Aquí la asimetría política se da la mano con la alienación social y cultural. La distancia entre los gobernantes y gobernados –entre "ellos" y "nosotros"– es el rasgo crucial de las hambrunas. Es verdad en Sudán y Somalia hoy como lo fue en Irlanda y la India en la última centuria.

Amartya Sen

Lamont University Professor, Harvard University Professor of Economics and Philosophy; Senior Fellow, Harvard Society of Fellows. Master, Trinity College, Cambridge, England, 1998-2004. La Real Academia Sueca de Ciencias en 1998 le entregó el Premio Nobel de Ciencias Económicas por sus contribuciones a la investigación del bienestar económico.

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