Bullous Pemphigoid and Amyotrophic Lateral Sclerosis

A New Clue for Understanding the Bullous Disease?

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Background: Bullous pemphigoid (BP) occurs in many patients with multiple sclerosis. Isolated cases of BP in patients with other neurological disorders further support a pathogenic association between cutaneous and neurological diseases. Any description of BP in patients with amyotrophic lateral sclerosis is lacking.

Observations: We studied a French population of 168 patients with typical amyotrophic lateral sclerosis. Among these, 3 had clinical and histological features of BP. The mean age of the patients was 54 years. None was known to have autoimmune disorders. Results of immunoblot analysis disclosed both anti-BP antigen 1 and anti-BP antigen 2 antibodies.

Conclusions: Bullous pemphigoid seems to be unexpectedly associated with amyotrophic lateral sclerosis. On the basis of the cases presented herein, we discuss the epidemiological significance of the association and the possible interrelation between BP antigen 1 and neurofilaments in the pathogenesis of both disorders.

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The coexistence of bullous pemphigoid (BP) with various neurological disorders has been reported, although the relationship between these entities has yet to be identified. An autoimmune process has been suggested to explain the association of BP with multiple sclerosis.1-11 To our knowledge, this is the first report of an association of BP with amyotrophic lateral sclerosis (ALS).

We studied a population of 168 patients presenting with ALS (Table).12 These patients were included in a multicenter, prospective, randomized clinical trial comparing an antiglutamate agent riluzole (Rhone-Poulenc Rorer, Antony, France) with placebo. Patients were enrolled from December 1992 through November 1993, and observed under double-blind conditions for 18 months.

Three French patients (mean age, 54 years) presented with BP (Table). None was known to have autoimmune disorders, and all of them had sporadic definite ALS with a limb-onset form. The 3 patients with BP underwent an immunoblot serum analysis using normal human skin as the substrate to detect anti-BP antigen 1 (BPAG1) and anti-BP antigen 2 (BPAG2) antibodies.13

CASE 1

A 47-year-old man, affected by ALS for at least 3 years, was enrolled in the placebo group. For more than 6 months, he received clomipramine hydrochloride, thioridazine hydrochloride, N-acetylcysteine, nicergoline, and fluindione. He had started treatment with 30 mg/d of bcofen 3 months prior to the onset of BP. The patient had severe functional disability with complete paralysis of the forelimbs, choking, and swallowing difficulties. Seven days after enrollment, he complained of cutaneous lesions. Fourteen days after enrollment, he developed tense, sometimes bleeding, bullous, 0.5- to 1.0-cm lesions on the forearms and lower limbs associated with urticarial plaques. He also had dyshidrotic and edematous lesions on the palms (Figure 1), post-bullous erosions of the meatus and labia, and hyper eosinophilia (670/mm3). Bullous pemphigoid was confirmed by the presence of subepidermal blisters associated with linear deposits of C3 and IgG along the basal membrane zone (Figure 2). Circulating antiepidermal antibodies were...
present (1/10) with antibodies binding to the roof of the salt-split skin. Immunoblot analysis results disclosed both anti-BPAG1 and anti-BPAG2 antibodies. Treatment was begun with 1 mg/kg per day (100 mg/d) of prednisone with antiseptic care and classic adjuvant corticosteroid therapy. Neither the study medication nor baclofen therapy was discontinued. The outcome was favorable, and the corticosteroid treatments were discontinued after 5 months. The patient died of respiratory failure 7 months after the onset of BP.

**CASE 2**

A 47-year-old woman, affected by ALS for at least 9 years, was enrolled in the riluzole group (100 mg/d). She had been treated for more than 3 years with dantrolene, dihydroergotamine mesylate, temazepam, amitriptyline hydrochloride, theophylline, and oral contraceptives. Because of acne, she had undergone 6 months of minocycline treatment. She had begun treatment with 30 mg/d of baclofen 10 months prior the onset of BP. The patient had severe functional disability with complete paralysis of the forelimbs, dysphonia and dysphagia, and stiffness and fasciculations of the tongue. Nine months after enrollment, she developed papulous lesions of the elbows diagnosed as prurigo. She also had dyshidrotic lesions on the palms and soles. After a week, she had extensive crusted and bullous lesions of the axillas and the flexor forearms, and she was hospitalized. She presented with a vesicular and bullous, annular, crusted, and surinfected dermatitis localized to the anterior chest, axillas, pubis, lower legs, and arms (Figure 3). Her mucous membranes were normal. She had hyper eosinophilia (630/mm3) and hypogammaglobulinemia (7.8 g/L), and BP was confirmed by the presence of subepidermal blisters associated with linear deposits of C3 and IgG along the basal membrane zone. Circulating antiepidermal antibodies were not found. Immunoblot analysis disclosed both anti-BPAG1 and anti-BPAG2 antibodies. Treatment was begun with 1 mg/kg per day (45 mg/d) of prednisone, antiseptic care, and classic adjuvant corticosteroid therapy. Neither the study medication nor baclofen treatment was discontinued. The outcome was dramatically favorable, and the prednisone dose was slowly decreased. The corticosteroid treatments were stopped after 14 months. A relapse occurred 9 months later, and treatment with oral prednisone was resumed with a good response. The patient was still alive at the end of the study.

![Figure 1](image1.jpg) **Figure 1.** Bullous dyshidrosiform pemphigoid in a 47-year-old man with amyotrophic lateral sclerosis (case 1).

![Figure 2](image2.jpg) **Figure 2.** Linear deposits of C3 and IgG along the basal membrane zone of the patient in case 1.

Neurological Status of Patients With Amyotrophic Lateral Sclerosis (ALS) and Bullous Pemphigoid (BP) and the General Population of the Study

<table>
<thead>
<tr>
<th>Patient/Sex</th>
<th>Age, y</th>
<th>ALS Duration, y</th>
<th>Slow Vital Capacity, %*</th>
<th>Manual Muscle Testing†</th>
<th>Limb Function‡</th>
<th>Bulbar Function‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M</td>
<td>47</td>
<td>3</td>
<td>23</td>
<td>47</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>2/F</td>
<td>47</td>
<td>9</td>
<td>NA</td>
<td>36</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>3/M</td>
<td>68</td>
<td>3</td>
<td>49</td>
<td>63</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>Total population mean (SEM)§</td>
<td>60.4 (1) (N = 168)</td>
<td>3.6 (0.2) (N = 168)</td>
<td>53.7 (2) (n = 133)</td>
<td>67.1 (2.1) (N = 168)</td>
<td>27.7 (1.5) (N = 168)</td>
<td>19.7 (1) (n = 166)</td>
</tr>
</tbody>
</table>

* Respiratory function was monitored with tests of vital capacity expressed as a percentage of the predicted normal value done at study entry and every 6 months thereafter. NA indicates not available.
† Muscle strength was assessed for 22 muscle groups according to the 5-grade scale of the Medical Research Council (maximum score 110), with the patient seated.
‡ Limb function and bulbar function were separately assessed with modified Norris scales12 (maximum score 63 for limb function, 39 for bulbar function).
§ The ratio of men to women in the total study population was 82:86.
A 68-year-old man, affected by ALS for at least 3 years, was enrolled in the placebo group. For more than 6 months, the patient received treatment with baclofen (40 mg/d), fluoxetine hydrochloride, vitamins B1, B2, B3, B4, and B5, thiamine hydrochloride, riboflavin, pyridoxine hydrochloride, tetracepam (25 mg/d), and hydroxyzine hydrochloride (25 mg/d). The patient had severe functional disability with paralysis of the lower limbs, swallowing difficulties, and dysphonia. He was hospitalized in a long-term unit when, 1 month after enrollment, pruritus, generalized eczema, and pseudo-urticarial lesions occurred. The lesions were localized on the anterior part of the trunk and the proximal part of the lower limbs. He had hypereosinophilia (1562/mm³), and BP was confirmed by the presence of subepidermal blisters associated with linear deposits of C3 and IgG along the basal membrane zone. Dosing of circulating anti-epidermal antibodies was not performed. Results of immunoblot analysis disclosed both anti-BPAG1 and anti-BPAG2 antibodies. Treatment was begun with 20 mg/d of prednisolone metasulfobenzoate, local betamethasone-17 valerate, and 120 mg/d of terfenadine. The decision was made to stop treatment with the study medication as well as tetracepam and vitamins, but baclofen therapy was still given during the following 4 weeks. Nineteen days later, dermatological lesions had disappeared, and eosinophils had returned to normal count. Treatment with the corticosteroids was stopped after 4 months of treatment. The patient died of respiratory failure 12 months after the onset of BP.

**COMMENT**

All 3 of the reported patients had advanced ALS of long standing, which is a progressive and fatal neurodegenerative disorder (incidence of 1 to 2 per 100 000 per year in the United States). Also, in all 3 patients, a bullous disease developed. The clinical course, results of laboratory data, including immunoblot analysis, and prompt response to oral corticosteroids were consistent with BP. Moreover, 2 patients presented with dyshidrosis pemphigoid, now recognized as a possible form of BP. The mean age of the 3 patients at the onset of BP was 52 years, which is substantially lower than the average age of onset of BP. The 3 patients belong to a French study population of 108 patients with ALS, giving a theoretical BP prevalence of 1.8% during the 11 months of the trial. As a recent epidemiologic study found the annual incidence of BP to be 7 cases per million people in 3 French regions, the 1.8% figure strongly suggests that the association between BP and ALS is more than coincidental.

As a matter of fact, various chronic neurological disorders have been reported in association with BP, eg, multiple sclerosis, posttraumatic (Jean-Claude Roujeau, MD, personal communication, 1991) or ischemic paresia, and Shy-Drager syndrome, suggesting that these diseases share a feature able to induce the bullous disease. The role of drugs should be considered. The experimental drug riluzole, given to our ALS population, cannot be considered an inducer because 2 of the 3 patients received the placebo. Baclofen, a muscle relaxant, could be a good candidate because it is quite commonly prescribed for patients with paralytic neurological disorders, but if baclofen were an inducer, the prevalence of BP in such patients would have been much higher. Moreover, baclofen had been taken for weeks to years by our patients with ALS, and that treatment was not discontinued even after clearing of BP under specific therapy. Also, BP has occurred in patients with multiple sclerosis without baclofen, and baclofen was not found to be a risk factor of BP in a recent case-control study. The high BP risk factor in these chronic neurological paralytic disorders could be the bedridden and/or parietic state. The occurrence of BP on only the parietic side of a hemiplegic patient would seem to support this clinical hypothesis. Moreover, we looked for the neurological status of the patients reported in the literature with both multiple sclerosis and BP. When it was specified (in at least 14 of 18 patients), all had long-standing, advanced multiple sclerosis with chronic definitive paresia. Lastly, our patients with BP had limb function that was much more altered than that in the total ALS population.

Neurologically, various pathogenic hypotheses have been forwarded for the causes of ALS, including immunological factors or increased susceptibility to gluteate toxic effects in critical parts of the nervous system. Cutaneously, light and electron microscopic alterations of skin connective tissue have recently been described in 7 patients with ALS, with a cutaneous deposition of β-amyloid protein. Moreover, 1 study showed a decreased type IV collagen immunoreactivity of the basement membrane of the skin, which was even more substantial in patients with disease of longer duration. The cutaneous consequences of these findings are not yet known. What could be the biological link between neurological and skin disorders? Interestingly, there are 2 isoforms of BPAG1, an epithelial one and a neuronal-specific one (BPAG1-n). Mice that are BPAG1 null have developed severe neurodegeneration and dystonia typical of dystonia muscularum mice. The candidate dystonia muscularum gene, dystonin, encodes cytoskeletal linker proteins capable of anchoring neuronal intermediate filaments to actin cytoskeleton. Massive neurofilament conglomeration in motor neurons has occurred in...
a transgenic mouse model of motoneuron disease and in the early stages of ALS. It could be postulated that the accumulation of intermediate filaments could favor an immune-specific response, including a cross-reaction between the 2 isoforms (nervous system and skin) of BPAG1. Surely, extrapolation of the concept should include neurological evaluation, eg, clinical, biochemical, or immunological, in the classic population of patients with BP. However, in a mouse superoxide dismutase 1–mediated form of ALS, neither initiation nor progression of pathology required an axonal neurofilament cytoskeleton. Moreover, many sorts of mutations occur in ALS, which raises the question of the mechanisms of the motor neuron death in patients with ALS with mutations of neurofilament-heavy genes.

In conclusion, more studies are warranted to explain why BP is sometimes associated with some chronic neurological paralytic disorders. These studies might also explain why BP is so strongly linked with old age.

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REFERENCES