Evaluation of Clinical Criteria for Diagnosis of Bullous Pemphigoid

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Objective: To check the potential usefulness of clinical criteria for the diagnosis of bullous pemphigoid when state-of-the-art techniques such as Western immunoblotting, immunoprecipitation, and indirect immunofluorescence on salt-split skin or direct immunoelectron microscopy are not available.

Design: Comparison of the clinical criteria between 2 groups (with and without bullous pemphigoid) as defined by immunoelectron microscopy used as standard criterion, in a prospective study. Multivariate logistic regression analysis was carried out by including all items that were statistically significant (at P<.05 level) in univariate analysis.

Setting: Five dermatology departments in teaching hospitals.

Patients: The 231 patients studied had subepidermal autoimmune bullous diseases with linear IgG or C3 deposits in the basement membrane zone (157 with bullous pemphigoid, 33 with cicatricial pemphigoid, 30 with epidermolysis bullosa acquisita, 5 with lupus erythematosus, and 6 others). A second set of patients was used to calculate predictive values.

Results: The multivariate logistic stepwise analysis resulted in a final set of predictors that included only 4 items: absence of atrophic scars, absence of head and neck involvement, absence of mucosal involvement, and age greater than 70 years. No additional variables met the .05 significance level to enter into the model. If 3 of these 4 characteristics were present, a diagnosis of bullous pemphigoid could be made with a sensitivity of 90% and a specificity of 83%; these predictive values were calculated on a sample of 70 new cases.

Conclusions: With an estimated incidence of bullous pemphigoid among subepidermal autoimmune bullous diseases of 80%, the presence of 3 of the 4 significant criteria allows the diagnosis of bullous pemphigoid, with a positive predictive value of 95%. Our set of clinical criteria thus allows the diagnosis of bullous pemphigoid with good validity for both clinical practice and therapeutic trials.

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Bullous pemphigoid (BP), cicatricial pemphigoid (CP), herpes gestationis, epidermolysis bullosa acquisita (EBA), and vesiculobullous systemic lupus erythematosus (VBSLE) are subepidermal autoimmune bullous dermatoses (AIBDs) characterized by tense blisters arising on apparently normal skin or on an erythematous plaque and by linear deposits of IgG and/or C3 complement component. The blisters result from interaction of autoantibodies with the target antigens of the basement membrane zone (BMZ)1,2. In the last 15 years, considerable progress has been made in the comprehension of subepidermal AIBDs.3-11 The molecular basis of most of these disorders has been elucidated by using several new tools. Western immunoblotting and immunoprecipitation of epidermal extracts define the molecular weight of target protein antigens. The location of immune reactants can be determined by indirect immunofluorescence on salt-split skin and by immunoelectron microscopy (IEM). Target proteins have been cloned and their biochemical composition analyzed. Such progress has led to the general agreement that each AIBD should be defined according to the antigen that is the target of autoimmunity in each disease. For example, BP is currently defined by the detection of autoantibodies directed against 1 or 2 of the BP antigens (BPAg 1 and BPAg 2). The therapeutic approach to each subepidermal AIBD is somewhat different.12 In agreement with this concept, we believed that at that time that such state-of-the-art techniques should be a prerequisite for including patients suffering from subepidermal AIBD in epidemiological or therapeutic clinical trials. Unfortunately it proved difficult to use these techniques in multcenter clinical trials.

For editorial comment see page 1137

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PATIENTS AND METHODS

All patients who had newly diagnosed subepidermal autoimmune disease were included in this prospective study. They were examined in 5 departments of dermatology from 1983 to 1989. Criteria for enrollment were age greater than 18 years, presence of bullous dermatosis, subepidermal blister in hematoxylin-eosin examination of biopsy specimens, and presence of linear IgG or C3 deposits in the BMZ of perilesional skin detected by direct immunofluorescence. Pregnant women and patients who exhibited only IgA deposits in the BMZ were excluded. Clinical findings were prospectively recorded by means of the same standardized questionnaire that had been used in previous studies. Examination by IEM was performed by a previously described technique. Two hundred thirty-one patients met the inclusion criteria and had IEM examination. Thirty-three patients seen during the period of the study in our departments with inclusion criteria were not included in the study because of the absence of IEM examination; thus, the participation rate was 88% of all eligible patients seen during the period of the study.

CLINICAL CRITERIA

All patients were seen by one of us at the time of initial examination before initiation of treatment. The standardized clinical evaluation included pruritus; vesicles or blisters; milia; atrophic scars; traumatic blisters, defined as skin detachment induced by minimal trauma, such as Nikolsky sign in normal or perilesional skin; erythematous plaques; mucosal involvement; ungual involvement; and alopecia. Each item was evaluated immediately after enrollment and its presence or absence noted before initiation of treatment.

The localization of blisters was precisely analyzed: presence or absence on head, neck, trunk, and lower and upper limbs. These parts of the body were subdivided and presence or absence was noted in each localization (the trunk was divided into chest, abdomen, umbilicus, upper back, lower back, and buttocks).

The standardized clinical evaluation included other items, such as onset of pruritus and blisters, number of blisters, and percentage of body skin detachment, that were not selected as criteria for this study. The clinical assessment of the patients was always performed before the diagnosis was made.

LABORATORY CRITERIA

All patients had standard laboratory tests. For evaluation we used only eosinophilia and the presence or absence of circulating anti-BMZ antibodies detected by indirect immunofluorescence.

RESULTS

Two hundred thirty-one patients were included in the study. Mean age at diagnosis was 73.5 years. According to IEM findings, 157 patients (86 women and 71 men) were included in the BP group and 74 (32 women and 42 men) in the non-BP group (32 women and 42 men). Because these state-of-the-art techniques are now available for the precise diagnosis of subepidermal AIBD, it is possible to evaluate the diagnostic values of clinical criteria in BP. We therefore decided to check the potential usefulness of clinical criteria for the diagnosis of BP when state-of-the-art techniques are not available. Sensitivity and specificity of an aggregation of clinical criteria were calculated, with IEM used as the criterion standard because it is one of the most sensitive of modern diagnostic criteria. The aim of our study was to determine a set of clinical diagnostic criteria for BP compared with autoimmune bullous diseases that could easily be used in clinical practice or in controlled clinical or therapeutic trials with well-established specificity and an acceptable level of sensitivity.

GROUPS

Patients were divided into 2 groups for evaluation of the criteria: a BP group and a non-BP group. As in other studies, the criterion standard for the diagnosis of BP in this study was IEM examination. The diagnosis of BP was made by IEM when there were strictly localized thin immune deposits in the upper lamina lucida (Figure 1). When deposits were localized in the lamina densa (Figure 2) or in the sublamina densa and the anchoring fibril zone, a diagnosis of non-BP (eg, CP, EBA, or VBSLE) was made. Many patients, particularly patients with non-BP, had serological examinations such as immunoblotting and salt-split skin indirect immunofluorescence; on 135 serum samples tested by immunoblotting, 97 were positive on epidermal extract, ie, showed reactivity with BP 230 and/or BP 180 antigens. Thus, the precise diagnosis of the subepidermal autoimmune diseases was made as follows: (1) EBA: reactivity with EBA antigen (290 or 145 kd) by immunoblotting, and immune deposits localized in the sublamina densa by IEM; (2) VBSLE: same characteristics as EBA with the additional presence of systemic lupus erythematosus; and (3) CP: localization of immune deposits on the epidermal or both dermal and epidermal sides of the split, and immune deposits localized in the lamina densa overflowing into the lamina lucida.

STATISTICAL ANALYSIS

Data on all patients studied were coded and entered into a computer. The frequency of each item in the BP group was compared with that in the non-BP group by means of the chi-square test. Odds ratios (ORs), determined by logistic regression analysis, were used to quantify the ability of each item to predict the diagnosis of BP. An OR of 1 corresponded to the absence of predictive value. An OR greater than 1 indicated positive predictive value, whereas an OR lower than 1 indicated a negative predictive value. The statistical significance of ORs was determined by the likelihood ratio test. Ninety-five percent confidence intervals for ORs were calculated. Multivariate logistic regression analysis was carried out by first including all items with univariate analysis (at P < .05 level) and backward elimination of nonsignificant (P > .05) variables (stepwise multivariate analysis). A set of diagnostic criteria was derived from this model. The sensitivity and specificity of this set of diagnostic criteria were calculated on a sample of 70 new patients (33 men and 37 women) who fulfilled the same inclusion criteria as the previous sample and who attended the same centers from 1991 to 1996.
42 men) were included in the non-BP group. The mean (±SD) age was 73.5 (±16.0) years. In the non-BP group it was possible to diagnose the disease precisely in 70 of 74 patients. Thirty-three patients had CP; 24, inflammatory EBA; 8, chronic EBA; and 5, VBSLE.

The characteristics used as independent variables were age, presence of erythematous plaques, hypereosinophilia, anti-BMZ antibodies, absence of atrophic scar mucosal involvement, head and neck involvement, epidermal cysts, and mechanical blisters. For all these characteristics, subsequently used to determine a set of diagnostic criteria, the differences between the 2 groups were significant at $P < .001$, except for the criterion of anti-BMZ antibodies, which was significant at $P < .01$. The sensitivity and specificity of each characteristic were then determined (Table 1). We examined the ability of each item to predict the diagnosis of BP by univariate analysis (Table 1). The OR for the absence of atrophic scars was much higher than the ORs for other criteria (nearly 3 to 4 times higher).

The multivariate logistic stepwise analysis resulted in a final set of predictors that included only absence of atrophic scars, absence of head and neck involvement, absence of mucosal involvement, and age greater than 70 years. The equation of the logistic regression function was as follows: logit $(p) = 7.06 - 2.64 \text{ scar} - 1.046 \text{ head} - 1.08 \text{ mucosal} - 0.06 \text{ age}$. This stepwise multivariate analysis demonstrated that no additional variables met the .05 significance level to enter into the model ($\chi^2 = 97.5$, $P < .001$). The characteristics of the validation sample population were BP ($n = 52$) and non-BP (EBA, 3; CP, 15). The mean age was 77.5 (±13.9) years for patients with BP and 62 ± 23 years for the non-BP group.

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<tr>
<th>Prevalence, %</th>
<th>Sensitivity, %</th>
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*PPV indicates positive predictive value; NPV, negative predictive value.

Table 2 shows the sensitivity, specificity, and calculated positive and negative predictive values in cases of estimated prevalence of 70% to 90% for the diagnosis of BP among the subepidermal AIBDs, as calculated on the second sample of 70 patients. According to IEM findings, these 70 patients were divided between BP (25 men and 27 women) and non-BP (EBA, 3; CP, 15). The mean age was 77.5 (±13.9) years for patients with BP and 62 ± 23 years for the non-BP group. Table 2 shows the sensitivity, specificity, and calculated positive and negative predictive values in cases of estimated prevalence of 70% to 90% for the diagnosis of BP among the subepidermal AIBDs, as calculated on the second sample of 70 patients. According to IEM findings, these 70 patients were divided between BP (25 men and 27 women) and non-BP (8 men and 10 women), consisting of CP in 12, inflammatory EBA in 2, and unclassified in 4.

**COMMENT**

Subepidermal AIBDs are blistering diseases characterized by tissue-bound and circulating autoantibodies that are directed against a component of the cutaneous membrane zone; 4 of them (BP, CP, EBA, and VBLE) have linear de-
postis predominantly of IgG and complement component C3 in the cutaneous BMZ. These 4 diseases may be easily distinguished from 2 other subepidermal AIBDs that were excluded in our study: herpes gestationis, because it occurs in pregnant women, and the so-called linear IgA dermatosis, the diagnosis of which is based on direct immunofluorescence pattern. All these diseases share clinical similarities, although the following clinical criteria have been suggested: (1) tense blisters on erythematous skin of flexural areas of limbs, trunk, and groin without scarring, milia, or mechanical bullae for BP; (2) predominance of mucosal involvement and bullae with scarring evolution for CP; (3) mechanical bullae with milia and scarring on extensor or acral surfaces for EBA; and (4) vesicles or bullae and erythematous plaques, without scarring and associated with systemic lupus erythematosus for VBSLE. Despite their reliability, the predictive diagnostic values of these proposed criteria have never been studied. The present study defined a small number of clinical criteria that allow confident and reliable diagnosis of BP and that distinguish BP from other subepidermal AIBDs, particularly EBA, with satisfactory sensitivity and specificity. With our model, BP can be diagnosed if 3 of 4 criteria are met. In addition, it was possible to estimate the predictive diagnostic values of these criteria, since the prevalence of BP among subepidermal AIBDs is known. Thus, this set of diagnostic criteria may be used in future studies on BP, particularly in multicenter studies and/or randomized therapeutic trials.

We chose direct IEM as the criterion standard for a definite diagnosis of BP. The use of IEM allows clear differentiation between EBA or VBSLE, CP, and BP, but not from herpes gestationis, which was excluded from our study. It is very sensitive, since all patients have such immunoreactants, and fairly reproducible. Serological techniques (mainly immunohistochemical) are not very sensitive, especially for non-BP subepidermal AIBDs. Anti-BMZ antibodies are detectable in 70% of patients with BP, 20% of those with CP, and 50% of those with EBA, and by immunoblotting and/or indirect immunofluorescence on salt-split skin in 80% to 85%. When standard indirect immunofluorescence is negative, they are detectable in only 45% of these cases. The specificity of immunoblotting is insufficient; there is an overlap between BP and CP, since a 180-kd protein is detected in 19% to 50% of the serum samples of patients with BP, and in 40% to 70% of the serum samples of patients with CP. On the other hand, the sensitivity and specificity of immunoprecipitation has not yet been evaluated in a prospective series of patients with BP. In the patients in whom no circulating antibodies are detected, direct immunofluorescence on salt-split skin by means of biopsy specimens of perilesional skin makes it possible to rule out the diagnosis of EBA if IgG appeared on the epidermal side of the blister, but not to separate BP and CP, since in CP, IgG may appear on both the epidermal and the dermal sides. Thus, although direct IEM is not a practical state-of-the-art technique for clinical routine, we decided to use it for the definitive diagnosis in our study, because the sensitivity and specificity are excellent and all the centers participating in the study were able to perform it.

None of the clinical criteria suggested in the literature have been validated, and our study is the first to evaluate the diagnostic value of these clinical criteria. The criteria suggested by the literature had high relative values in our study, but the ORs that we calculated suggest that their respective weights are very different. The OR for the absence of scarring was nearly 3 to 5 times greater than those of other criteria. The other clinical criteria suggested in the literature were also found in our study, with nearly the same range. However, the weighting of each criterion may appear surprising, eg, epidermal plaques and age greater than 70 years. In our study, the biological criteria (hypereosinophilia, presence of anti-BMZ antibodies detected by indirect immunofluorescence on normal skin) were more frequent in BP than in non-BP, but the odds ratios were low, and lower than the majority of clinical criteria. All the criteria with statistically significant ORs in our study were consistent with the clinical and biological features of BP, and there was no discrepancy in the expected results, although it was impossible to predict the weighting of each criterion.
than 5% of the patients who fulfilled our suggested diagnostic criteria for BP had false-positive results. This seems acceptable both in clinical practice and for future therapeutic trials. A positive predictive value greater than 95% is acceptable because it allows inclusion of a few patients with AIIBDs other than BP (in particular, a very few with EBA) in such a therapeutic trial and does not rule out too many patients. On the other hand, when a patient did not fulfill our set of diagnostic criteria, the probability that the patient really had non-BP disease was 48% to 78% (Table 2). The predictive value of our set of criteria suggests than a patient with fewer than 3 of the criteria (age less than 70 years, presence of atrophic scarring, mucosal involvement, head and neck blisters) might undergo further examinations if a precise diagnosis is needed to make a medical decision. In such cases, salt-split skin immunofluorescence could be helpful.

In conclusion, our study supports the usefulness of this set of diagnostic criteria for BP for diagnosing the individual case as well as for ensuring uniformity of groups of patients for clinical and therapeutic studies. The positive predictive value of salt-split skin immunofluorescence might be as good as that of our set of diagnostic criteria, and further studies are necessary to demonstrate this hypothesis.

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