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EVALUATION OF NUTRITIONAL STATUS IN PATIENTS WITH ENDEMIC PEMPHIGUS FOLIACEUS

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SUMMARY

Sixteen patients with endemic pemphigus foliaceus were submitted to nutritional evaluation. Ten had the localized form of the disease (Group G_1) and six the disseminated form (Group G_2). The patients were submitted to anthropometric measurements (weight, height, Quetelét index, tricipital skin fold, subscapular skin fold, arm circumference, arm muscle circumference, arm area, arm muscle area, and arm adipose area) and to laboratory evaluation by protein electrophoresis.

Arm circumference, arm area and arm muscle area showed lower values in G_2 than in G_1. Weight and arm muscle circumference tended to the lower in G_2 than in G_1. Protein electrophoresis showed decreased albumin levels in both groups, with lower values in G_2.

Overall analysis of the results permits us to conclude that patients with endemic pemphigus foliaceus present signs and symptoms of protein, but not calorie, malnutrition and that this malnutrition is more marked in patients with disseminated pemphigus foliaceus.

KEYWORDS: Endemic pemphigus foliaceus; Nutritional status; Fogo Selvagem.

INTRODUCTION

Pemphigus foliaceus is a disease of worldwide occurrence characterized by the spontaneous appearance of bullous skin lesions [20]. In South America the disease peculiarly occurs endemically in certain regions and is variously called endemic pemphigus foliaceus, South American pemphigus foliaceus, and "wild fire". This epidemiologic characteristic is only one of the differences in relation to the classic pemphigus foliaceus described by Cazenave in 1844 [5, 20].

Bullous lesions are formed by a process called acantholysis, i.e., by a decrease or loss of adhesion between cells of the Malpighian or spinous layer due to changes in the intercellular bridges in the intercellular cement [16].

The etiology of these changes is still unknown. Today pemphigus foliaceus is believed to be an autoimmune disease with circulating autoantibodies in

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the patient's sera directed against the desmossomal protein desmoglein (desmoglein I) [16, 20, 22].

A few concomitant factors possibly triggering or facilitating the autoimmune process have been suggested to be present in pemphigus foliaceus, among them still undefined nutritional deficiencies [15]. No references to nutritional evaluation are available in the literature, except for some data related to serum protein electrophoresis [8, 10, 14].

The objective of the present study was to correlate the clinical signs and symptoms and laboratory data of previously untreated patients with pemphigus foliaceus with their nutritional profile as an indispensable preliminary determination in the study of the participation of nutritional factors in the etiopathogenesis of the disease.

MATERIAL AND METHODS

Material

The study was conducted on 16 patients from the endemic areas of the state of São Paulo and Paraná, with endemic pemphigus foliaceus diagnosed on the basis of clinical signs and symptoms, histopathologic examination of the lesions and results of the immunofluorescence test applied to such lesions. In the direct immunofluorescence (DIF), frozen sections are incubated with the appropriate fluorescein labeled non immune sera (goat or rabbit). To obtain maximum tissue-specific fluorescence with minimum background fluorescence the optimum dilution of the conjugates should be used. This is achieved by utilizing a chessboard titration procedure using a known positive tissue specimen.

For routine DIF screening, five coverslips with at least two or more 4μm-thick sections are required for each biopsy. These are then fan-dried for 10 minutes and washed in phosphate buffered saline (PBS) at pH 7.2 for a further 10 minutes. The sections are fan-dried again, covered with on the following fluorescein isothiocyanate labeled antisera: anti-human IgM, IgG, IgA, complement 3 (C_3), fibrinogen and incubated for 20 minutes in a moist, closed plastic container at room temperature. The unreacted antiserum is washed off in PBS for 30 minutes (three 10 - minutes changes). The coverslips are fan-dried once again, mounted on to microslides using a drop of buffered glycerin as mounting medium and examined with a fluorescence microscope [23].

The clinical classification of the patients utilized for group characterization was that proposed by the "Cooperative Pemphigus Group" and systematized in the literature (DIAZ et al. apud FRIEDMAN et al. [9]), which recognizes two active forms of the disease, i.e., a localized form and a generalized form. Thus, the patients were divided into two groups, G_1 and G_2, having the clinical characteristics described below.

Group G_1: small quantities of localized lesions on the scalp, face and anterior and posterior trunk.

Group G_2: lesions of generalized distribution intensely involving the scalp, face, anterior and posterior trunk, and limbs (pre-erythrodermal or erythrodermal phase).

Group G_1 consisted of ten previously untreated individuals, seven females and three males aged 15 to 68 years.

TABLE 1

Reference values utilized for comparison of anthropometry in individuals older than 18 years (ANSELMO, 1987) [1].

	Males			Females		
	18-30 years	30-50 years	50-70 years	18-30 years	30-50 years	50-70 years
Height (cm)	175.8 ± 6.0	172.0 ± 5.8	171.0 ± 5.7	159.6 ± 5.0	157.8 ± 7.7	159.4 ± 5.1
Weight (kg)	72.3 ± 10.0	73.9 ± 10.8	73.5 ± 10.4	54.6 ± 6.9	62.1 ± 9.4	64.1 ± 10.0
QI (kg/m²)	23.3 ± 2.4	25.0 ± 3.2	25.1 ± 2.9	21.4 ± 2.2	25.0 ± 3.8	25.2 ± 3.6
TSF(mm)	15.2 ± 6.9	12.8 ± 5.1	12.4 ± 3.4	19.4 ± 4.5	24.9 ± 7.8	25.1 ± 9.3
SSF(mm)	-	20.0 ± 8.2	17.8 ± 6.5	-	22.7 ± 10.9	22.9 ± 8.7
AC(mm)	297 ± 25.2	303 ± 29.4	302 ± 27.1	263 ± 23.6	297 ± 32.4	301 ± 34.0
AMC(mm)	249 ± 16.5	263 ± 22.2	263 ± 24.4	202 ± 19.2	219 ± 20.4	22 ± 23.3
AA(mm²)	7051 ± 1223	7378 ± 1462	7323 ± 1294	5547 ± 994	7106 ± 1567	7278 ± 1694
AMA(mm²)	4944 ± 645	5539 ± 929	5564 ± 1024	3281 ± 635	3850 ± 719	3958 ± 815
AAA(mm²)	2108 ± 1034	1839 ± 861	1759 ± 554	2266 ± 606	3258 ± 1258	3321 ± 1409

Group G_2 consisted of six previously untreated individuals with the generalized form of pemphigus foliaceus, three females and three males aged 12 to 68 years.

METHODOLOGY

Anthropometric evaluation

Anthropometric evaluation was carried out by measuring height (H), weight (W), Quetelét index (QI), tricipital skin fold (TSF), subscapular skin fold (SSF), arm circumference (AC), arm muscle circumference (AMC), and arm adipose area (AAA) according to BLACKBURN and THORTON [4] and BASTOW [2].

The data obtained were compared to those of ANSELMO, 1987 [1] who established nutritional reference standards for adults older than 18 years (Table 1), and to those of GOLDENBERG, 1989 [11] who established reference standards for individuals aged 10 to 19 years (Table 2).

Laboratory evaluation

Blood was collected from a peripheral vein of each patient in G_1 and G_2 for quantification of total protein by the biuret method [13], and for protein electrophoresis on agarose gel stained with amido black, with readings performed using a Zenit densitometer [13].

TABLE 2

Reference values utilized for comparison of anthropometry in individuals younger than 18 years (GOLDBERG, 1989) [11].

	Females (12 years)	Females (15 years)
Height (cm)	136.6 — 161.8	147.3 —172.4
Weight (kg)	24.624 — 56.350	36.780 — 68.460
QT (kg/m2)	-	-
TSF (mm)	15.6 ± 6	19.1 ± 5.2
SSF (mm)	-	-
AC (mm)	233.0 ± 32.0	252.0 ± 21.0
AMC (mm)	58.1 ± 6.0	60.6 ± 4.1
AA (mm2)	4414.4 ± 1262.9	5098.7 ± 881.8
AMA (mm2)	2729.2 ± 570.8	2948.1 ± 402.7
AAA (mm2)	1685.1 ± 822.7	2150 ± 689.4

Statistical analysis

The anthropometric and biochemical data were compared between groups (G_1 x G_2) as follows:

a) Use of the LI-LS interval, where LI = x - s and LS = x + s (mean ± SD), in age- and sex-matched healthy individuals, using as x and s standard laboratory data for the biochemical tests, and data from ANSELMO and GOLDBERG for anthropometric evaluation of adults and individuals younger than 18, respectively;

TABLE 3

Distribution of anthropometric values in groups G_1 and G_2

Group	Age years	Sex	Weight Kg	Height cm	AC mm	TSF mm	SSF mm	AMC mm	AA mm^2	AMA mm^2	AAA mm^2	QI kg/m^2
G_1	68	M	69.400	166.5	315	13.65	16.00	272.14	7900.00	5896.47	2003.58	25.03
G_1	23	F	69.100	155.0	340	32.05	21.05	239.36	9203.82	4561.56	4642.26	28.76
G_1	36	F	54.500	157.0	290	22.75	12.05	218.56	6695.85	3803.22	2892.63	22.11
G_1	59	F	42.400	155.5	238	15.90	5.65	188.07	4509.87	2816.10	1693.77	17.53
G_1	43	M	80.000	164.0	340	28.75	20.50	249.72	9203.82	4964.90	4238.92	29.74
G_1	58	F	56.900	146.5	325	29.65	27.60	231.89	8409.63	4281.28	4128.35	26.51
G_1	15	F	46.200	160.5	232	13.40	9.10	189.92	4285.30	2871.78	1413.52	17.93
G_1	27	F	73.200	159.5	325	39.40	22.10	201.28	8409.63	3225.60	5184.03	28.77
G_1	31	F	121.600	157.0	460	63.50	54.25	260.61	16847.13	5407.45	11439.68	49.33
G_1	46	M	63.900	172.0	278	8.55	9.85	251.15	6153.18	5022.00	1131.18	21.59
G_2	57	F	59.500	160.0	300	26.55	15.75	216.79	7165.60	3741.80	3423.73	23.24
G_2	55	M	62.600	166.0	265	13.75	14.95	221.82	5591.16	3917.52	1673.64	22.71
G_2	57	F	71.000	153.0	320	26.15	19.20	237.88	8152.86	4505.38	3647.56	30.33
G_2	12	F	29.300	145.5	185	10.75	6.25	151.24	2724.92	1821.14	1821.14	13.84
G_2	68	M	62.750	168.5	270	13.60	12.90	227.29	5804.14	4113.11	1691.03	22.10
G_2	59	M	43.700	160.0	185	4.45	6.20	171.03	2724.92	2328.84	396.08	17.07

b) Considering y as the value for a given individual for a variable, we calculated the distance of the individual from the LI-LS interval the y - LI difference when $y < LI$, or the y - LS difference when $y > LS$, or $y = 0$ if $LI < y < LS$;

c) With the indices thus obtained, the groups were compared by the nonparametric Mann-Whitney test described by SIEGEL [21], with calculations of the median (Md), middle rank (R) for each group, U statistical value, and the p level of significance. The difference between groups was considered to be significant when $p<0.05$. A tendency to a difference was considered to be present when $0.05 < p < 0.10$.

RESULTS

Anthropometry

The values obtained by anthropometric evaluation for each individual in G_1 and G_2 are presented in Table 3.

Table 4 presents the medians of the distances of the anthropometric values of G_1 and G_2 from the confidence intervals for normal individuals. In G_1, all values obtained were within the confidence interval. In G_2, the median values for height, tricipital skin fold, subscapular skin fold, arm adipose area and Quetelét index within the confidence interval, whereas the median values for weight, arm circumference, arm muscle circumference, arm area, and arm muscle area were below the lower confidence limit.

No statistically significant difference was detected between G_1 and G_2 with respect to height, tricipital skin fold, subscapular skin fold, arm adipose area, or Quetelét index.

Arm circumference, arm area and arm muscle area were lower in G_2 than G_1, and weight and arm muscle circumference tended to be lower in G_2 than in G_1.

Protein Electrophoresis

The protein electrophoresis data obtained for G_1 and G_2 patients are presented in Table 5, and the median distances of the protein electrophoresis values from the confidence interval for normal individuals are presented in Table 4. In G_1, the median values for total protein and alpha 1, alpha 2, beta and gammaglobulins

TABLE 4

Distribution in groups G_1 and G_2 of the median (Md) distances of the values from the confidence interval expected for normal individuals for the following parameters: weight, height, arm circumference (AC), tricipital skin fold (TSF), subscapular skin fold (SSF), arm muscle circumference (AMC), arm area (AA), arm muscle area (AMA), arm adipose area (AAA), and Quetelét index (QI). Mean ranks (R) of the groups (values utilized for statistical analysis).

Group		Weight (A)	Height (B)	AC (C)	TSF (D)	SSF (E)	AMA (F)	AA (G)	AMA (H)	AAA (I)	QI (J)
G_1	Md	0	0	0	0	0	0	0	0	0	0
	R	10.1	8.8	10.5	9.75	6.57	10.15	10.5	10.6	9.75	9.5
G_2	Md	-0.175	0	-7.4	0	0	-8.33	-352.7	-382.4	0	0
	R	5.83	8	5.16	6.41	6.4	5.75	5.16	5	6.41	6.83

Statistical analysis, U test.

(G_1 A x G_2 A)	U=14 ; p = 0.10	Tendency G_1 A > or = G_2 A
(G_1 B x G_2 B)	U=27 ; p > 0.10	G_1 B = G_2 B
(G_1 C x G_2 C)	U=10 ; p < 0.05	G_1 C > G_2 C
(G_1 D x G_2 D)	U=17.5 ; p > 0.10	G_1 D = G_2 D
(G_1 E x G_2 E)	U=17 ; p > 0.10	G_1 E = G_2 E
(G_1 F x G_2 F)	U=13.5 ; 0.05 < p < 0.10	Tendency G_1 F > or = G_2 F
(G_1 G x G_2 G)	U=10 ; p < 0.05	G_1 G > G_2 G
(G_1 H x G_2 H)	U=9 ; p < 0.05	G_1 H > G_2 H
(G_1 I x G_2 I)	U=17.5 ; p > 0.10	G_1 I = G_2 I
(G_1 J x G_2 J)	U=20 ; p > 0.10	G_1 J = G_2 J

TABLE 5

Distribution of serum protein data obtained by electrophoresis in groups G_1 and G_2

Group	Total Proteins	Albumin	Alpha 1	Alpha 2	Beta	Gama	A/G
G_1	7.40	4.07	0.19	0.75	0.61	1.78	1.22
G_1	7.20	4.18	0.23	0.82	0.74	1.23	1.39
G_1	7.60	4.64	0.18	0.59	0.81	1.38	1.37
G_1	6.40	3.00	0.20	0.70	0.90	1.60	0.90
G_1	7.40	3.00	0.30	0.90	0.90	2.30	0.70
G_1	6.70	3.90	0.25	0.72	0.70	1.13	1.39
G_1	7.10	3.59	0.21	0.75	0.82	1.73	1.02
G_1	7.00	3.33	0.22	0.71	0.83	1.90	0.90
G_1	6.40	3.03	0.29	0.71	0.71	1.66	0.89
G_1	6.60	3.41	0.35	0.71	0.65	1.49	1.07
G_2	5.50	2.54	0.43	0.80	0.55	1.18	0.85
G_2	6.50	3.30	0.36	0.66	0.57	1.61	1.03
G_2	6.60	3.47	0.28	0.62	0.46	1.77	1.11
G_2	6.00	2.90	0.30	0.80	0.80	1.20	0.90
G_2	6.10	2.80	0.30	0.70	0.90	1.40	0.80
G_2	5.40	1.70	0.48	0.73	0.72	1.76	0.45
Normal	6.0-8.0	3.5-5.5	0.1-0.4	0.4-0.9	0.6-1.1	0.7-1.7	1.3-3.3
Pattern	g	g	g	g	g	g	g

were within the confidence interval, whereas the median values for albumin and the albumin/globulin ratio were below the confidence interval.

In G_2, the median values for total protein and alpha 1, alpha 2, and gammaglobulins were within the confidence interval, whereas the median values for albumin, beta globulin and the albumin/globulin ratio were below the confidence interval.

Comparison of G_1 and G_2 data showed no significant difference between groups for total proteins, alpha 1, alpha 2, beta and gamma-globulins and the albumin/globulin ratio.

Albumin values were lower in G_2 than in G_1.

DISCUSSION

Albumin levels were lower than normal in 100% of the patients with the disseminated form of the disease and in 50% of the patients with the localized form, showing that albumin levels are inversely correlated with extent of skin involvement.

These findings do not agree with those reported by FURTADO & RODRIGUES [10] who found the lowest albumin levels in patients whose dermatosis was not so extensive. However, these findings agree with those of FERRI et al. [8] who reported that of 18 patients whose lesions involved more than 50% of the body surface, 15 presented albumin levels below normal, whereas albumin was slightly decreased in only one of three patients with localized lesions. OLIVEIRA et al. [14] studied ten patients with pemphigus foliaceus, four of them untreated and six under treatment with corticosteroids, and found reduced serum albumin levels in only one patient in the treated group. The low incidence of hypoalbuminemia in the patients reported by OLIVEIRA et al. [14] may be explained by the increased hepatic albumin synthesis induced by the corticosteroids (ROTHSCHILD et al. [19]; GROSSMAN et al. [12]).

Here, in addition to the association detected between the extent of cutaneous involvement and plasma albumin levels suggests that the decrease albumin levels in relation to normal parameters may be due to the loss of protein substances through the skin due to the multiple exulcerations presented by the patients. This loss may be compared to that occurring after skin

TABLE 6

Distribution in groups G_1 and G_2 of the median (Md) distances of the values from the confidence interval expected for normal individuals for protein electrophoresis data, and of the mean rank (R) values utilized for statistical analysis.

Group		Total Proteins (A)	Albumin (B)	Alpha 1 (C)	Alpha 2 (D)	Beta (E)	Gamma (F)	A/G (G)
G_1	Md	0	-0.45	0	0	0	0	-0.255
	R	9.5	10.7	7.5	8.5	10.0	8.9	9.9
G_2	Md	0	-0.65	0	0	-0.015	0	-0.425
	R	6.83	4.83	10.16	8.5	6	7.83	6.16

Statistical analysis, U test

(G_1A x G_2A)	U = 20 ; p > 0.10	$G_1A = G_2A$
(G_1B x G_2B)	U = 8 ; p < 0.05	$G_1B > G_2B$
(G_1C x G_2C)	U = 20 ; p > 0.10	$G_1C = G_2C$
(G_1D x G_2D)	U = 30 ; p > 0.50	$G_1D = G_2D$
(G_1E x G_2E)	U = 15 ; p > 0.10	$G_1E = G_2E$
(G_1F x G_2F)	U = 26 ; p > 0.10	$G_1F = G_2F$
(G_1G x G_2G)	U = 16 ; p > 0.10	$G_1G = G_2G$

burns, although in the latter condition, in addition to albumin loss there is reduced albumin synthesis due to acute stress [18]. The skin is an organ representing 6% of body weight and containing a third of the total extravascular albumin (ROTHSCHILD et al. [18]).

In burns affecting approximately 50% of the body surface, more than one third of albumin may be lost through the affected areas [17, 18]. In such cases, in addition to the loss there is a change in hepatic circulation due to the acute stress, with a consequent deficiency in hepatic nutrition contributing to a decrease in albumin production during this period [17].

In pemphigus foliaceus, evidence that hypoalbuminemia is provoked by the loss of proteins through the damage skin does not exclude the possibility of a defect in protein synthesis or of an insufficient dietary protein supply to overcome the deficiency caused by loss through the skin. This hypothesis is supported by the socioeconomic characteristics of the patients [7]. These observations suggest the need for protein synthesis studies, as well as the study of nutritional factors in pemphigus foliaceus.

In addition to having been submitted to laboratory tests, the present patients were evaluated for nutritional status by anthropometry. G_2 patients, i.e., those patients with the disseminated form of the disease, tended to present lower body weights than those expected for normal individuals of the same sex and age and for G_1 patients.

Changes in body weight may reflect changes in body fat; disequilibrium of water-salt metabolism may easily mask these changes in an individual, and malnourished subjects may keep a constant weight for several weeks [2]. However, changes in body weight lasting long periods of time should be considered as the most likely indicators of changes in nutritional status [2].

Thus, we may conclude that the generalized form of pemphigus foliaceus leads to a deficiency in nutritional status directly correlated with the extent of skin involvement.

There was no difference in height between G_1 an G_2, an expected result in view of the fact that all patients were adults. CASTRO & TAKAHASHI, in 1986 [6], published a study of 21 children with pemphigus foliaceus who were followed up over a period of 22 years. No growth retardation was detected in any of these children, a fact attributed by the authors to the early institution of treatment.

Arm circumference, arm area and arm muscle area

showed lower values in patients with the disseminated form of the disease than in patients with the localized form. Arm muscle circumference, in turn, tended to show lower values in G_2 than in G_1.

In 1974, BISTRIAN et al. [3] proposed that arm muscle circumference measurements may be used as indicators of nutritional status, and BLACKBURN, apud BASTOW [2], has suggested that these are the best parameters for the evaluation of protein-energy malnutrition. Their proposal is that arm circumference reflects a fundamental muscle mass that can be used as a general indicator of skeletal muscle protein and that changes in these measurements reflect alterations in somatic protein mass.

Thus, the changes detected in the present patients may reflect alterations in body protein mass, i.e., protein malnutrition, which was more evident in the disseminated form of the disease.

There was no difference in tricipital or subscapular skin fold or in arm adipose area compared to normal values, nor did the two groups differ from each other. These measurements are used to evaluate body fat stores since the subcutaneous fat reservoir is suggested to be a good index of total body fat [3, 24].

Thus, patients with pemphigus foliaceus did not present changes in total body fat [3, 24].

The Quetelét index, used to evaluate the weight/height ratio [2], did not differ between G_1 and G_2 or between the two groups and normal values.

In conclusion, patients with pemphigus foliaceus had lower serum albumin levels than normal individuals, this reduction being correlated with skin involvement. These patients also presented a tendency to decreased body weight, decreased values of measurements indicating the amount of total body protein, and normal values of measurements indicating the amount of body fat.

Thus, these patients seem to present a picture of nutritional alteration characterized by protein, rather than calorie, deficiency. This protein deficiency is probably due to cutaneous loss of albumin, and a possible defect in albumin synthesis due to a nutritional defect or to stress-induced changes cannot be led out.

RESUMO

Avaliação do estado nutricional em pacientes portadores de pênfigo foliáceo endêmico.

A avaliação nutricional foi realizada em dezesseis doentes portadores de pênfigo foliáceo endêmico, sendo dez portadores da forma localizada da doença (Grupo G_1) e seis portadores da forma disseminada da mesma (Grupo G_2).

Foram realizadas avaliações antropométricas (peso, altura, índice de Quetelét, prega cutânea tricipital, prega cutânea subescapular, circunferência braquial, circunferência muscular do braço, área do braço, área muscular do braço, área adiposa do braço) e laboratorial (eletroforese de proteínas séricas).

Quanto aos parâmetros antropométricos, observaram-se as seguintes alterações: a circunferência do braço, área do braço, e área muscular do braço mostraram valores mais baixos nos doentes do grupo G_2 que nos do grupo G_1.

O peso e a circunferência muscular do braço, por sua vez, mostraram tendência a valores mais baixos nos doentes do grupo G_2 que nos do grupo G_1.

A eletroforese de proteínas revelou valores de albumina diminuídos em ambos os grupos, e menores nos doentes do grupo G_2. Quanto às demais frações, com exceção das beta globulinas, não foram evidenciadas alterações.

A análise global dos resultados permite concluir que os doentes com pênfigo foliáceo endêmico apresentam um quadro de desnutrição proteica, mas não calórica. Esta desnutrição mostrou-se mais acentuada no pênfigo foliáceo disseminado.

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