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INVESTIGATIVE REPORT

Risk of Death in Bullous Pemphigoid: A Retrospective Database Study in Finland

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Bullous pemphigoid (BP) is an autoimmune skin disease of elderly people, which is associated with increased mortality. The aim of this study was to investigate the standardized mortality ratio (SMR) for BP in Finland, and concomitant comorbidities and medications. This was a retrospective database study of all cases of BP diagnosed at the Department of Dermatology, Oulu University Hospital, Finland, between 1985 and 2012. A total of 198 immunologically confirmed cases of BP were found. One-year mortality was 16.7%, and SMR 7.56 (95% confidence interval (CI) 4.98–10.14). The most common comorbidities were cardiovascular diseases (76.3%) and neurodegenerative diseases (40.9%). Malignancies (8.6%) were associated with increased mortality (hazard ratio = 2.4, 95% CI 1.1–5.5, $p = 0.047$). A novel finding was that polypharmacy was very common in patients with BP, and the higher the number of drugs, the greater the mortality. In conclusion, the mortality for BP in Finland is 7.6-fold that of a reference population, and malignancies and polypharmacy are associated with increased mortality. ***Key words: bullous pemphigoid; autoimmune bullous disease; epidemiology; mortality; standardized mortality ratio; Finland.***

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Bullous pemphigoid (BP) is an autoimmune bullous skin disease of elderly people, with severe symptoms, such as widespread blistering and itching. The incidence of BP is 2.5–42.8 per 1 million person-years, and it has been reported to have increased in the UK, France, USA and Finland (1–10).

BP is associated with significant mortality; 10.8–41% within the first year after diagnosis (11–23). Patients with BP also have increased mortality compared with their age- and sex-adjusted counterparts in the general population; the standardized mortality ratio ranges from 1.9 to 9.6 with an exception of one study by Parker et al. (17) (SMR 0.4–0.7). Old age has been shown to be related to poorer prognosis in BP (16–19, 23). Also, poor general condition, high doses of oral glucocorticoids, low serum albumin, and high erythrocyte sedimentation rate have been associated with increased mortality (14, 16). On the other hand, in most studies, the severity of BP did not affect survival (1, 12, 16, 17, 20, 21, 23), and the predictive value of comorbidities for mortality is contradictory (16–23).

There have been few controlled trials of BP treatment (24). According to the British Association of Dermatologists' (BAD) 2012 guidelines for the management of bullous pemphigoid: "systemic steroids are the best established treatment for BP". Superpotent topical corticosteroids are recommended as first-line treatment in localized and moderate disease, and in recent European guidelines also for extensive BP (25–28). However, evidence for the effectiveness of adjuvant, steroid-sparing therapy which is commonly used in widespread BP, is poor (25, 27). In clinical practice adjuvant therapies have been combined to reduce oral corticosteroid doses, since systemic corticosteroids have many side-effects, especially when used in elderly patients with BP (14, 27).

The aims of this study were to investigate, firstly, the SMR of patients with BP in Finland and, secondly, the comorbidities and concomitant medications. A study population of all immunologically confirmed cases of BP in our University Hospital District (The Northern Ostrobothnia Hospital District, Finland) was collected and complete mortality data was extracted from comprehensive Finnish registers.

MATERIALS AND METHODS (see Appendix S1[1])

RESULTS

Mortality in patients with bullous pemphigoid

A total of 198 cases of BP, confirmed by direct or indirect IF between 1985 and 2012, were found. There were 102 females (51.5%) and 96 males (48.5%), mean age 77.5 years (standard deviation (SD) 10.4), range 40–96 years. Of these, 33/198 died within the first year after diagnosis, and 60/198 within 2 years, the 1- and 2-year mortalities were 16.7% and 30.3%, respectively. Compared with the age-matched reference population, the SMR was 7.56 (95% CI 4.98–10.14).

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Comorbidities and concomitant medications

The most common comorbidities were cardiovascular diseases, diagnosed in 76.3% of patients, followed by neurodegenerative diseases in 40.9%, other skin conditions prior to the diagnosis of BP (non-melanoma skin cancers included) in 37.4%, diabetes type 2 in 23.2%, malignant disease in 8.6% (non-melanoma skin cancers not recorded here) and other autoimmune diseases besides BP in 3.5%. Of these comorbidities, only malignancy predicted significantly increased 1-year mortality, the age- and sex-adjusted hazard ratio (HR) being 2.4 (95% CI 1.1–5.5, $p = 0.047$).

Concomitant medications used for other diseases were very common in patients with BP; the number of regularly used drugs ranging from 0 to 19. While 7.1% of patients (14/197) had no concomitant medication, 43.1% (85/197) had 1–5 drugs, 37.6% (74/197) 6–10 drugs, and 12.2% (24/197) up to 11 or more. The number of concomitant medications has increased over time, since the mean (median) number of drugs given to patients according to the date of diagnosis was 4.6 (4), 5.1 (5), 6.3 (6) and 7.4 (7) in 1985–1989, 1990–1999, 2000–2009 and 2010–2012, respectively, with a linear 1.17-fold (95% CI 1.07–1.31) increasing trend between time periods. Interestingly, polypharmacy had a significant association with mortality: the higher the number of drugs, the greater the 1-year and 2-year mortality (Fig. 1).

Treatment for bullous pemphigoid

The most common first-line treatment for BP was oral prednisolone together with topical corticosteroids (usually 0.1% betamethasone), which was started for 62.6% (124/198) of cases. Topical corticosteroid alone was initiated for 29.8% (59/198) of cases, usually for patients with milder symptoms, and tetracycline (together with topical corticosteroids) in 7.6% (15/198) of cases. Half of the patients (50.5%, 100/198) were treated solely with prednisolone and topical corticosteroids, whereas in 25 cases azathioprine, and in 2 cases methotrexate, was combined with prednisolone. Dapsone was used at some point for 7 patients. Adjuvant therapy with prednisolone has become more common in recent years, since 12%, 16%, 28% and 44% of patients treated with azathioprine were diagnosed in the 1980s, 1990s, 2000s and 2010s, respectively. Correspondingly, the doses of prednisolone have decreased over time: the mean starting dose (or the highest dose used) in the 4 decades of this study were: 59 (SD 18.3), 55 (SD 16.6), 38 (SD 10.0) and 35 mg/day (SD 11.2), respectively.

To compare the effect of treatment on mortality the BP patients were divided into 3 groups (see Materials and Methods). Group 1 comprised 100 patients, group 2 40 patients, and group 3 26 patients. The mean ages at time of diagnosis for groups 1–3 were 77.8 years, 82.0 years, and 72.5 years ($p = 0.0013$), respectively. The patients in group 1, who were treated with prednisolone only (together with topical corticosteroids), had the lowest 1-year survival (Fig. 2). Groups 2 and 3 appeared to have better prognosis (Fig. 2); however, due to the small number of cases, we were not able to compare groups statistically. The mean starting dose of prednisolone did not differ between groups (45.6 mg and 46.5 mg in groups 1 and 3, respectively, $p = 0.79$), nor did the total number of concomitant drugs in regular use (6.1, 6.3 and 5.0 in groups 1, 2 and 3, respectively, $p = 0.41$). No trends in mortality were seen over the study period (data not shown).

DISCUSSION

This study found that the SMR mortality for immunologically confirmed BP was 7.6-fold that of an age-matched reference population and the 1- and 2-year mortalities were 16.7% and 30.3%, respectively. In addition, a novel finding was that polypharmacy was associated with increased mortality in patients with BP; the greater the number of drugs, the greater the mortality. In general, polypharmacy in elderly patients has been shown to be an independent marker of increased mortality (30). Thus, polypharmacy itself might be a reason for the increased mortality in our BP population. On the other hand, polypharmacy, albeit a rough indicator, might also be a sign of poorer general health, which has also been associated with increased mortality in previous studies (16). Compared with other countries (Table SI[1]), the 1-year mortality in Finland (17%) is relatively low, whereas SMR is second highest. This is probably due to the older age structure of the Finnish population compared, for example, with the European standard population.

All studies, including ours, agree that patients with BP have increased mortality compared with the general population of the same age (1, 3, 12, 18, 20, 23). A possible explanation for this is that BP itself affects those who are in poorer general

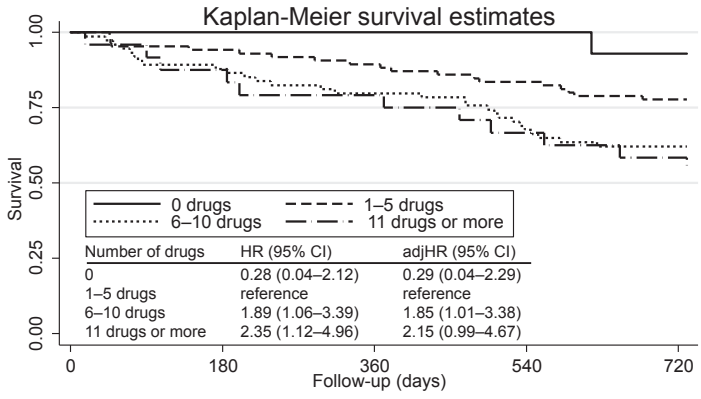

Fig. 1. Mortality for bullous pemphigoid patients by the total number of regularly used concomitant drugs. *p*-value for log-rank test for equality of survival function = 0.0124. When the hazard ratio (HR) was adjusted for comorbidities recorded in this study, the result did not change significantly (data not shown). adjHR: age- and sex-adjusted hazard ratio; 95% CI: 95% confidence interval.

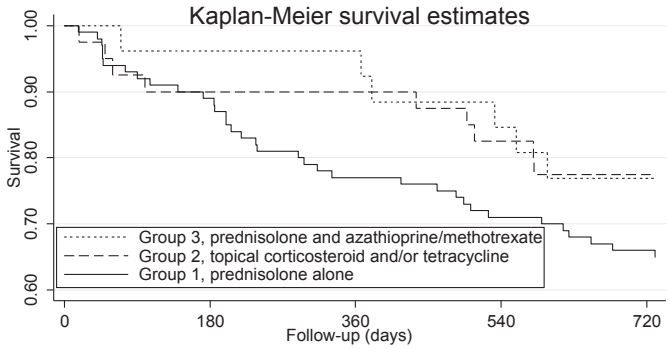

Fig. 2. Two-year mortality for patients with bullous pemphigoid (BP) according to the treatment used for BP. The patients who were treated with prednisolone only (group 1) appeared to have the lowest 1-year survival, while groups 2 and 3 had better prognoses. However, due to the low number of cases, it was not possible to compare groups statistically.

condition and have comorbidities with poor prognosis. In our study population the prevalence of cardiovascular diseases (76.3%), neurodegenerative diseases (40.9%) and diabetes type 2 (23.2%) was very high, albeit close to figures recently reported in Denmark and Spain (23, 31). The association between BP and neurological disorders has been established in many studies; the mechanism behind this could be an autoinflammatory reaction to BP180 and/or BP230 neuronal isoforms which are present in the human brain (26, 32–35). However, in our study, neurodegenerative comorbidity did not increase mortality, unlike in some previous studies (17, 18, 21).

The role of therapy in increased mortality for BP has been discussed in many studies; however, in our study the number of cases was too low to carry out statistical procedures. Prospective studies of therapy for BP have all involved different treatment modalities, and comparison is thus difficult. These studies have not established the benefit of adjuvant therapies combined with corticosteroid (azathioprine, plasma exchange or mycophenolate mofetil) or alternative treatment with tetracycline and nicotinamide in disease control, but adjuvant therapies have decreased the doses of prednisolone. In many studies high doses of oral prednisolone have increased the risk of side-effects (24, 27, 36). Thus, in Oulu University Hospital, we have started to use lower doses of prednisolone combined with adjuvant therapies. No trends in mortality were found over the study period, although a larger study population may have revealed different results. As there are no data or consensus on the use of adjuvant therapy (25), clinical practice varies in Europe. In Finland and Denmark, azathioprine is often combined with oral prednisolone (31). In Sweden, monotherapy with methotrexate is preferred (37), while in France the first-line treatment is topical corticosteroid (3).

Study strengths and limitations

The strengths of this study are as follows: (*i*) exact diagnostics were performed, with every case of BP confirmed by direct or indirect IF; (*ii*) a long study period in the same geographical area, and (*iii*) a study population that included both patients who were hospitalized and those who were treated in the outpatient clinic. In addition, in cases of missing information about the date of death, it was obtained from local or national registers and thus follow-up data was included for every patient.

The limitations of this study are that it was retrospective, and data on the severity of BP or the disease control are lacking, since it was thought to be too difficult to evaluate reliably afterwards. For reliable comparison, the severity of BP should be recorded according to the internationally accepted disease activity index Bullous Pemphigoid Disease Area Index (38). Finally, mortality data for the whole of Finland would have been more comprehensive, and a larger study population would have resulted in greater statistical power; however, considering that BP is a rare disease, this would have required a multicentre study in Finland.

In conclusion, patients with BP have increased mortality compared with the general population. In the BP population, factors that cause excess mortality are general health and polypharmacy, and medications used to treat BP may also have a role. Topical and systemic corticosteroids are the best established treatments for BP, but data concerning the benefits of adjuvant therapies are lacking. However, high doses of systemic corticosteroids increase the risk of side-effects, especially in elderly people, and doses higher than 0.75 mg/kg should usually be avoided (24, 27, 28).

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