

CLINICAL REPORT

A Retrospective Epidemiological Study on the Association of Bullous Pemphigoid and Neurological Diseases

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Bullous pemphigoid is a rare chronic recurrent dermatosis that is often reported in association with various neurological diseases. No investigation involving a large number of patients has ever been carried out to demonstrate such an association. This study was accomplished by analysing the discharge diagnosis of all hospitalized patients, both day-patients and inpatients, during a 5-year period (1995–2000) covering a total population group of 934,023 living in a region of Italy that has approximately 1,200,000 inhabitants. The results support the hypothesis of an association between bullous pemphigoid, multiple sclerosis and Parkinson's disease on a highly significant statistical basis. The aetiopathogenic mechanisms and the causes that induce the loss of immunological tolerance are not yet understood.

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Bullous pemphigoid (BP) is a rather uncommon, chronic relapsing and non-hereditary dermatosis that generally appears after the age of 50 and is increasingly prevalent in elderly people. Histologically, the blisters are subepidermal and immunofluorescence studies show auto-antibodies directed towards antigens of the basal membrane: BP230 or BPAg1, of about 230 Kda, localized in the intracellular portion of the hemidesmosomes (1–5), and BP180 or BPAg2, corresponding to type XVII collagen, a transmembrane protein with a molecular weight varying from 160 to 180 Kda (6).

There are several publications in the literature (7–20) that refer to occasional associations between BP and certain neurological diseases, particularly multiple sclerosis, amyotrophic lateral sclerosis and Parkinson's disease. To confirm or reject the hypothetical association between BP and neurological diseases we have carried out a retrospective study on a large population to evaluate the statistical significance of this association.

MATERIALS AND METHODS

The study was carried out on patients discharged from various hospitals in Friuli Venezia Giulia (FVG), a region in the north-eastern part of Italy, over the 5-year period 1995–2000. A total of 934,023 subjects out of a resident population of 1,187,000 (as of 31 December 2000) were involved. We used the regional computerized database system that collects data on patients' discharge diagnosis from all the hospitals present in the region and took into consideration those patients whose clinical records reported a concomitant diagnosis of BP and neurological diseases. We primarily considered the pathologies quoted in the study by Foureur et al. (18) such as Alzheimer's disease, senile degeneration of the brain, other cerebral degenerations, epilepsy, hereditary peripheral and idiopathic neuropathies, hemiplegia and hemiparesis, Parkinson's disease, multiple sclerosis and inflammatory and toxic neuropathies. From a preliminary analysis of the data we focused our attention on the associations of BP with multiple sclerosis and Parkinson's disease, as all other associations were numerically insignificant. From the hospitalization events, through the patient's Regional Health Card code number, we traced back to the cases of BP, multiple sclerosis and Parkinson's disease. The histological reports were verified and subsequently the clinical records relating to hospitalization of these patients were examined. We evaluated their sex, age of onset of the disorders, clinical features and the presence of criteria proposed by Vaillant and the French Bullous Study Group (21), the seriousness and the evolution of the neuropathy, the degree of autonomy and self-management of the patients, the presence of indwelling catheters, the therapy adopted and any other pathology that could eventually be associated.

A population of patients hospitalized for traumas during the same period (1995–2000) was used as a comparison, i.e. a large population that is in general good health (except for the traumatic pathologies) and of an age close to that of the neurological population (Fig. 1). Finally we isolated those cases presenting with both BP and traumas.

Statistics

We calculated the prevalence of BP both in neurological patients and in patients with trauma. The precision of the estimates was expressed by 95% confidence intervals (95% CI), which were calculated by Fisher's exact method. The prevalence of BP in the two groups of patients was compared with the prevalence ratio.

RESULTS

Excluding all multiple hospitalizations, we determined that 238 patients were hospitalized for BP, 1704 for multiple sclerosis, 2426 for Parkinson's disease and

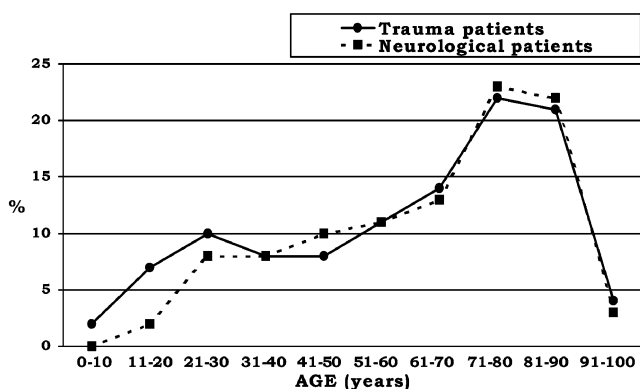


Fig. 1. Age of patients hospitalized for trauma (●) and neurological causes (■) in the studied region from 1995 to 2000.

57,380 for trauma. By crossing the hospital discharge codes between BP and the other pathologies considered, we found an association of BP with Parkinson’s disease in six cases, with multiple sclerosis in three cases, and with trauma in two cases.

The three cases with BP and multiple sclerosis were female patients. Their average age at the time of onset of the neurological disorder was 46 years and the appearance of BP occurred after an average interval of 4 years (Table I), i.e. at a mean age of 53 years, which is significantly earlier than expected. All three patients presented severe neurological and neurodegenerative damage to the extent that they were bedridden with the consequent development of bedsores and the permanent use of bladder catheters.

The history, clinical features, histological examination of the lesions and direct immunofluorescence findings (IgG and C3 deposits along the basal membrane) were typical for BP cases in all three patients. There was an immediate response to prednisone treatment at a dose of 1 mg/kg/day in two of the three cases. As the third patient was resistant to high doses of steroids (prednisone 125 mg/day) she was treated with azathioprine (150 mg/day) and plasmapheresis (10 sessions), which resulted in an improvement.

Table I. Characteristics of three female patients affected by multiple sclerosis (MS) and bullous pemphigoid (BP)

Age at onset of MS	Age at onset of BP	Drugs taken	Other notes
43/54*	57	Baclofen	Bedridden
43	49	Baclofen	Bedridden
50	53	Delorazepam	Bedridden

*Age at which the last clinically significant episode of worsening of MS occurred, a worsening so severe as to result in a rapid state of invalidity and consequent loss of autonomy for the patient. Reference was made to this age when calculating the time interval between onset of the two pathologies.

Table II. Characteristics of six patients affected by Parkinson’s disease (PD) and bullous pemphigoid (BP)

Sex	Age at onset of PD	Age at onset of BP	Drugs taken	Other notes
F	65	68	Imipramine, levodopa, bromocriptine	Bedridden
F	82	88	Levodopa	Bedridden (deceased)
F	83	85	Levodopa	
M	73	77	Bromocriptine	
M	75	77	Carbidopa	
M	79	80	Levodopa	Bedridden

The association between BP and Parkinson’s disease was found in six cases (Table II). In this group the mean age at onset of Parkinson’s disease was 76 years and the mean age at onset of BP was 79 years. In these patients too the diagnosis of BP was confirmed by the history, clinical features, laboratory and immunohistological tests.

In addition we found that one male patient with Parkinson’s disease presented with a kappa IgA-type monoclonal gammopathy, another male patient was affected by a squamous cell carcinoma of the lung with hepatic metastasis, and one female patient had died because of a cardio-circulatory decompensation.

The prevalence of BP among neurological patients and those with trauma is shown in Table III. In comparison, the prevalence of BP was much higher in patients hospitalized for neurological diseases than in those hospitalized for traumas.

DISCUSSION

The results of this study showed a highly significant association of BP with multiple sclerosis or Parkinson’s disease. The dermatosis always followed the onset of the neurological pathology at intervals varying from a few months to a maximum of 4 years, as also shown in other cases reported in the literature (16, 19). In patients afflicted by multiple sclerosis, BP had its onset at an earlier age compared with the usual situation (16).

It has been suggested that drugs, decubital lesions, traumatic events and immunity are triggering factors for BP during the course of neurological pathologies (8–20). Drugs, for example, myo-relaxants, such as Baclofene, as well as other topical iodates and drugs containing sulphur (10–13, 17), have often been considered possible precipitating agents for BP. However, the pharmacological hypothesis is frequently contradicted by the absence of a temporal correlation between the intake of drugs and the appearance of bullous manifestations

Table III. Prevalence of bullous pemphigoid (BP) among neurological patients and patients hospitalized for various physical traumas

Hospital admission diagnosis	Number of patients with BP	Prevalence (P) of BP/10,000 hospitalizations	Prevalence ratio		
			95% CI	P _{N+} /P _{T+}	95% CI
Multiple sclerosis or Parkinson's disease (N+)	9	21.79	9.96-41.37	62	12-594
Trauma (T+)	2	0.35	0.04-1.26		

(17). In our patients a time correlation between the onset of BP and the intake of drugs was not noticed.

The idea that physical traumas, decubital lesions or paralysis could be involved in the onset of BP goes back to when the disease was first described (16). Although this hypothesis has often been formulated, a causal link has never been confirmed. Speculatively, damage to the dermo-epidermal junction with subsequent antigen exposure and activation of the immune system might be involved (17). In our study, bed confinement, paralysis, decubital ulcers or the use of indwelling catheters did not seem to be the causes of BP, as it occurred without any temporal relation to these events.

Another hypothesis which seems to be plausible is that the appearance of neurodegenerative processes could trigger the development of BP through an autoimmune mechanism (17). An immunological link between BP and multiple sclerosis could therefore be found in the presence of two isoforms of the BP antigen, an epithelial one (BPAG1) and a neuronal one (BPAG1-n), as demonstrated in the mouse model by Brown et al. (22). In fact, a gene called dystonin that codifies cytoplasmatic proteins present both at dendritic and axonal levels and is capable of anchoring the intermediate neuronal filaments to the cytoskeleton has only recently been identified (22). It has been proven that the inactivation of this gene in mice generates muscular dystonia characterized by a diffused neuronal degeneration and by a massive conglomeration of the neurofilaments. Recently, it has been proven that dystonin presents homologies in the C terminal region with BPAG1; experimental proof has confirmed that the antibodies directed against BPAG1, in particular those that recognize the epitope in its central part, cross-react with the neuronal protein in the cerebral sections in the mouse (22). These observations are certainly not surprising in view of the fact that the skin and the nervous system both originate from the neural crest.

Furthermore, it is possible that nervous system alterations in humans in the course of multiple sclerosis and Parkinson's disease could expose the neuronal isoform, thus triggering an immune reaction that, along with the immunological cross-reactions, determines cutaneous damage (17). Recently, using magnetic resonance imaging, it has been observed that during the acute phase of neurological pathologies there is serious damage to the haemato-encephalic barrier

(23-25). In such circumstances it is certainly plausible that the peripheral immune system activates itself against the antigens mentioned, amplifying the damage to the central nervous system and, due to the presence of isoantigens, also involving other organs such as the skin. This would explain why the bullous pathology follows the neurological one.

It would indeed be interesting to analyse the anti-BPAG1 antibodies in the serum and cerebrospinal fluid of these patients to test the suggested hypothesis explaining an association between neurological diseases and BP.

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