Dermatology Reports
https://www.pagepress.org/journals/index.php/dr/index

eISSN 2036-7406

Please cite this article as: D'Astolto R, Quintarelli L, Corrà A, et al. Environmental factors in autoimmune bullous diseases with focusing on seasonality: new insights. Dermatol Rep 2023 [Epub Ahead of Print] doi: 10.4081/dr.2023.9641

Submitted: 03/12/2022 – Accepted 08/02/2023

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

Roberto D'Astolto,[1] Lavinia Quintarelli,[2] Alberto Corrà,[2] Marzia Caproni,[2] Luca Fania,[3] Giovanni Di Zenzo,[3] Biagio Didona,[3] Giulia Gasparini,[4,5] Emanuele Cozzani,[4,5] Claudio Feliciani[1]

[1]Section of Dermatology, Department of Medicine and Surgery, University of Parma; [2]Division of Dermatology, Department of Surgery and Translational Medicine, University of Florence; [3]IDI-IRCCS, Dermatological Research Hospital, Rome; [4]Section of Dermatology, Department of Health Sciences, University of Genova; [5]Dermatology Unit, Ospedale Policlinico San Martino IRCCS, Genova, Italy

Correspondence: Roberto D'Astolto, Section of Dermatology, Department of Medicine and Surgery, University of Parma, via Gramsci 14, IT-43100 Parma, Italy.
Tel.: +39.3298185388.
E-mail: roberto.dastolto@gmail.com

Key words: pemphigus, pemphigoid, autoimmune diseases.

Contributions: the authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Ethical approval and consent to participate: written informed consent was obtained from the patients.

Availability of data and material: data and materials are available by the authors.

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 on 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.

Family history of autoimmune disease can often be found, and demonstrating that genetic predisposition is crucial in the development of them. 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 BP and PV, 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. Further, blood chemistry assay and, for some patients, enzyme-linked immunosorbent assay were executed in order to evaluate antibodies. Regarding the severity of the disease BPDAI (Bullous Pemphigoid Area Index) and PDAI (Pemphigus Disease Area Index), score systems were used.

Results showed a complex interplay between environmental factors such as seasons and autoimmune conditions.

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 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.

For pemphigus vulgaris (PV), instead, 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 pemphigus via different mechanisms, including the production of autoantibodies by plasma B cells, the activity of autoreactive CD4+ T helper (Th) cells and CD8+ T cells[2].

It is stated that genetic predisposition is crucial for the development of autoimmune bullous disease, 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, ACE-inhibitors, calcium channel blockers, glibenclamide, and dipyrone could also be involved[3].

Recently, use of certain dipeptidyl peptidase 4 (DPP-4) inhibitors appears to be associated with a significant elevated risk for developing BP[4].

Contact with tincture of benzoin, chromate, phenols, also, can induce PV[5].

Moreover, the development of pemphigus vulgaris and pemphigus foliaceous following herpes simplex (HSV) and cytomegalovirus (CMV) infection and following artificial immunizations were 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 pemphigus vulgaris, but also in the exacerbation of it. Nevertheless, the study could not demonstrate the role of these virus 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, season may play a role.

In literature, some studies discuss about this topic but none of them found a definitive association between a particular season of the year and PV onset.

Some authors had reported that the first manifestations of PV in around three-quarters of patients were in spring and summer, while the onset was little in winter[11,12].

Conversely, in another study conducted in South-Western 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 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 a negative correlation between vitamin D level and 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 done[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.

892 patients with a diagnosis of BP or PV were assessed, 530 female and 362 male afferent to the Department of Dermatology and Venereology of "Ospedale Maggiore" in Parma, to "Istituto Dermopatico dell'Immacolata" in Roma, to "Presidio Ospedaliero Palagi" in Firenze and to "Ospedale San Martino" in Genova.

Total number of hospitalizations in the twelve months of the year were evaluated.

Further, blood chemistry assay and, for some patients, enzyme-linked immunosorbent assay (ELISA) were executed in order to evaluate anti-BP180, anti-BP230, anti-desmoglein1 (Dsg-1) and anti-desmoglein3 (Dsg-3) antibodies, separately.

Both qualitative and quantitative assessment of these antibodies were performed.

The patients were therefore divided into groups identified by four combinations of antibodies for each disease (*Fig.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 BPDAI (Bullous Pemphigoid Area Index) and PDAI (Pemphigus Disease Area Index) score systems were used. For the first score reference cut-off is 56 while for the second one is 53.

Results

Taking into account the sex difference, data showed, both for BP and PV *(Fig.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 accessed in the months of June, July and September, with a drastic drop in August; in women there is another peak at the beginning of spring.

Taking account serology assessment, for BP the group of patients that made 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 off positivity of anti-BP230 and negativity of the other antigen (*Fig.3*).

Furthermore, in BP there is a higher antibody titer of BP180 and BP230 in the warm months compared to cold months *(Fig.4)*.

Regarding PV, the group of patients that made 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 off negativity of both of the antigens *(Fig.3)*.

Also, a particularly marked variation in the antibody title over the months could be observed. Precisely, an increase in antibodies anti-Dsg1 and Ab anti-Dsg3 between June and September, thwarted by a reduction between April and May, October and November *(Fig.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 (*Fig.5*).

Discussion

There is a wide range of triggers for autoimmune bullous diseases. Most environmental factors, together to genetic factors, are certainly related to BP and PV[19].
Since drugs are probably the most frequent trigger, it is of great importance 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 onset of the disease[21].
The pathogenesis of drug-induced autoimmune bullous disease is controversial and often difficult to demonstrate. Various mechanisms are hypothesized[22].
In Chinese patients, the haplotype HLADQB1*03:01, which had also been described as a significant risk factor for BP[23], was found to be a biomarker for genetic susceptibility to gliptin-induced BP[24].
Among others, the interaction between two different drugs with similar molecular structures and the immune system could represent the first and second "hit" to trigger and to enhance an immune reaction. Drugs can also act as antigens through molecular mimicry[25].
It is known that the "*in vitro interferon-gamma release from lymphocytes test"* has a diagnostic value in almost all drug-induced skin reactions, including BP and PV, being 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 viruses 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-desmoglein antibodies and a cross-reaction of viral/vaccine antigens with pemphigus antigens[27].
Central focus of this study is certainly the seasonality and how it is correlated to autoimmune bullous disease; hospitalizations data suggest an exacerbation of BP and PV in the summer months. This feature could be associated with sun exposure and air temperature.
It is clear, in fact, that in spring and summer high temperature 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 (UV) rays in summer might also reactivate herpesviruses, resulting in a greater immune response.

The drastic drop in August probably it is likely due to the holiday of most of 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 temperature that could activate the immune system[28]; hormonal factors or different perception of the disease in women could explain increase of hospitalizations in only one sex. However, a sharp rise in the incidence of respiratory infections in winter may also stimulate immune responses. This could be followed by an exacerbation of manifestations of pemphigus in genetically susceptible patients.

Greater number of cases of autoimmune bullous diseases in winter in South-Western Iran can be explained by the fact that in most of the Middle-East climate is hotter than Italy and Central Europe, with mild temperatures also in January and February. So this data may not be so much 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 disease are not considered photodermatosis, using a high SPF sunscreen as well as the avoidance of exposure to sunlight is recommended both for BP and PV patients[29].

There is growing epidemiological evidence of a beneficial effect of higher vitamin D status in 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 administration of vitamin D and its metabolites for treatment of autoimmune diseases have been conducted in the last years[30].

There are though confounders like comorbidities, no control on vitamin D dietary intake in the studied participants, information on sun exposure limited to face and hands with no reproducible period of time[34].

It is known that sunlight exposure induces vitamin D synthesis, so summer on one side could be related to exacerbation and on other side to reduction of incidence of autoimmune bullous diseases, suggesting 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 bullous autoimmune 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 all cases, the result of a high number of hospitalizations in September, after holidays, confirms a possible role of hot climate as a trigger for autoimmune bullous disease like BP and PV.

Definitely, also other factors have a role. The results obtained so far encourage us to continue our work in order 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.

References

1) Didona D et al. Humoral Epitope Spreading in Autoimmune Bullous Diseases. Front Immunol. 2018 Apr 17;9:779.
2) Wang WM et al. Role of B cells in immune-mediated dermatoses. Mol Immunol. 2020 Oct;126:95-100.
3) Pile HD et al. Drug Induced Pemphigus. StatPearls Publishing; 2020 Jan. 2020 Aug 25.
4) Hibi A et al. Dipeptidyl peptidase-4 inhibitor-associated bullous pemphigoid, likely triggered by scabies, in a hemodialysis patient with human leukocyte antigen-DQB1*03:01. CEN Case Rep. 2020 Aug; 9(3): 189–194.
5) Tur E et al. Contributing exogenous factors in pemphigus. Int J Dermatol. 1997 Dec;36(12):888-93.
6) Krain LS (1974) Pemphigus. Epidemiologic and survival characteristics of 59 patients, 1955–1973. Arch Dermatol 110:862–865.
7) Ruocco E, Ruocco V, Lo Schiavo A, Brunetti G, Wolf R (2014) Viruses and pemphigus: an intriguing never-ending story. Dermatology 229:310–315.
8) Mohammadi F et al. The potential roles of herpesvirus and cytomegalovirus in the exacerbation of pemphigus vulgaris. Dermatol Pract Concept. 2018 Oct 31;8(4):262-271.
9) Ren Z et al. Association between climate, pollution and hospitalization for pemphigus in the USA. Clin Exp Dermatol. 2019 Mar;44(2):135-143.
10) Fisher KR et al. Pesticide-associated pemphigus vulgaris. Cutis 2008 Jul;82(1):51-4.
11) Tsankov N et al. Epidemiology of pemphigus in Sofia, Bulgaria. A 16-year retrospective study (1980-1995). Int J Dermatol. 2000 Feb;39(2):104-8.
12) Kyriakis KP et al. Environmental factors influencing the biologic behavior of patterns of pemphigus vulgaris: epidemiologic approach. Int J Dermatol. 1995 Mar;34(3):181-5.

13) Salmanpour R et al. Epidemiology of pemphigus in south-western Iran: A 10-year retrospective study (1991–2000). Int J Dermatol. 2006 Feb;45(2):103-5.
14) Robati RM et al. Pemphigus vulgaris and season: are they really related or not? J Eur Acad Dermatol Venereol. 2011 Oct;25(10):1235-6.
15) Marzano AV et al. Evidence for vitamin D deficiency and increased prevalence of fractures in autoimmune bullous skin diseases. Br J Dermatol. 2012 Sep;167(3):688-91.
16) Marzano AV et al. Vitamin D and skeletal health in autoimmune bullous skin diseases: A case control study. Orphanet Journal of Rare Diseases, 10 (2015), p. 8.
17) Tukaj S et al. Vitamin D status in bullous pemphigoid patients. The British Journal of Dermatology, 168 (2013), pp. 873-874.
18) Zarei M et al. Evaluation of Vitamin D Status in Newly Diagnosed Pemphigus Vulgaris Patients. Iran J Public Health. 2014 Nov; 43(11): 1544–1549.
19) Tavalkopour S et al. Pemphigus trigger factors: special focus on pemphigus vulgaris and pemphigus foliaceus. Arch Dermatol Res (2018) 310:95–106.
20) Shear NH. Diagnosing cutaneous adverse reactions to drugs. Archives of Dermatology. 1990;126(1):94–97.
21) Brenner S et al. Drug-induced pemphigus. Clin Dermatol. Jul-Aug 2011;29(4):455-7.
22) Lo Schiavo A et al. Bullous pemphigoid: Etiology, pathogenesis, and inducing factors: Facts and controversies. Clinics in Dermatology (2013)31, 391–399.
23) Fang H et al. Association of HLA class I and class II alleles with bullous pemphigoid in Chinese Hans. J Dermatol Sci. 2018 Mar;89(3):258-262.
24) Ujiie H et al. HLA-DQB1*03:01 as a Biomarker for Genetic Susceptibility to Bullous Pemphigoid Induced by DPP-4 Inhibitors. J Invest Dermatol. 2018 May;138(5):1201-1204.
25) Moro F et al. Bullous Pemphigoid: Trigger and Predisposing Factors. Biomolecules. 2020 Oct; 10(10): 1432.
26) Halevy S, Cohen AD, Grossman N. Clinical implications of in vitro drug-induced interferon gamma release from peripheral blood lymphocytes in cutaneous adverse drug reactions. Journal of the American Academy of Dermatology. 2005;52(2):254–261.
27) De Simone C et al. Exacerbation of pemphigus after influenza vaccination. Clin Exp Dermatol. 2008 Nov;33(6):718-20.
28) Kano Y et al. Pemphigus foliaceus induced by exposure to sunlight. Report of a case and analysis of photochallenge-induced lesions. Dermatology. 2000;201(2):132-8.
29) Charoenngam N et al. Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients. 2020 Jul 15;12(7):2097.

30) Sarre ME et al. Association between bullous pemphigoid and hypovitaminosis D in older inpatients: Results from a case-control study. Eur J Intern Med. 2016 Jun;31:25-8.

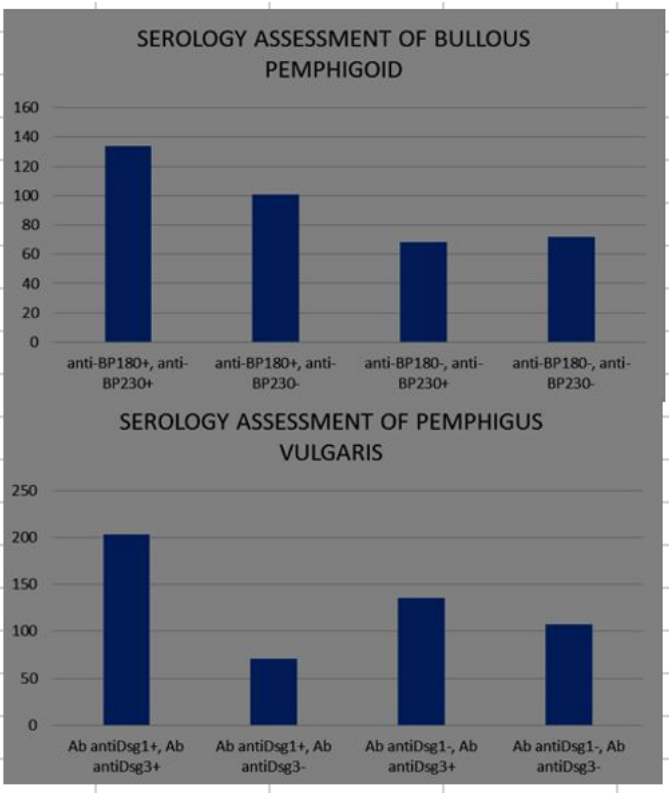

Figure 1. Patients with bullous pemphigoid from 2006 to 2020. Group A includes patients with a diagnosis of bullous pemphigoid and positivity to the antibodies directed against the two antigens BP180 and BP230. Group B includes patients with positivity of anti-BP180 and negativity of the antibody directed 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.Fig.2: Patients with pemphigus vulgaris from 2006 to 2020. Division by sexes.

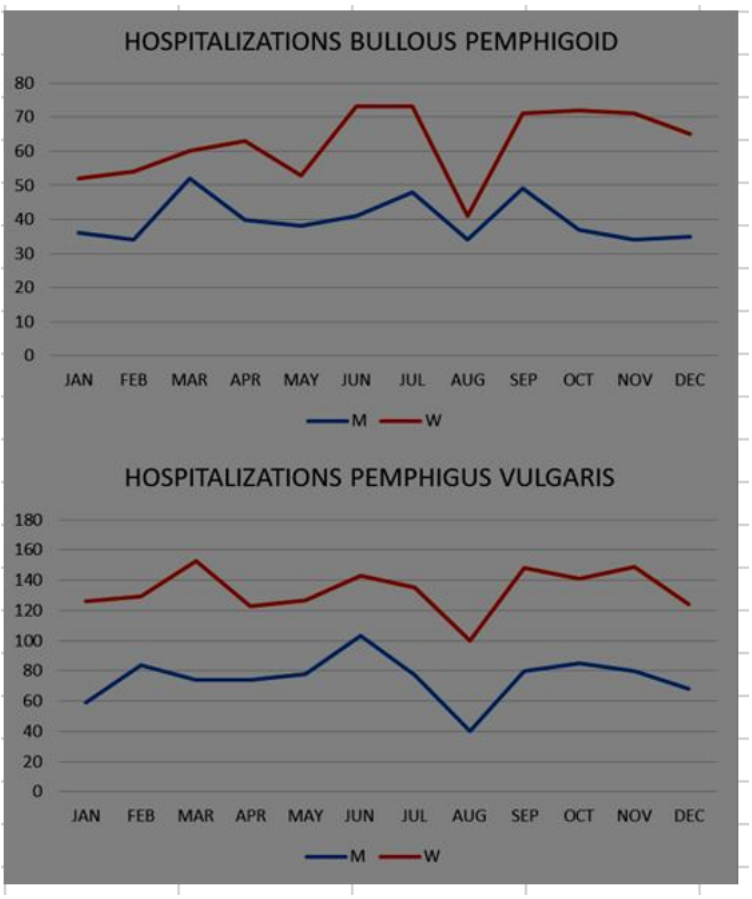

Figure 2. Patients with pemphigus vulgaris from 2006 to 2020. Group E includes patients with a diagnosis of pemphigus vulgaris and positivity to the antibodies directed against the two antigens Dsg-1 e Dsg-3. Group F includes patients with positivity of ant-Dsg1 and negativity of the antibody directed against the other antigen. Group G includes patients with positivity of anti-Dsg3 and negativity of the other one. Group H includes patients with negativity of both. Division by sexes.

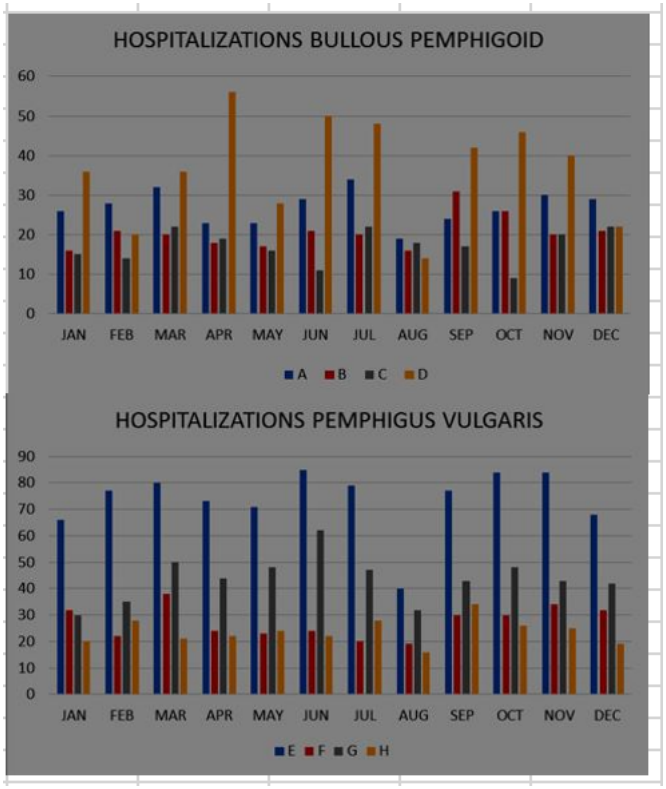

Figure 3. Total number of hospitalizations from 2006 to 2020 in patients with bullous pemphigoid and pemphigus vulgaris (blu line for men, red line for women).

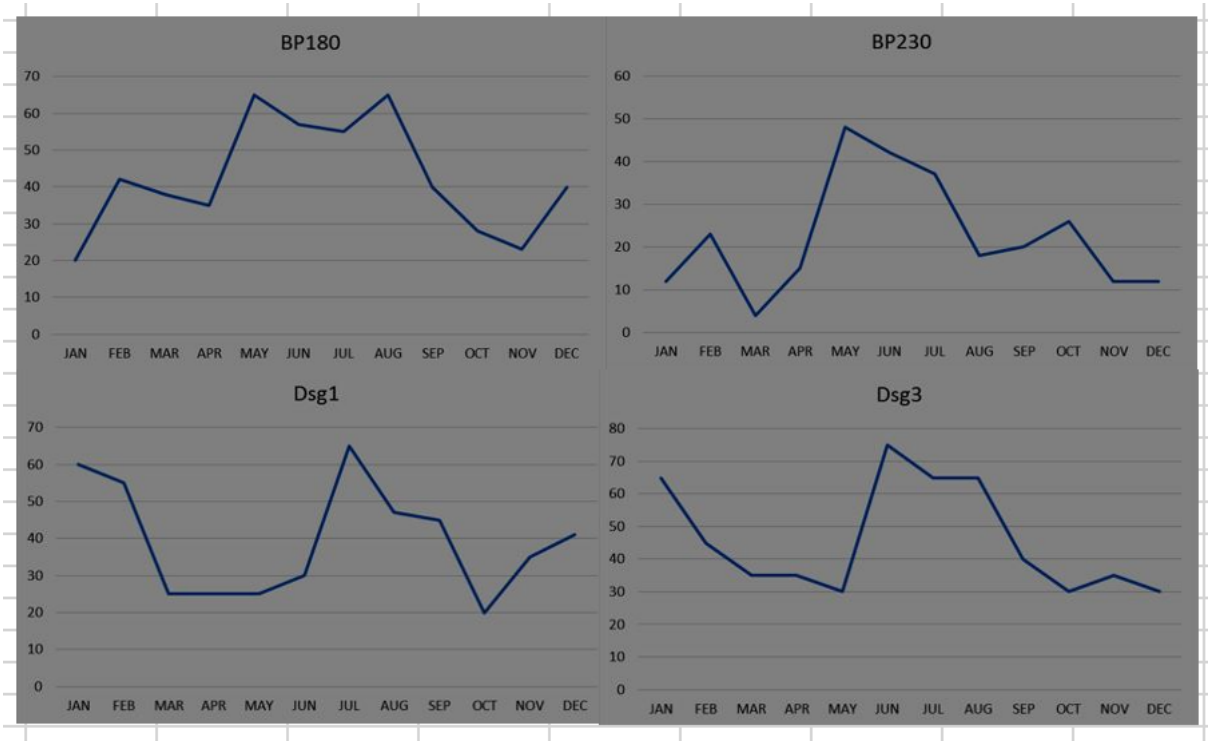

Figure 4. Antibody titer of BP180, BP230, Dsg-1 and Dsg-3 during the year.

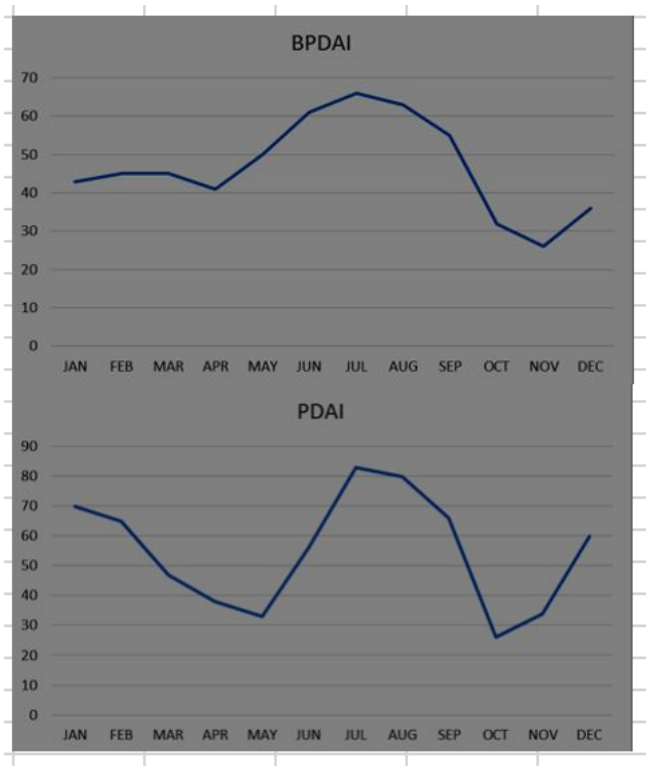

Figure 5. BPDAI and PDAI values during the year.