Environmental factors in autoimmune bullous diseases with a focus on seasonality: new insights

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Abstract

Autoimmune bullous diseases are a heterogeneous group of rare conditions clinically characterized by the presence of blisters and/or erosions on the skin and the mucous membranes. Practically, they can be divided into two large groups: the pemphigoid group and the pemphigus group, depending on the depth of the autoimmune process on the skin. A family history of autoimmune diseases can often be found, demonstrating that genetic predisposition is crucial for their development. Moreover, numerous environmental risk factors, such as solar radiation, drugs, and infections, are known. This study aimed to evaluate how seasonality can affect the trend of bullous pemphigoid and pemphigus vulgaris, especially considering the number of hospitalizations recorded over the course of individual months. The total number of hospitalizations in the twelve months of the year was evaluated. Moreover, blood chemistry assay and, for some patients, enzyme-linked immunosorbent assay were executed to evaluate antibodies. Regarding the severity of the disease, the bullous pemphigoid area index and the pemphigus disease area index score systems were used. Results showed a complex interplay between environmental factors such as seasons and autoimmune conditions.

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Introduction

Autoantibodies against structural adhesion proteins of the skin and mucous membranes are the main feature of autoimmune blistering diseases. Extensive characterization of their targets has improved our understanding of pathogenesis.[1]

In particular, the physiopathological base of bullous pemphigoid (BP), the most common subepidermal autoimmune bullous disease, is the production of autoantibodies directed against the hemidesmosomal anchoring proteins BP180 and BP230.

Instead, for pemphigus vulgaris (PV), autoantibodies against desmoglein 1 (Dsg-1) and desmoglein 3 (Dsg-3) seem to be responsible for blisters. Aggressive and aberrant immune responses contribute to the development and progression of PV *via* different mechanisms, including the production of autoantibodies by plasma B cells, and the activity of autoreactive CD4+ T helper cells and CD8+ T cells.[2]

It is stated that genetic predisposition is crucial for the development of autoimmune bullous diseases, but exogenous factors play a role in their induction and exacerbation.

In particular, for drugs, we have thiol drugs like captopril and penicillamine and phenol drugs like aspirin, rifampin, and levodopa. In addition to these drugs, nonsteroidal anti-inflammatory drugs, angiotensin-converting-enzyme inhibitors, calcium channel blockers, glibenclamide, and dipyrone could also be involved.[3] Recently, the use of certain dipeptidyl peptidase 4 inhibitors appears to be associated with a significant elevated risk of developing BP.[4] Contact with tinctures of benzoin, chromate, and phenols can also induce PV.[5]

Moreover, the development of PV and pemphigus foliaceous following herpes simplex virus (HSV) and cytomegalovirus (CMV) infection and following artificial immunizations was mentioned by many authors, suggesting that this phenomenon is not rare.[6,7]

Mohammadi *et al*. speculated that HSV and CMV could have a role not only in the onset of PV but also in its exacerbation.

Nevertheless, the study could not demonstrate the role of these viruses as triggering factors, and further studies are needed.[8]

Furthermore, small-particle air pollution and contact with pesticides can be related to increased hospitalizations for PV.[9,10]

Among exogenous factors, seasons may play a role. In the literature, some studies discuss this topic, but none of them found a definitive association between a particular season of the year and PV onset. Some authors reported that the first manifestations of PV in around three-quarters of patients were in the spring and summer, while in the winter, there was little onset.[11,12] Conversely, in another study conducted in southwestern Iran, winter was introduced as the most powerful season for the development of PV, followed by autumn, spring, and summer, with no significant difference.[13] In contrast to the discussed studies, Robati *et al*. found no association between the seasons and the risk of PV onset.[14] Furthermore, some studies focused specifically on the association between low serum vitamin D concentrations and BP, reporting discordant results.[15,16] Regarding PV, there might be a negative correlation between vitamin D level and the severity of oral mucosa lesions.[17] Given the presence of conflicting data, no definite considerations regarding the involvement of hypovitaminosis D in the etiopathogenesis of bullous disease can be made.[18]

Materials and Methods

To evaluate how seasonality can affect the trend of BP and PV, a systematic review covering a period of 15 years, from 2006 to 2020, was carried out. A total of 892 patients (530 females and 362 males) with a diagnosis of BP or PV were assessed; they were afferent to the Department of Dermatology and Venereology of Maggiore Hospital in Parma, to the Immacolata Dermopathic Institute in Rome, to the Palagi Hospital Presidium in Florence, and to the San Martino Hospital in Genoa. The total number of hospitalizations in the twelve months of the year was evaluated. Furthermore, a blood chemistry assay and, for some patients, an enzyme-linked immunosorbent assay were executed to evaluate anti-BP180, anti-BP230, anti-Dsg-1, and anti-Dsg-3 antibodies, separately. Both qualitative and quantitative assessments of these antibodies were performed. The patients were therefore divided into groups identified by four combinations of antibodies for each disease (Figure 1). For each combination, a count of hospitalizations that took place between 2006 and 2020 in relation to each month of the year was considered. For the severity of the disease, the bullous pemphigoid area index (BPDAI) and pemphigus disease area index (PDAI) score systems were used. The reference cut-off for the first score is 56, while the reference cut-off for the second is 53.

Results

Taking into account the sex difference, data showed, both for BP and PV (Figure 2), a greater number of hospitalizations in women (737, 1592) compared to men (476, 898). Moreover, for both sexes, there is a peak in hospital access in the months of June,

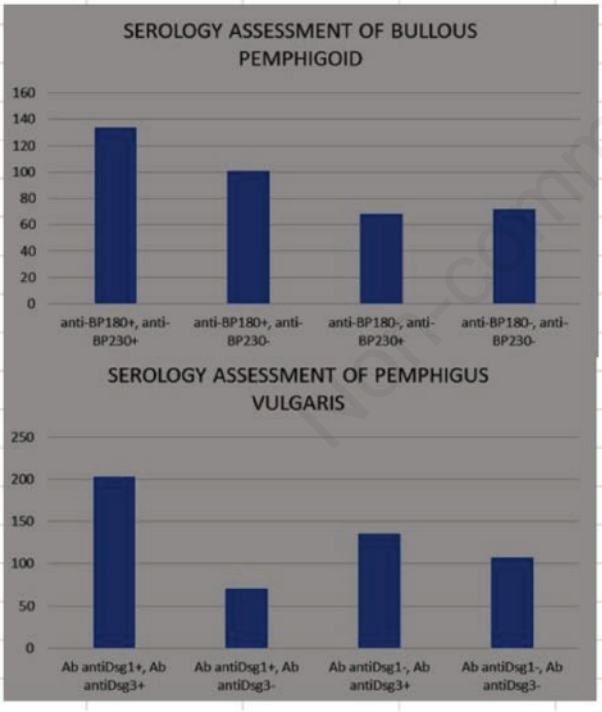

Figure 1. Patients with bullous pemphigoid from 2006 to 2020. Group A includes patients with a diagnosis of bullous pemphigoid and positivity to the antibodies directed against the two antigens BP180 and BP230. Group B includes patients with positivity of anti-BP180 and negativity of the antibody directed against the other antigen. Group C includes patients with positivity of anti-BP230 and negativity of the other one. Group D includes patients with negativity of both. Ab, antobody; Dsg1, desmoglein 1; Dsg3, desmoglein 3.

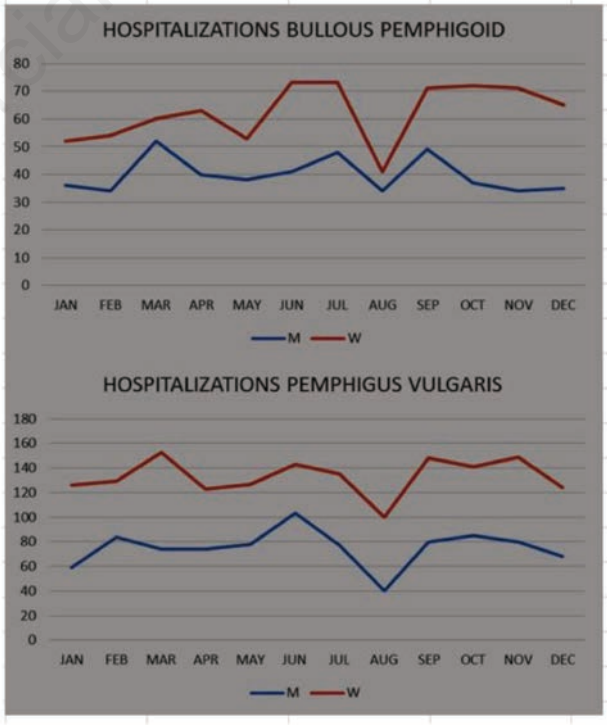

Figure 2. Patients with pemphigus vulgaris from 2006 to 2020. Division by sexes. Group E includes patients with a diagnosis of pemphigus vulgaris and positivity for the antibodies directed against the two antigens desmoglein 1 and desmoglein 3. Group F includes patients with positivity for ant-desmoglein 1 and negativity for the antibody directed against the other antigen. Group G includes patients with positivity for anti-desmoglein 3 and negativity for the other one. Group H includes patients with negativity for both.

July, and September, with a drastic drop in August; in women, there is another peak at the beginning of spring.

Taking into account the serology assessment, for BP, the group of patients that had the highest number of hospitalizations between 2006 and 2020 was the group with negativity of anti-BP180 and anti-BP230, while the group with the fewest hospitalizations showed positivity of anti-BP230 and negativity of the other antigen (Figure 3). Furthermore, in BP, there is a higher antibody titer of BP180 and BP230 in the warm months compared to the cold ones (Figure 4).

Regarding PV, the group of patients that had the highest number of hospitalizations between 2006 and 2016 was the group with positivity of anti-Dsg1 and anti-Dsg3, while the group with the fewest hospitalizations showed negativity of both of the antigens (Figure 3).

Specifically, an increase in anti-Dsg1 and anti-Dsg3 antibodies between June and September was thwarted by a reduction between April and May, October, and November (Figure 4).

The BPDAI study, referring to twelve months, shows an increase in the value between May and September and a reduction in November.

At the same time, the twelve-month PDAI study showed an increase in the value between June and September, with minimum values in May and October (Figure 5).

Discussion

There is a wide range of triggers for autoimmune bullous diseases. Most environmental factors, together with genetic factors, are certainly related to BP and PV.[19]

Since drugs are probably the most frequent trigger, it is important to take an accurate history that includes all drugs taken by the patient, including homeopathic agents, non-prescription drugs, and even medications that the patient discontinued. Moreover, a repeated drug history should be taken in cases in which there is no response to therapy.[20]

The diagnosis of drug-induced BP or PV is challenging because patients have often been exposed to multiple drugs, and some drugs may have a prolonged latency period between exposure and the onset of the disease.[21] The pathogenesis of drug-induced autoimmune bullous diseases is controversial and often difficult to demonstrate. Various mechanisms are hypothesized.[22]

In Chinese patients, the haplotype *HLA-DQB1*03:01*, which was also described as a significant risk factor for BP, was found to be a biomarker for genetic susceptibility to gliptin-induced BP.[23,24]

Among others, the interaction between two different drugs with similar molecular structures and the immune system could

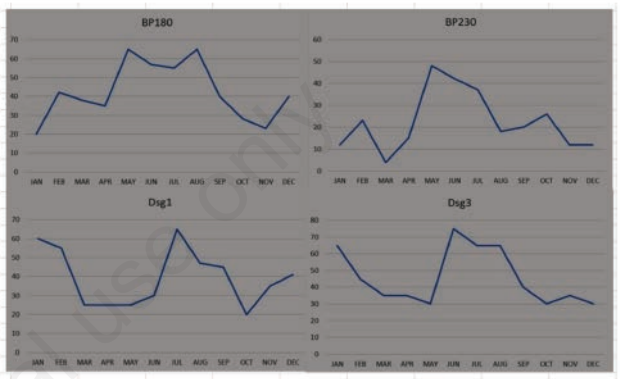

Figure 4. Antibody titer of BP180, BP230, desmoglein 1 and desmoglein 3 during the year.

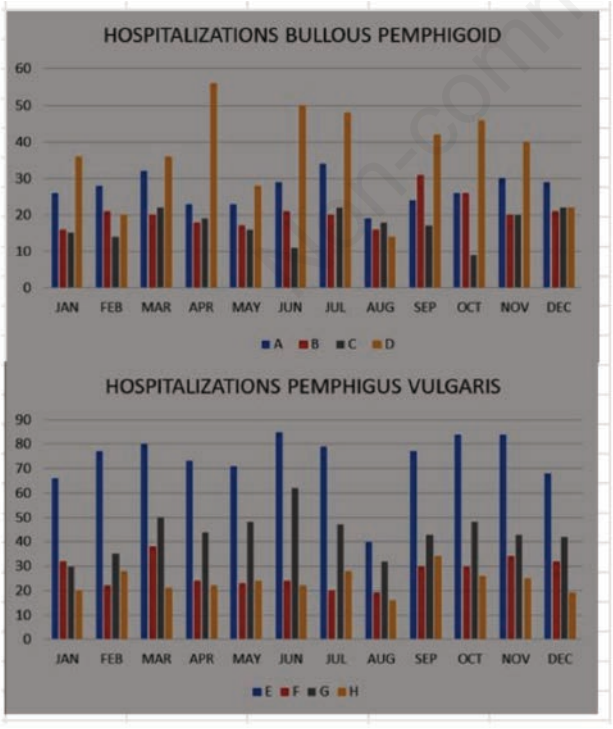

Figure 3. Total number of hospitalizations from 2006 to 2020 in patients with bullous pemphigoid and pemphigus vulgaris.

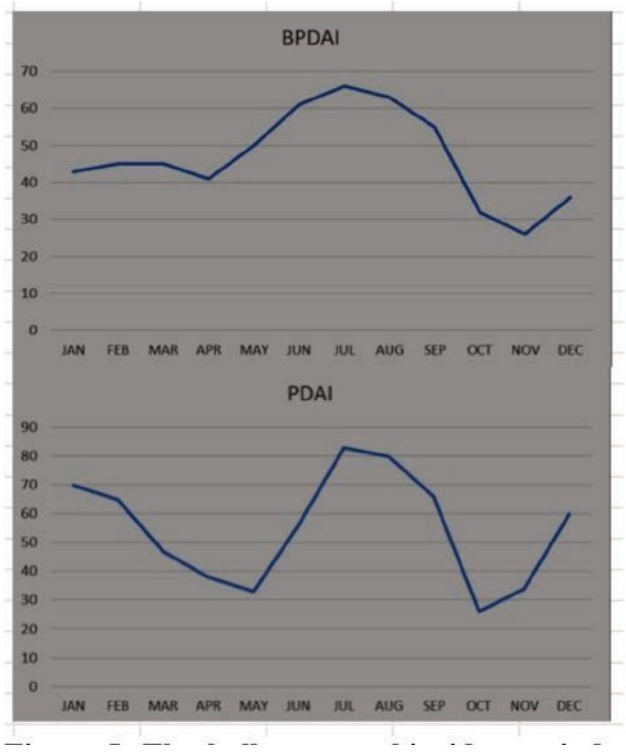

Figure 5. The bullous pemphigoid area index (BPDAI) and pemphigus disease area index (PDAI) values during the year.

represent the first and second "hits" to trigger and enhance an immune reaction. Drugs can also act as antigens through molecular mimicry.[25] It is known that the "*in vitro* interferon-g release from lymphocytes test" has diagnostic value in almost all drug-induced skin reactions, including BP and PV, and it is useful to recognize an immune sensitization for a culprit drug and identify it among the different drugs the patient uses.[26]

The mechanisms for induction of BP and PV after virus infection (HSV, CMV) and vaccines are unclear, but two main hypotheses can be advanced: a hyperimmune reaction induced in genetically predisposed subjects with eventual formation of anti-Dsg antibodies, and a cross-reaction of viral/vaccine antigens with pemphigus antigens.[27]

Certainly, the central focus of this study is seasonality and how it is correlated to autoimmune bullous diseases; hospitalization data suggest an exacerbation of BP and PV in the summer months. This feature could be associated with sun exposure and air temperature.

In fact, it is clear that in spring and summer, high temperatures and usually higher sun exposure compared to winter and autumn may make these seasons more potent for de-epithelialization and therefore BP and PV inducement. Ultraviolet rays in the summer might also reactivate herpes viruses, resulting in a greater immune response.

The drastic drop in August is probably due to the holidays of most dermatologists and the consequent reduction of activities in the hospital. The peak in April, resulting only in women and not in men, is not easy to interpret.

It may be related to the change between cold and hot temperatures that could activate the immune system;[28] hormonal factors or a different perception of the disease in women could explain the increase in hospitalizations in only one sex. However, a sharp rise in the incidence of respiratory infections during winter may also stimulate immune responses. This could be followed by an exacerbation of manifestations of pemphigus in genetically susceptible patients.

A greater number of cases of autoimmune bullous diseases in winter in southwestern Iran can be explained by the fact that in most of the Middle East, the climate is hotter than in Italy and Central Europe, with mild temperatures also in January and February. So this data may not be very reliable; other factors besides sun exposure and air temperature might be involved in the pathogenesis of BP and PV. Other studies, involving more variables, are necessary to establish a certain correlation.

While autoimmune bullous diseases are not considered photodermatosis, using a high SPF sunscreen and avoiding sunlight exposure are recommended both for BP and PV patients.[29]

There is growing epidemiological evidence of a beneficial effect of higher vitamin D status on the onset and progression of autoimmune disorders, so vitamin D supplements could also be suggested to prevent BP and PV flare-ups. A number of clinical trials aiming to determine the efficacy of the administration of vitamin D and its metabolites for the treatment of autoimmune diseases have been conducted in the last few years.[30] However, there are confounders like comorbidities, no control on vitamin D dietary intake in the studied participants, and information on sun exposure limited to the face and hands with no reproducible time period.[30]

It is known that sunlight exposure induces vitamin D synthesis, so on the one hand, summer could be related to exacerbation and, on the other, to a reduction in the incidence of autoimmune bullous diseases, suggesting the involvement of other climate factors like latitude and air humidity.

Some well-designed clinical trials and cohort studies are recommended.

Conclusions

Our study has highlighted interesting aspects about the origin of autoimmune bullous diseases; however, the role that the environment can play is still partially obscure. The possible significance of external environmental factors such as sun exposure, drugs, infections, and vaccinations on the trend of BP and PV could be objectively assessed only through the use of laboratory methods and clinical observations.

In any case, the high number of hospitalizations in September, after the holidays, confirms the possible role of the hot climate as a trigger for autoimmune bullous diseases like BP and PV.

Definitely, other factors also play a role. The results obtained so far encourage us to continue our work to find new evidence that allows us to explain the course of BP and PV over the months in relation to exposure to various risk factors.

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