Incidence and Mortality of Pemphigus in France

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Abbreviations

CI Confidence Interval

HR Hazard Ratio

IQ Interquartile

PNP Paraneoplastic pemphigus

PF Pemphigus Foliaceus

PV Pemphigus Vulgaris

SMR Standardized Mortality Ratio

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TO THE EDITOR

The incidence of pemphigus varies from 0.5 to 34 cases/million inhabitants/year, with the highest incidence rates in Brazil (Hans-Filho *et al.*, 1996; Ishii *et al*., 2008; Langan *et al.*, 2008; Meyer *et al.*, 2010). Additionally, whereas the prognosis of pemphigus patients is considered good in the literature, recent findings reported unusually high mortality rates (Almugairen *et al.*, 2013; Langan *et al.*, 2008).

We estimated the incidence and mortality of pemphigus among 13 regions in France (Figure 1a), over a 10-year period. Inclusion criteria were: i) patient living in one of the 13 regions; ii) newly-diagnosed pemphigus. Cases were identified using the computerized databases of the pathology laboratories of the university and general hospitals and private-practice laboratories which perform direct immunofluorescence. Statistical analyses are described in Supplementary material.

From January 2004 to December 2013, 629 patients were identified in included regions, which corresponded to a population size of 13.75 million inhabitants (Figure 1a). Among them, 380 were excluded: i) diagnosis of pemphigus not confirmed (n=74); ii) patient not domiciled in the selected regions (n=194) and iii) diagnosis of pemphigus made before or after the study period (n=112). A total of 249 incident cases (125 women, 124 men) were included. Mean age at diagnosis was 59.4 ± 18.7 years and was similar between male and female patients (p=0.93). The age distribution of the population is shown in Figure 1b. Pemphigus types were: Pemphigus Vulgaris (PV), n=155 (62%); Pemphigus Foliaceus (PF), n=67 (27%); Paraneoplastic Pemphigus (PNP), n=12 (5%); and other subtypes, n=15 (6%), (Table 1).

The mean annual crude incidence of pemphigus was 1.85 cases/million inhabitants/year (95% Confidence Interval (CI) =1.63-2.08). The mean world-population standardized incidence was 1.45 cases/million inhabitants/year (95%CI=1.11-1.79). Mean

annual French population-standardized incidence rates ranged from 0.99 cases/million inhabitants/year (95%CI=0.64-1.45) in the North region of France to 3.39 cases/million inhabitants/year (95%CI=1.94-5.58) in the Haute-Vienne region. The linear North-South gradient was significant (p=0.004) with an incidence rate ratio estimated to 1.11 (95%CI=1.04-1.18) for a move of 100 kilometres to the South (Figure 1a and Supplementary material). The annual incidence rate ratio per calendar year over the study period was 1.05 (95%CI=0.97-1.06), showing no significant increase of incidence over the study period (p=0.45). Otherwise, the incidence rate of pemphigus increased with age (Figure 1c).

The median follow-up duration of the cohort was 5.4 years (Interquartile (IQ) range: 3.0-8.1 years). Thirteen patients were lost to follow-up (5.2%). A total of 66 (27%) patients died during the study period (Table 1). The 1-, 2-, and 5-year overall survival rates were 92% (95%CI=88-95%), 88% (95%CI=83-91%) and 77% (95%CI=71-82%), respectively, in the whole population, 97% (95%CI=92-99%), 93% (95%CI=87-96%) and 83% (95%CI=76-89%) in PV patients, 88% (95%CI=78-94%), 84% (95%CI=72-91%) and 74% (95%CI=61-83%) in PF patients and 67% (95%CI=34-86%), 58% (95%CI=27-80%) and 39% (95%CI=8-70%) in PNP patients, respectively (Figure 1d). Relative to expected age-, gender and region-specific overall death rates in the general population in France, the Standardized-Mortality-Ratio (SMR) of pemphigus patients was 1.67 (95%CI=1.46-1.93). The median age of death was 82.4 years (IQrange=76.9-87.5 years) in the whole pemphigus population, corresponding to 82.3 years (IQrange=76.6-86.0) in PV patients, 87.4 years (IQrange=81.6-88.5) in PF patients, 74.9 years (IQrange=67.7-80.7) in PNP patients and 80.7 years (IQrange=77.4-82.9) in patients with other pemphigus subtypes. All deaths were observed in patients older than 60 years at diagnosis. Interestingly, the proportion of PF patients older than 75 years at diagnosis (22 of 67, 32.8%) was 2-fold higher than that of PV patients (25 of 155, 16.1%). The cause of death could be recorded in 57 of the 66 deceased patients. Main causes of death were

malignancy (n=17, 29.8%), cardiovascular disease (n=16, 28.1%), infection (n=8, 14.0%) and dementia (n=7, 12.3%) (Table 1). Older age at diagnosis and association with neoplasia were statistically associated with mortality. Indeed, the risk of mortality in patients older than 75 years corresponded to a Hazard Ratio (HR) of 16.3 (95%CI=9.4-28.3) relative to younger patients, and the risk of mortality in patients with neoplasia adjusted on age by left-truncation from birth to diagnosis, corresponded to a HR of 2.44 (95%CI=1.35-4.40; p=0.005). The left-truncated age-adjusted mortality rate of PF was not significantly higher than that of PV mortality (HR=1.55; 95%CI=0.84-2.84; p=0.16).

The crude incidence rate of PV was estimated at 1.15/million inhabitants/year, which is more than 6-fold lower than the crude incidence rate of PV reported by Langan *et al.* in the UK (Langan *et al.,* 2008) and lower than that reported from Southern European countries, ranging from 4 to 4.4 cases/million inhabitants/year (V'lckova-Laskoska *et al*., 2007; Baican *et al*., 2010). Interestingly, we observed higher incidence rates of pemphigus in Southern regions of France compared to Northern regions, which is in accordance with the North to South gradient of pemphigus incidence in Europe. We observed an increasing incidence of pemphigus with age, with the highest incidence in people aged more than 80 years.

Importantly, the 92%, 88% and 77% one-, two- and five-year survival rates calculated in the present study suggest that the prognosis of pemphigus is worse than the 5% mortality rate usually reported in general reviews (Bystryn *et al.*, 2005; Chams-Davatchi *et al.*, 2005).

Our data suggest that the high mortality rate observed in our population of pemphigus patients was mainly related to the old age of patients, since the median age at death of PF and PV patients was 87.4 and 82.4 years, respectively. Indeed these elderly patients poorly tolerated corticosteroids and immunosuppressant side effects as demonstrated by their main causes of death.

We observed an unexpectedly high mortality rate in PF patients, which was likely related to the high proportion (32.8%) of patients older than 75 years among PF patients.

The second prognostic factor was the association with neoplasia, although the 58% mortality rate of PNP patients in the present series was lower than the 75 to 90% mortality rate reported in the literature (Wieczorek *et al.*, 2016).

In conclusion, this study highlights the high mortality of pemphigus in elderly patients, including PF, which is often presented as a more benign subtype than PV (Bystryn *et al.*, 2005).

CONFLICT OF INTEREST

The authors state no conflict of interest.

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REFERENCES

Almugairen N, Hospital V, Bedane C, Duvert-Lehembre S, Picard D, Tronquoy AF et al. (2013) Assessment of the rate of long-term complete remission off therapy in patients with pemphigus treated with different regimens including medium- and high-dose corticosteroids. J Am Acad Dermatol 69:583–8

Baican A, Baican C, Chiriac G, Chiriac MT, Macovei V, Zillikens D et al. (2010) Pemphigus vulgaris is the most common autoimmune bullous disease in Northwestern Romania. Int J Dermatol 49:768–74

Bystryn J-C, Rudolph JL (2005) Pemphigus. Lancet Lond Engl 366:61–73

Chams-Davatchi C, Valikhani M, Daneshpazhooh M, Esmaili N, Balighi K, Hallaji Z et al. (2005) Pemphigus: analysis of 1209 cases. Int J Dermatol 44:470–6

Hans-Filho G, dos Santos V, Katayama JH, Aoki V, Rivitti EA, Sampaio SA et al. (1996) An active focus of high prevalence of fogo selvagem on an Amerindian reservation in Brazil. Cooperative Group on Fogo Selvagem Research. J Invest Dermatol 107(1):68-75

Ishii N, Maeyama Y, Karashima T, Nakama T, Kusuhara M, Yasumoto S et al. (2008) A clinical study of patients with pemphigus vulgaris and pemphigus foliaceous: an 11-year retrospective study (1996-2006). Clin Exp Dermatol 33(5):641-3

Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J (2008) Bullous pemphigoid and pemphigus vulgaris incidence and mortality in the UK: population based cohort study. BMJ 337:a180–a180

Meyer N, Misery L (2010) Geoepidemiologic considerations of auto-immune pemphigus. Autoimmun Rev 9:A379-382

V'lckova-Laskoska MT, Laskoski DS, Kamberova S, Caca-Biljanovska N, Volckova N (2007) Epidemiology of pemphigus in Macedonia: a 15-year retrospective study (1990-2004). Int J Dermatol 46:253–8

Wieczorek M, Czernik A. Paraneoplastic pemphigus: a short review (2016). Clin Cosmet Investig Dermatol. 9:291–5.

	Pemphigus vulgaris (n=155)	Pemphigus foliaceus (n=67)	Paraneoplastic pemphigus (n=12)	Other pemphigus subtypes[1] (n=15)
Sex ratio (female/male)	1.07/1	0.68/1	2/1	2/1
Age at diagnosis, mean±SD (years)	57.5±17.3	61.3±20.4	71.1±11.0	61.3±25.8
Distribution by age category, n (%)				
< 40 years	30 (19.4)	10 (14.9)	0	3 (20.0)
40-59 years	50 (32.3)	20 (29.9)	0	2 (13.3)
60-74 years	50 (32.3)	15 (22.4)	8 (66.7)	3 (20)
75-89 years	24 (15.5)	21 (31.3)	3 (25.0)	7 (46.7)
≥90 years	1 (0.6)	1 (1.5)	1 (8.3)	0
Clinical presentation, n (%)				
-mucosal and skin lesions	105 (67.7)	4[2] (6.0)	10 (83.33)	8 (53.3)
-exclusive skin lesions	9 (5.8)	63 (94.0)	1 (8.33)	7 (46.7)
-exclusive mucosal lesions	41 (26.5)	0	1 (8.33)	0
Comorbidities, n (%)				
-malignancy	15 (9.7)	5 (7.5)	8 (66.7)	3 (20.0)
-cardiovascular disorder	28 (18.1)	17 (25.4)	5 (41.7)	6 (40.0)
-hypertension	43 (27.7)	15 (22.4)	8 (66.7)	6 (40.0)
-pulmonary disorder	23 (14.8)	7 (10.4)	3 (25.0)	2 (13.3)
-diabetes mellitus	20 (12.9)	4 (6.0)	5 (41.7)	4 (26.7)
-neurological disorder	6 (3.9)	5 (7.5)	0	4 (26.7)
First line treatment regimens, n (%)				
- oral prednisone alone	95 (61.3)	25 (37.3)	7 (58.3)	4 (26.7)
- oral prednisone + IS	36 (23.2)	9 (13.4)	1 (8.3)	1 (6.7)
- rituximab + oral prednisone	9 (5.8)	1 (1.5)	0	1 (6.7)
- dapsone without oral prednisone	5 (3.2)	21 (31.3)	0	5 (33.3)
- topical corticosteroid	10 (6.5)	11 (16.4)	4 (33.3)	4 (26.7)
Follow-up duration, mean±SD (years)	5.9 ± 3.2	5.5 ± 3.4	2.7 ± 2.7	5.0 ± 4.0
Lost to follow-up, n (%)	9 (5.8)	3 (4.5)	0	1 (6.7)
Deaths, n (%)	30 (19.4)	21 (31.1)	7 (58.3)	8 (53.3)
-males	15 (20.0)	17 (42.5)	1 (25.0)	3 (60.0)
-females	15 (18.8)	4 (14.8)	6 (75.0)	5 (50.0)
- oral prednisone alone	17 (17.9)	8 (32.0)	4 (57.1)	2 (50.0)
- oral prednisone + IS	6 (16.7)	6 (66.7)	1 (100.0)	-
- rituximab + oral prednisone	0	1 (100.0)	0	1 (100.0)
- dapsone without oral prednisone	0	2 (9.5)	0	3 (60.0)
- topical corticosteroid	7 (70.0)	4 (36.4)	2 (50.0)	2 (50.0)
Causes of death, n (%)				
-malignancy	7 (23.3)	3 (14.3)	4 (57.1)	3 (37.5)
-cardiovascular disorder	8 (26.7)	6 (28.6)	1 (14.3)	1 (12.5)
-infectious disorder	2 (6.7)	4 (19.0)	1 (14.3)	1 (12.5)
-dementia	3 (10.0)	2 (9.5)	0	2 (25.0)
-pulmonary disorder	1 (3.3)	2 (9.5)	1 (14.3)	0
-digestive disorder	1 (3.3)	1 (4.8)	0	0
-alcoholic hepatitis	0	1 (4.8)	0	0
-hyponatremia	0	1 (4.8)	0	0
-diabetes mellitus	1 (3.3)	-	0	0
-unknown cause	7 (23.3)	1 (4.8)	0	1 (12.5)

Table 1. Baseline characteristics and evolution of the 249 patients with newly diagnosed pemphigus

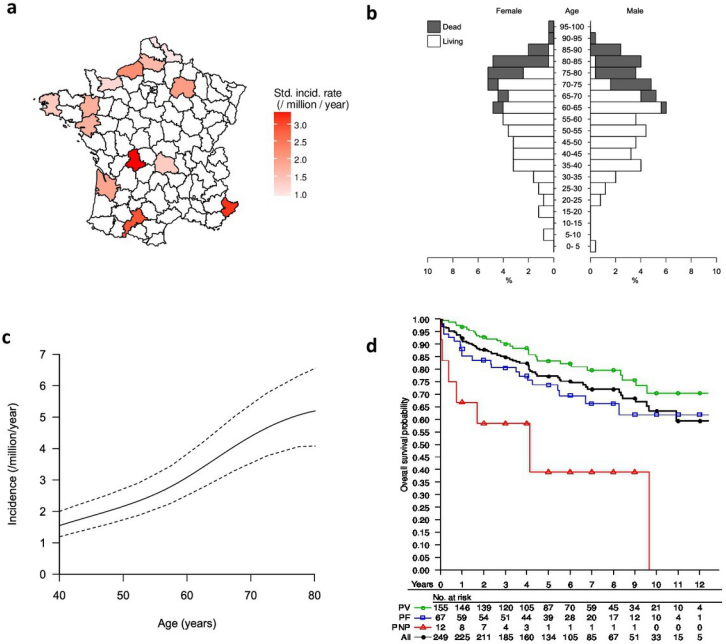
Abbreviations: SD, standard deviation; IS, immunosuppressant

[1]Other pemphigus subtypes: IgA pemphigus (n=7); pemphigus vegetans (n=4); pemphigus herpetiformis (n=3); drug-induced pemphigus (n=1)

[2]These 4 patients were classified as PF since they mainly presented skin lesions. The histological examination of a skin biopsy showed an acantholysis in the upper layers of the epidermis. Three of these four patients had negative serum anti-DSG3 antibodies, and one had very low (22 U) anti-DSG3 antibody ELISA values (N<20), whereas all these four patients had elevated anti-DSG1 antibody ELISA values.

FIGURE LEGENDS

Figure 1. a: Map of France showing the French population standardized annual incidence rate in the 13 administrative regions which participated in the study. France is characterized by a Mediterranean climate in the Southern regions and a continental climate in the Northern regions. **b:** Age at diagnosis (years), gender distribution and mortality of patients with pemphigus in the 13 administrative areas in France. **c:** Incidence rate of pemphigus by age (in plots: 95% Confidence Interval). **d:** Kaplan-Meier survival curves of patients with newly diagnosed pemphigus between 2004 and 2013. *Abbreviations: PV= Pemphigus Vulgaris; PF= Pemphigus Foliaceus; PNP= Paraneoplastic Pemphigus*


a
Std. incid. rate
(/ million / year)
3.0
2.5
2.0
1.5
1.0
b
Female
Age
Male
Dead
Living
95-100
90-95
85-90
80-85
75-80
70-75
65-70
60-65
55-60
50-55
45-50
40-45
35-40
30-35
25-30
20-25
15-20
10-15
5-10
0- 5
10 8 6 4 2 0
%
0 2 4 6 8 10
%
c
Incidence (/million/year)
0 1 2 3 4 5 6 7
40 50 60 70 80
Age (years)
d
Overall survival probability
1.00 0.95 0.90 0.85 0.80 0.75 0.70 0.65 0.60 0.55 0.50 0.45 0.40 0.35 0.30 0.25 0.20 0.15 0.10 0.05 0.00
Years 0 1 2 3 4 5 6 7 8 9 10 11 12
No. at risk
PV 155 146 139 120 105 87 70 59 45 34 21 10 4
PF 67 59 54 51 44 39 28 20 17 12 10 4 1
PNP 12 8 7 4 3 1 1 1 1 1 0 0 0
All 249 225 211 185 160 134 105 85 67 51 33 15 5