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Prevalence of Metabolic Syndrome and its components in a Brazilian sample of pemphigus patients[*]

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Abstract: BACKGROUND: Pemphigus foliaceus and pemphigus vulgaris are endemic in the northeastern region of São Paulo State, Brazil. They are treated mainly with systemic corticosteroids, which may provoke osteoporosis; atherosclerosis, higher blood pressure, insulin resistance, glucose intolerance, hyperlipidemia and abdominal obesity. These side effects of corticoids also constitute criteria for the diagnosis of metabolic syndrome.
OBJECTIVE: The prevalence of metabolic syndrome and each component of metabolic syndrome in Pemphigus foliaceus and pemphigus vulgaris groups was compared with Brazilian casuistic samples.
METHODS: Data of 147 patients (pemphigus foliaceus 48.9% and pemphigus vulgaris 51.1%) were compiled from medical records regarding metabolic syndrome and its components, and included in the analysis.
RESULTS: There was no significant difference regarding the prevalence of metabolic syndrome in pemphigus groups compared with the Brazilian casuistic samples. The analysis of each component of metabolic syndrome showed a higher prevalence of: higher blood pressure in male subjects with pemphigus vulgaris, and in pemphigus foliaceus in both genders; diabetes mellitus in both genders for pemphigus vulgaris and pemphigus foliaceus; obesity in females for pemphigus vulgaris and pemphigus foliaceus, and hypertriglyceridemia in both genders for pemphigus vulgaris and pemphigus foliaceus groups that were statistically significant compared to the Brazilian reports. Furthermore, the study noted a higher incidence of cardiovascular events in both genders in pemphigus foliaceus and pemphigus vulgaris groups than in Brazilian casuistic samples.
CONCLUSION: The components of metabolic syndrome are more numerous in pemphigus when compared with Brazilian casuistic samples. Future studies are necessary to assure that metabolic syndrome may be associated with pemphigus per se, including a greater casuistic sample of patients who have not taken corticoids.
Keywords: Diabetes mellitus; Dyslipidemias; Glucocorticoids; Metabolic syndrome X; Obesity, abdominal; Pemphigus; Triglycerides

INTRODUCTION

Pemphigus conditions are blistering autoimmune skin diseases, characterized by IgG autoantibodies against several molecules of the surface of keratinocytes, leading to acantholysis.[1] Pemphigus foliaceus (PF) affects only the skin due to the production of autoantibodies against desmoglein (Dsg) 1, a protein constituent of desmosomes, responsible for maintaining the architectural cohesion of keratinocytes, mainly in the subcorneal layer of the epidermis. Pemphigus vulgaris (PV) can affect both the skin through the production of anti-Dsg1, and the mucosa, by producing anti-Dsg3, expressed mainly in the suprabasal layer of the epidermis and predominantly in mucosal membranes.[1,2] PF and PV are endemic in the northeastern region of São Paulo State, Brazil.[3-5] Our research group has studied certain aspects of

pemphigus pathogenesis which environmental factors allied to genetic predisposition need to be determined.[6-10] Treatment consists mainly of systemic corticosteroids, administered orally or by venous pulse therapy, associated, or not, with cyclophosphamide.[11,12] Due to the introduction of rituximab, it is now possible to avoid corticosteroids and minimize their side effects.[13]

The side effects of glucocorticoids include osteoporosis, atherosclerosis, higher blood pressure (HBP), insulin resistance, glucose intolerance, hyperlipidemia and central obesity. These side effects of corticoids also constitute criteria for the diagnosis of metabolic syndrome (MetS).[14-17] MetS comprehends an aggregation of biochemical and physical conditions that presage the development of atherosclerotic car-

diovascular disease. MetS is the name given to a set of risk factors that favor the development of cardiovascular diseases or diabetes mellitus type 2.[14,16,18,19]

Brazilian population-based studies estimate that the prevalence of MetS is approximately 30% in individuals over 25 years of age.[20] In recent years, the growing sedentary lifestyle and unhealthy eating habits have contributed to the simultaneous increase in diabetes and obesity throughout the world. As the incidence of infectious diseases has decreased and life expectancy has increased, diabetes has become a major public health problem and remains one of the ten leading causes of death in the USA.[19,20]

The pathophysiology of MetS is complex and not yet fully elucidated. An initial screening of the factors in a large proportion of patients highlighted an unbalanced diet and sedentary lifestyle as major causes. Today, it is known that obesity, particularly central obesity, is related to increased peripheral resistance insulin. This increased resistance insulin may provoke dysfunction of vascular endothelium, altered lipid metabolism, HBP and vascular inflammation, all of which can lead to the development of atherosclerotic disease.[14,20]

There are only two reports in the literature showing a possible association between pemphigus and MetS and its components.[21,22]

As the main treatment for pemphigus is still steroids, it is necessary to have knowledge of the prevalence of MetS in pemphigus patients, since the results may also contribute to the standardization of diagnosis and treatment of pemphigus. Our objective was to compare data on prevalence of MetS and its components in patients with pemphigus, with Brazilian casuistic reports.

METHODS

This study was approved by the Ethics Committee at the Hospital of Clinics, School of Medicine of Ribeirao Preto, University of São Paulo. The data regarding MetS and its components were collected from all medical records of patients with PF and PV living in the northeastern region of São Paulo State, Brazil, treated in the autoimmune skin diseases outpatient clinic in the last decade, between 1999 and 2009. Only patients with a confirmed laboratory diagnosis of pemphigus (skin biopsy showing acantholysis and the presence of IgG between keratinocytes on direct immunofluorescence) were included in this study. One hundred and forty-seven medical records were reviewed, regardless of age, gender and origin of the patients. Cases of death caused by pemphigus were also included in the analysis. Data on the MetS components not included in the medical records were registered as "missing." The National Cholesterol Education Program's Adults Treatment Panel III (NCEP – ATPIII, 2004) protocol was

used as a pattern to compile the data from pemphigus patients (Table 1).[15] The data were registered in Excel, sorting the cases of PV and PF into distinct groups, and subsequently analyzed using frequencies.

The prevalence of MetS in PF and PV groups was compared with a Brazilian population-based randomized study performed in Vitória, Espírito Santo State, between 1999 and 2000.[18] In this study, 1,663 individuals over 25 years-old were evaluated for the prevalence of MetS using the same NCEP/ATPIII protocol. For this comparison, the pemphigus patients from our casuistic sample were grouped by gender, and only those over 25 were included in the analysis.

In order to compare the components of MetS and cardiovascular events (myocardial infarction and stroke) the VIGITEL study was used, conducted in 26 Brazilian capitals plus the Federal District in 2008.[23] In this study, an estimate was made based on frequencies of risk and protective factors for chronic diseases in 54,353 individuals over 18 years of age. The patients of our casuistic sample were grouped by gender, and only included those over 18 years of age, for proper comparison with the VIGITEL study.

To compare the frequencies obtained in our casuistic sample of pemphigus with those from Brazilian casuistic samples, confidence intervals for proportions based on binomial distribution were constructed and the analyses were performed using SAS version 9.

RESULTS

Of the 147 patients included in the analysis, 72 were diagnosed with PF (48.9%) and 75 with PV (51.1%). The mean age was 39.5 years ± 17.4 years. The average time from the onset of the pemphigus diagnosis until this analysis was 18-310 months (median of 116 months) for PF, and 13-209 months (median of 82 months) for PV. Usually, the prescription of oral prednisone begins with 0.5 to 1.0 mg/kg/day, taken alone

TABLE 1: National Cholesterol Education Program's Adults Treatment Panel III (NCEP - ATPIII)

NCEP-ATP III Criteria
1. Abdominal obesity (waist circumference):   Men >102 cm (>40 in)   Women >88 cm (>35 in)
2. Triglycerides ≥150 mg/dL
3. Blood pressure ≥135/≥85 mm Hg
4. Fasting glucose ≥100 mg/dL
5. HDL cholesterol: Men <40 mg/dL   Women <40 mg/dL

The combination of three or more criteria confirms the diagnosis of MetS.

or in conjunction with immunosuppressant drugs, with subsequent reduction of the dose in accordance with the clinical control for each case. The PF group took corticosteroids for between 13 months and 19 years, and the PV group for between 12 months and 16 years, but the patients did not receive corticosteroids continuously throughout the whole period. Most of the patients received corticosteroids for at least one year, others for over 5 years, sometimes intermittently, in accordance with the periods of remission and relapse of the disease.

Among the PV patients, 32 were males (42.6%) and 43 females (57.3%). The mean age was 41. The diagnosis of MetS was confirmed in 15 patients (20%). The prevalence of MetS was diagnosed in 16.2% of females (7 cases) and 25% of males (8 cases) (Table 2). Of the PF patients, 38 were female (52.7%) and 34 (47.2%) were male. The mean age was 37.4. The diagnosis of MetS was performed in 12 patients (16.6%), 7 females (18.42%), and 5 males (14.7%) (Table 2).

The prevalence of MetS and its components, comparing the pemphigus groups with the Brazilian casuistic reports, are shown in table 3.[18,23] There was no significant difference between the prevalence of MetS in pemphigus groups and the rate mentioned in Brazilian casuistic reports (18). However, data analysis showed a higher prevalence, statistically significant compared with the Brazilian casuistic samples, of: HBP in male subjects with PV, and in PF sufferers of both genders; diabetes mellitus in both genders for PV and PF; obesity in females for PV and PF, and hypertriglyceridemia in both genders for PV and PF. In addition, there was a higher incidence of cardiovascular events in both genders for PF and PV patients, compared with findings in the Brazilian casuistic reports.[23]

DISCUSSION

In this survey, some of the MetS components were not present in all the medical records, mainly the data related to laboratory findings and basic information such as blood pressure and abdominal circumference measures. This resulted in "missing" data, which were not included in the analysis. We can speculate that this "missing" information can be attributed to the lack of professionals registering the data in medical records within normal limits, or overlooking them in assessing the basic proceedings during treatment of patients. Moreover, the criteria for fulfilling the diagnosis of MetS may have been underestimated by the professionals, resulting in the data not being registered in medical records.

TABLE 2: Distribution of MetS and its components in patients with pemphigus vulgaris (PV) and pemphigus foliaceus (PF) according to gender

		PV				PF			
		Women	**(%)**	**Men**	**(%)**	**Women**	**(%)**	**Men**	**(%)**
Metabolic Syndrome	No	36	(81.58)	24	(69.23)	31	(81.58)	29	(85.30)
	Yes	7	(18.42)	8	(30.77)	7	(18.42)	5	(14.70)
HBP	No	23	(63.89)	18	(60.00)	14	(46.67)	13	(52.00)
	Yes	13	(36.11)	12	(40.00)	16	(53.33)	12	(48.00)
DM	No	31	(77.50)	22	(73.33)	26	(78.79)	20	(76.92)
	Yes	9	(22.50)	8	(26.67)	7	(21.21)	6	(23.08)
Abdominal Obesity	No	21	(70.00)	15	(71.43)	16	(66.67)	13	(76.47)
	Yes	9	(30.00)	6	(28.57)	8	(33.33)	4	(23.53)
Cardiovascular Disease	No	38	(82.86)	27	(79.31)	35	(85.71)	31	(82.35)
	Yes	5	(11.52)	5	(15.62)	3	(7.80)	3	(8.80)

		Both genders (%)	Both genders (%)
High LDL	No	35 (76.09)	27 (75.00)
	Yes	11 (23.91)	9 (25.00)
Low HDL	No	35 (76.09)	27 (75.00)
	Yes	11 (23.91)	9 (25.00)
High TGL	No	30 (65.22)	20 (55.56)
	Yes	16 (34.78)	16 (44.44)

* Statistically significant (p<0.05) when compared with Brazilian casuistic report

HBP: High Blood Pressure; **DM:** glucose intolerance and Diabetes Mellitus; **LDL:** low density lipoproteins; **HDL:** high density lipoproteins; **TGL:** triglycerides. **Cardiovascular disease:** myocardial infarction or stroke.

Table 3: Comparison of the distribution of MetS and its components in patients with pemphigus vulgaris (PV) and pemphigus foliaceus (PF) with the Brazilian casuistic reports

	PV		PF		Brazilian Reports	
	Women (%) (IC95%)	Men (%) (IC95%)	Women (%) (IC95%)	Men (%) (IC95%)	Women (%)	Men (%)
Metabolic syndrome	7 (18.42) (7.7-34.3)	8 (30.77) (14.3-51.8)	8 (29,2) (12.6-51.1)	5 (14.70) (2.7-32.4)	30.10	29.30
HBP	13 (36.11) (20.8-53.8)	12 (40.0)* (22.7-59.4)	16 (53.33)* (34.4-71.7)	12 (48.00)* (27.8-68.7)	25.50	20.30
DM	9 (22.50)* (10.8-38.5)	8 (26.67)* (12.3-45.9)	7 (21.21)* (9.0-38.9)	6 (23.08)* (9.0-43.7)	5.60	4.60
Abdominal obesity	9 (30.00)* (14.7-49.4)	6 (28.57) (11.3-52.2)	8 (33.33)* (15.6-55.3)	4 (23.53) (6.8-49.9)	13.60	12.40
Cardiovascular disease	5 (11.52)* (6.6-33.7)	5 (15.62)* (8.0-39.7)	3 (7.8)* (4.0-32.7)	3 (8.80)* (3.8-43.4)	2.10	3.30
High LDL	Both genders (%)		Both genders (%)		Both genders (%)	
	11 (23.91) (12.6-38.8)		9 (25.00) (12.1-42.2)		15.40	
Low HDL	11 (23.92) (12.6-38.8)		9 (25.00) (21.1-42.2)		41.60	
High TGL	16 (34.78)* (21.4-50.3)		16 (44.44)* (27.9-61.9)		9.40	

* Statistically significant (p<0.05) when compared with Brazilian casuistic report

HBP: High Blood Pressure; **DM:** glucose intolerance and Diabetes Mellitus; **LDL:** low density lipoproteins; **HDL:** high density lipoproteins; **TGL:** triglycerides. **Cardiovascular disease:** myocardial infarction or stroke.

Nevertheless, the statistically significant, higher prevalence of MetS components and cardiovascular events found in patients with pemphigus compared with Brazilian casuistic samples, corroborates the impact of MetS on the health of these patients. In order to compare the prevalence of MetS and its components in the pemphigus group, we chose Brazilian studies to minimize possible biases. A complex interaction between dietary habits, physical activity, socioeconomic conditions and even genetic predisposition may influence the genesis of MetS, characterizing the multifactorial factors.[14-20] Since neither MetS nor its components featured in a same Brazilian report, we used two Brazilian casuistic samples for the purposes of comparing of MetS and its components to pemphigus data.[18,20]

To compare the prevalence of MetS, a population-based study was applied, conducted in Vitória-ES.[18] In our series, the prevalence of MetS was 18.42% in females for both types of pemphigus, and the comparative study revealed a rate of 30.1%. For males, the prevalence was 30.77% in PV, 14.7% in PF, and 29.3% in the comparative study. There was no significant difference between the prevalence of MetS in pemphigus when compared with this study, in which all subjects were fully evaluated in accordance with the MetS criteria, unlike ours.

The VIGITEL study was applied to evaluate the MetS components and prevalence of cardiovascular events in the pemphigus group.[23] Analysis of our data showed a higher, statistically significant prevalence of: HBP in male subjects with PV, and in PF in both genders; diabetes mellitus in both genders for PV and PF; obesity in females for PV and PF, and hypertriglyceridemia in both genders for PV and PF.

Recent studies have shown similar results in relation to serum levels of triglycerides. Wohl *et al*. discovered a higher prevalence of hypertriglyceridemia and increased total cholesterol in 255 patients with pemphigus, compared with controls matched by sex and age.[22] There was no difference in the prevalence of increased LDL or decreased HDL. In our study, hypertriglyceridemia was observed in both genders in the PV and PF groups.

Cunha *et al*. compared serum lipids in 15 patients with PF in chronic steroid therapy, using controls, showing a higher prevalence of hypertriglyceridemia pemphigus sufferers.[21] There was no difference between the prevalence of decreased HDL, increased LDL and total cholesterol in that study.

Data from the current study showed that the occurrence of cardiovascular events, considered the last events in MetS, was also higher in patients of both sexes for both types of pemphigus compared with the Brazilian casuistic samples.[23]

The impact of cardiovascular impairment on public health throughout the world is widely acknowledged. As MetS represents the major risk factor for cardiovascular events, it is imperative to seek actively its criteria in treating patients using corticoids, so as to minimize cardiovascular risks.

Recently, we studied the affinity of the receptors for corticoids in pemphigus samples.[6] The increased affinity of these receptors for corticosteroids may be associated with good response to the treatment, but also to MetS allied with corticoid side effects.

CONCLUSIONS

The study revealed no significant difference in the prevalence of MetS in the pemphigus group, but did find a higher prevalence of HBP, diabetes mellitus, obesity and hypertriglyceridemia, when compared with Brazilian casuistic samples. Further, the study reported a greater incidence of cardiovascular events in patients of both genders for both types of pemphigus, compared with the Brazilian samples.

Future studies are necessary to assure that MetS may be associated with pemphigus per se, including a greater casuistic sample of patients who have not taken corticoids.

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How to cite this article: Ambiel MV, Roselino AM. Prevalence of Metabolic Syndrome and its components in a Brazilian sample of pemphigus patients. An Bras Dermatol. 2014;89(5):752-6.