

Incidence of pemphigus vulgaris exceeds that of pemphigus foliaceus in a region where pemphigus foliaceus is endemic: Analysis of a 21-year historical series *

Incidência do pênfigo vulgar ultrapassa a do pênfigo foliáceo em região endêmica para pênfigo foliáceo: análise de série histórica de 21 anos

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Abstract: BACKGROUND: There are two main clinical subsets of pemphigus: pemphigus vulgaris and pemphigus foliaceus. Clinical and epidemiological changes related to both types of pemphigus have been observed in the last years.

OBJECTIVES: To analyze a 21-year historical case series of pemphigus vulgaris and pemphigus foliaceus in the northeast region of the state of Sao Paulo, where pemphigus foliaceus is endemic.

METHODS: In this descriptive study, data related to annual incidence and age of onset of symptoms compatible with pemphigus vulgaris or pemphigus foliaceus were analyzed, comparing both forms, in the period from 1988 to 2008.

RESULTS: The overall results cover a period of 21 years, with 103 cases of pemphigus vulgaris and 163 cases of pemphigus foliaceus. An evaluation of the trend lines regarding incidence has shown that pemphigus foliaceus is decreasing while pemphigus vulgaris is increasing. There was great variation in the age ranges, with persistence of the minimum range, from 10 to 20 years old, for pemphigus foliaceus (mean age = 32.1 years old), and clear downward in the minimum age for pemphigus vulgaris (mean age = 41.5 years old), especially from the middle of the first decade of the total period studied.

CONCLUSION: The incidence of pemphigus vulgaris has been exceeding that of pemphigus foliaceus since 1998. The results of this case series comprehending 21 years corroborate the change in the epidemiology of both clinical forms of pemphigus in Brazil, raising new hypotheses for their etiology and pathogenesis.

Keywords: Epidemiology; Epidemiology, descriptive; Pemphigus

Resumo: FUNDAMENTO: Há dois tipos principais de pênfigo: pênfigo vulgar e pênfigo foliáceo. Nos últimos anos, mudanças clínicas e epidemiológicas relacionadas aos pênfigos têm sido observadas.

OBJETIVOS: Teve-se por objetivo analisar uma série histórica de 21 anos de casos de pênfigo vulgar e pênfigo foliáceo no nordeste do estado de São Paulo, área endêmica para o pênfigo foliáceo.

MÉTODOS: Neste estudo descritivo, foram analisados os dados relacionados à incidência anual e à idade de início do quadro clínico compatível com pênfigo vulgar ou pênfigo foliáceo, no período de 1988 a 2008, comparando-se ambas as formas de pênfigo.

RESULTADOS: O conjunto dos resultados abrange um período de 21 anos, com 103 casos de pênfigo vulgar e 163 casos de pênfigo foliáceo. A comparação das linhas de tendência em relação à incidência mostrou ser esta decrescente para o pênfigo foliáceo em comparação àquela de crescimento para o pênfigo vulgar. Houve variação ampla nas faixas de idade, com persistência da faixa mínima de 10 a 20 anos para o pênfigo foliáceo (média de idade de 32,1 anos), e clara tendência de diminuição da idade mínima para o pênfigo vulgar (média de idade de 41,5 anos), principalmente a partir da metade da primeira década do período total analisado.

CONCLUSÕES: A incidência do pênfigo vulgar ultrapassa aquela do pênfigo foliáceo a partir de 1998, permanecendo assim até os dias de hoje. Esta série histórica de 21 anos vem consubstanciar a modificação da epidemiologia dos pênfigos no Brasil, suscitando novas hipóteses para a sua etiopatogênese.

Palavras-chave: Epidemiologia; Epidemiologia descritiva; Pênfigo

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INTRODUCTION

The term pemphigus describes a group of autoimmune bullous diseases involving the skin and mucous membranes. It is histologically characterized by formation of acantholytic intraepidermal blister and IgG deposits on the surface of keratinocytes. There are two main types of pemphigus: pemphigus vulgaris (PV), when acantholysis occurs in the suprabasal spinous layer, and pemphigus foliaceus (PF), with acantholysis in the subcorneal granular layer. While PF has autoantibodies only against desmoglein 1 (anti-Dsg1), PV is characterized by the presence of anti-desmoglein 3 (anti-Dsg3) antibodies in the mucous form and anti-Dsg1 and 3 in the mucocutaneous form.¹ PV has a worldwide distribution, affects both sexes similarly, has a peak incidence between the fourth and sixth decades of life and may affect any age group. The worldwide incidence of pemphigus is 0.75-5 cases/1,000,000 per year, varying by country. Most cases of PV in North America, Europe and Asia are sporadic, with a higher incidence among Ashkenazi Jews, with an estimate of 1.6 per 100,000 population per year in Jerusalem.²

As for PF, there are two forms of presentation: a sporadic one, known as Cazenave's pemphigus foliaceus, with worldwide distribution, and an endemic one related to certain geographic areas, known as Fogo Selvagem – FS (Wild Fire). The difference between both presentation forms of PF is its epidemiology. FS is endemic in Brazil, affecting young adults living in rural areas, neighbors and family members.³ Other countries that also have geographic areas where PF is endemic are Colombia and Tunisia.^{4,5}

There has been an increase in the number of cases of FS in the states of Sao Paulo, Goias, Mato Grosso and Minas Gerais since the 30s. At the Pemphigus Foliaceus Hospital in Sao Paulo, the following distribution was registered between 1940 and 1962: 92.5% of PF with a mortality rate of 28.7% and 7.5% of PV with a mortality rate of 66.6%.⁶

The epidemiological history of FS shows an increase followed by a decrease in the incidence of the disease. At the Pemphigus Hospital in Goiania, the following numbers were registered: 502 cases (1952 to 1959), 1822 cases (1960 to 1969), 1624 cases (1970-1979), 1064 cases (1980-1989), a decrease to 441 patients (1990 to 1998).⁷ Between 1996 and 2001, 210 cases were registered, with a basically stable annual incidence.⁸ FS is still endemic in the northeastern region of Sao Paulo, including the cities of Ribeirao Preto and Franca.⁹

Although PV and PF are clearly distinct, there are reports of transitions from PV to PF and from PF to PV. This transformation is associated with serological changes of anti-Dsg1 and 3 auto-antibodies.¹⁰ On the

other hand, Artega et al., 2000, detected the presence of anti-Dsg 3 by ELISA in 19 patients in a study involving 276 cases of PF (25 North-Americans, 10 Japanese and 241 cases of FS from various Brazilian states). None of them had clinical or laboratory findings suggestive of PV.¹¹

A recent study developed by Rocha-Alvarez et al., 2007, involving residents of Brasília (Federal District) and of the state of Goias, regions where FS is endemic, found eight individuals from rural areas with mucocutaneous clinical manifestations and histological findings compatible with PV, confirmed by anti-Dsg3 antibodies.¹² Among them, four individuals also had anti-Dsg1 titers. In addition, 15% of 27 healthy controls from the same region presented titers of anti-Dsg3 antibodies. The authors suggest a rare form of PV in an area where FS is endemic, which was called endemic PV. No similar study was found in the literature.

Thus, this study aimed at presenting a change in the epidemiology of pemphigus manifestations in the northeastern region of Sao Paulo, with increased incidence of PV cases over cases of PF in an area where PF is endemic, as well as a decrease in the age range of patients affected by PV.

METHODS

In this descriptive study, we carried out a retrospective analysis of the medical records of patients seen at the Outpatient Clinic for Autoimmune Diseases at Hospital das Clinicas, Faculdade de Medicina de Ribeirao Preto – Universidade de Sao Paulo (FMRP-USP), between January 1988 and December 2008 using ICDs for pemphigus, PF, PV and vegetating pemphigus. The study period is limited to the local computerization of data. Medical records were reviewed to confirm the diagnosis of PF and PV with regard to age of onset of symptoms and corresponding year. These data were available in the form filled out in the first visit. The clinical and epidemiological data were entered into Excel[®] spreadsheets, followed by tabulations concerning the annual incidence in the corresponding period, as well as age. In order to compare annual incidence, a linear trend analysis of these time series was carried out from a simple linear regression using the Pearson correlation coefficient. The significance level was set at 0.05 for hypothesis testing. The description of the distribution of ages annually recorded was particularized.

RESULTS

In 21 years, we reviewed 266 medical records, whose clinical and histological description, including direct immunofluorescence, allowed the diagnosis of

pemphigus (163 PF, 103 PV). Graph 1 shows the series for annual incidence (number of new cases) for the two manifestations of pemphigus.

The figure is instructive because it shows the trend lines for each series: decreasing for PF in relation to the growing incidence of PV in patients from a region where PF is endemic. In the series for PF, we obtained the Pearson correlation coefficient value of $r = -0.73$ ($p = 1.7 \times 10^{-4}$), and the line that best fits these data is:

$$y = -0.49x + 998.96. (1)$$

The errors obtained for the intercept and slope of the line were: 213.10 ($p = 1.5 \times 10^{-4}$) and 0.11 ($p = 1.7 \times 10^{-4}$), respectively.

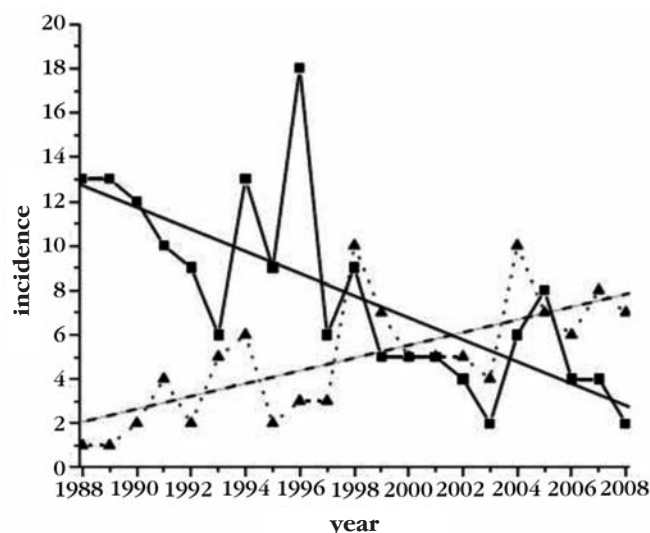
In the series for PV, we obtained $r = 0.69$ ($p = 5.5 \times 10^{-4}$) and the linear trend model for this series is:

$$y = 0.29x - 571.09. (2)$$

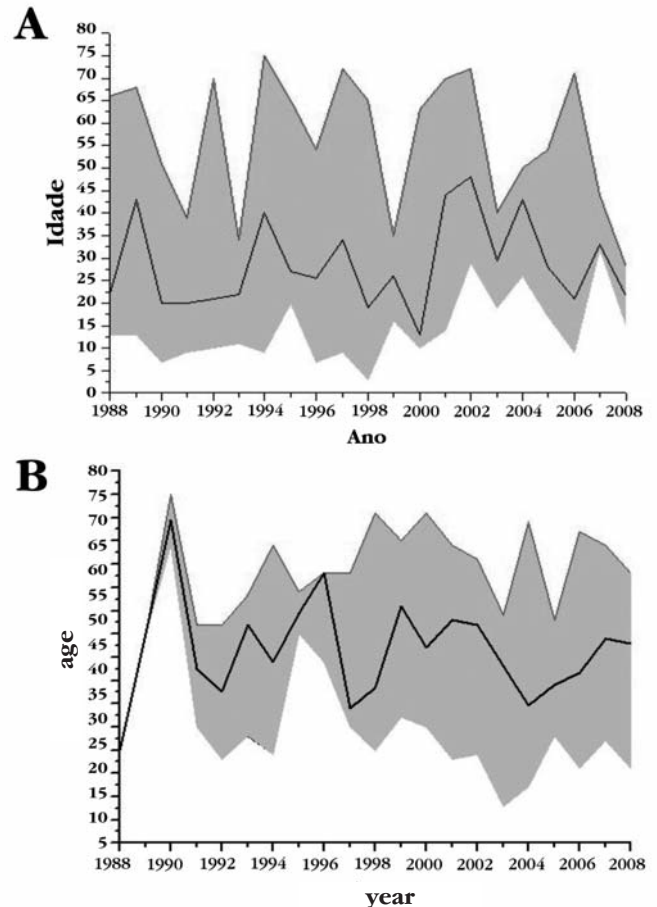
and the errors for intercept and slope in this case are: 139.14 ($p = 6.0 \times 10^{-4}$) and 0.07 ($p = 5.5 \times 10^{-4}$), respectively.

Thus, even in the case of population data, the significance level was set at 0.05 for all hypothesis tests. The p values for all tests in relation to the correlation coefficient ($H_0: R=0$) and slope ($H_0: a=0$) in the two straight lines found were lower than 0.01.

It is important to note that, although linear models explain the comparison of data and serve as evidence of the change in behavior of both manifestations of pemphigus, the lines characterizing the time series are enough for this observation. The number of cases of PF has remained lower than that of PV since 1998.



GRAPH 1: Annual incidence of PV (▲: dashed line) and PF (■: solid line) in a 21-year historical series. It is possible to observe upward trends (dashed line) and downward trends (solid lines) for each data set



GRAPH 2: Annual distribution of the ages of patients with confirmed PF (A) and PV (B). The central line (black) in each graph shows the annual variation of age medians

Graph 2 shows the annual distribution of age ranges for the PF and PV groups, as well as the line corresponding to annual variation in the age medians of the patients.

The maximum and minimum ages for each year reported should be noted. There is a wide age variation in both groups. It is possible to observe that the trend lines for minimum age persist in the range 10 to 20 years for PF and that there is a clear downward trend for the minimum age for PV, especially from the middle of the first decade of the total period analyzed. It should also be noted that the mean age was 32.11 years (3-72 years) for the 163 cases of PF, with a median of 29 years, while the mean age was 41.49 years (8-75 years) for the 103 cases of PV, with a median of 42 years.

DISCUSSION

The increased incidence of PV in an area where PF is endemic had already been reported in a series of cases registered from 1977 to 1998, when the inciden-

ce of PF was 7.1 cases/year and that of PV was 1.7 cases/year.⁹ The results confirm that the incidence of PV exceeded that of PF in 1998, remaining higher until this day. At that same time, two patients with PV had HLA class II genes of susceptibility similar to those reported for PF.¹³

In relation to age in PF, both the mean and median are within expected values. As for PV, the mean and median values confirm the downward trend in age at diagnosis, whose incidence above the 4th decade of life is reported.

CONCLUSION

This 21-year historical series corroborates the change in the epidemiology of pemphigus manifestations in Brazil, prompting new hypothesis to explain its etiopathogenesis. □

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