

PEMPHIGUS: AN EPIDEMIOLOGICAL STUDY OF PATIENTS TREATED IN FINNISH HOSPITALS BETWEEN 1969 AND 1978

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Abstract. Between 1969 and 1978, 44 pemphigus (p.) patients were treated in Finnish hospitals. The number of new cases was 36, giving an annual incidence of 0.76 cases per million inhabitants. The male/female ratio was 0.9:1. Nine patients had p. vulgaris (p.vu.); one p. vegetans (p.ve.); 9, p. foliaceus (p.fo.); 22, p. erythematodes (p.er.); and 3, p.NUD (p.NUD). One patient with p.er. also had myasthenia gravis. The mean age at onset was 57½ years. The disease started in the mouth only in p.vu. (78% of cases) and in p.NUD (67%). Prednisone (or its derivatives) was most commonly used for systemic treatment, the mean initial dose being 61.4 mg/day. P.vu. and p.NUD required higher initial doses of prednisone and a longer duration of the high-dose treatment. The smallest mean daily dose of prednisone required to achieve a remission of at least 6 months was 5.2 mg. The mean duration of remission was 30½ months. The frequency of side effects of systemic drug therapy was low (18%), possibly because only comparatively low doses of prednisone were used in Finland. The cause of death in 3 (6.8%) out of 44 patients was attributable either to p. itself or to its treatment. The mean annual number of hospitalization days for the whole material was 16.4 days and the mean annual number of hospital admissions 0.7.

Key words: Pemphigus; Epidemiology; Incidence; Treatment; Remission; Mortality

Pemphigus is a rare disease, often involving both skin and mucous membranes. Since 1953, when Lever (10) distinguished pemphigus from pemphigoid, only a few reports have been published dealing with the epidemiological aspects of pemphigus. Pisanti et al. (15) have reported an incidence of 1.62/100 000 among Jews within the Jerusalem area. Lynch et al. (14) have found an annual pemphigus incidence rate of 0.5/100 000 in southern Arizona. Pemphigus was found in 0.2% of first-consultation cases in El Salvador (5). To our knowledge, no epidemiological study of pemphigus has been carried out in Scandinavia.

In Finland the diagnoses of all patients treated in hospitals are reported to a national registry and it is

thus possible to obtain comprehensive information about the use of hospitals as a result of different diseases. It was therefore possible to obtain reliable data for a study of the epidemiological aspects of pemphigus in Finland.

PATIENTS AND METHODS

Every hospital in Finland is obliged to report to the National Board of Health the diagnoses of all patients treated. These data are processed each year according to hospital number and the social security number of the patient. The patients treated between 1969 and 1978 for diseases classified by the WHO diagnosis numbers 694.00 (pemphigus vulgaris, vegetans, foliaceus), 694.01 (pemphigus erythematodes), 694.09 (pemphigus NUD) in the international nomenclature of diseases (18) were listed by computer. A list of suspected pemphigus patients was sent to all Finnish central hospitals having a dermatology department, together with a request for the case records of these patients.

The information obtained from these case records was collated and analysed. The primary computer list of patients and WHO pemphigus diagnosis numbers totalled over 400 cases. The initial material also included many cases which did not fulfil the diagnostic criteria of pemphigus. In addition to these, several cases of pemphigus neonatorum were found. They were analysed and omitted from the present study. Forty-four patients were accepted for final analysis because they fulfilled at least two of the following diagnostic criteria: clinical diagnosis, biopsy report, direct or indirect immunofluorescence.

RESULTS

Between 1969 and 1978, 44 patients with pemphigus were treated in Finnish central hospitals. In 8 of the 44 cases the onset of pemphigus occurred before 1969 (Table I), giving an incidence of 36 new cases in 10 years, or 3.6 new cases per year.

The male/female ratio was 0.9:1. The numbers of patients with different forms of pemphigus are shown in Table II. Nine of the 44 cases (20%) had pemphigus vulgaris (p.vu.); one (2%) pem-

Table I. Annual distribution of new pemphigus patients in Finnish central hospitals

Diagnosis of pemphigus	Before 1969		1970	1971	1972	1973	1974	1975	1976	1977	1978	Total
	1969	1969										
P. vulgaris	2	—	1	—	1	2	2	—	1	—	—	9
P. vegetans	—	—	—	—	—	—	—	—	—	—	1	1
P. foliaceus	—	2	1	—	1	2	1	—	—	2	—	9
P. erythematodes	6	1	—	4	—	6	1	2	1	1	—	22
P. NUD	—	—	—	—	1	1	—	—	—	1	—	3
Total	8	3	2	4	3	11	4	2	2	4	1	44

phigus vegetans (p.ve.); 9 (20%) pemphigus foliaceus (p.fo.); 22 (50%) pemphigus erythematodes (p.er.); and 3 (7%) pemphigus NUD (p.NUD).

The mean age at onset was 57½ years, ranging from 49.3 years for p.vu. to 67 years for p.fo. (Table II).

In 7 out of 9 cases of p.vu. (78%) and 2 out of 3 cases of p.NUD (67%), the first lesions appeared in the mouth. None of the patients with p.ve., p.fo. or p.er. presented initial oral lesions.

The extent of the initial lesions before treatment was assessed as a percentage of the total skin area. Extensive initial lesions (>30% of the total skin area) were slightly more common than moderate lesions (10–30%) in p.fo. However, moderate and restricted initial lesions (<10%) prevailed over extensive ones in the other forms of the disease.

The first blood samples were always taken at the beginning of hospital treatment before commencing systemic drug therapy. The initial values of haemoglobin, total white cell count, and eosinophilic leukocytes were within the range of normal values in the majority of cases. Elevated ESR was initially found in the majority of the patients, except in those with p.vu.

The systemic treatment was usually started with prednisone or one of its derivatives. The mean initial daily dose of prednisone varied for different subgroups of pemphigus (see Table III), the mean for the series as a whole being 61.4 mg/day.

In 78% of p.vu. and 67% of p.NUD cases the treatment was started with a dose of prednisone higher than 50 mg. In other forms of pemphigus high doses were rarely necessary. The duration of the initial administration of prednisone higher than 50 mg/day is also shown in Table III. The initial daily dose of prednisone was kept above 50 mg for a longer time in the p.vu. group than in the other pemphigus groups.

The maintenance therapy of the patients at the last follow-up visit is presented in Table IV. Two patients with p.vu. and one with p.er. received no treatment. Twelve out of 44 cases (27%) received topical skin treatment only. The most commonly used systemic drug for maintenance was prednisone, or one of its derivatives (22 cases, 50%).

The lowest daily dosage of prednisone during a remission of at least 6 months was also recorded from the case records. The daily dose of prednisone (or equivalent) ranged between 2 and 10 mg in 16

Table II. Number of patients, age at onset according to variety of pemphigus and length and frequency of hospitalization, 1969–78

Diagnosis of pemphigus	Number of cases			Age at onset (years)		Length of hospitalization (days/year)		Number of admissions per year	
	♂	♀	Total	Range	Mean	Range	Mean	Range	Mean
P. vulgaris	4	5	9	35–66	49.3	0.6–86.7	30.0	0.1–3.7	1.3
P. vegetans	1	—	1	—	82	—	17	—	1
P. foliaceus	4	5	9	34–85	67.0	0.9–62.5	16.8	0.1–2.0	0.5
P. erythematodes	12	10	22	9–80	55.6	1.1–34.7	10.9	0.1–2.5	0.5
P. NUD	—	3	3	52–63	59.0	6.5–23.0	14.2	0.4–1.8	0.9
All patients	21	23	44	9–85	57.5	0.6–86.7	16.4	0.1–3.7	0.7

Table III. Details of dosage and length of initial administration of prednisone

Diagnosis of pemphigus	Highest initial daily dose of prednisone (mg)			No. of pemphigus cases treated daily with					No. of cases without initial systemic prednisone	Total
	No. of cases	Range	Mean	over 50 mg of prednisone				less than 50 mg of prednisone		
				0-2 wks	3-5 wks	6-8 wks	9-11 wks			
P. vulgaris	9	40-300	101.1	3	1	-	3	2	-	9
P. vegetans	-	-	-	-	-	-	-	-	1	1
P. foliaceus	6	20-80	40.0	-	1	-	-	5	3	9
P. erythematodes	14	10-100	46.8	5	1	-	-	8	8	22
P. NUD	3	40-60	53.3	2	-	-	-	1	-	3
All patients	32	10-300	61.4	10	3	-	3	16	12	44

out of 44 cases, the mean being 5.2 mg. In 9 cases a remission of 6 months was recorded without prednisone and in 6 cases no remission of 6 months was documented. In the other 13 cases, the information regarding the length of remission could not be evaluated reliably.

The longest continuous remission for each variant of pemphigus was also recorded. The duration of remission ranged between 4 and 123 months, the mean being 30½ months. No remission was documented in 4 cases. The mean duration of remission was 39.3 months for p.vu., 40.5 months for p.fo., 24.2 months for p.er., and 21.7 months for p.NUD.

The complications that may have been due to systemic drug therapy included osteoporosis (3 cases), candidiasis (2 cases), diabetes, pneumonia and leukopenia (1 case each).

One patient with pemphigus erythematodes also had another autoimmune disease (myasthenia gravis).

Eight out of 44 patients died during the 10-year follow-up period, giving an overall mortality rate of

18.2% (Table V). P.vu. was the immediate cause of death in only one case. After giving up steroid treatment and starting homeopathic treatment this patient had a severe relapse, resulting in death. P.vu. was reported as the principal cause of death in 2 cases. The mean age at death was 71 years.

The numbers of both hospitalization days and hospital admissions to the departments of dermatology of various central hospitals between 1969 and 1978 are presented in Table II. The mean annual number of hospitalization days during the 10-year period varied from 30.0 days for p.vu. to 10.9 days for p.er. The mean annual number of nursing days for the series as a whole was 16.4 days and the mean annual number of hospital admissions was less than one (0.7).

DISCUSSION

The incidence of pemphigus in the 4.76 million population of Finland was 3.6 cases/year (0.76 cases/1 000 000/year). This is considerably lower than the incidences reported by Pisanti et al. (15)

Table IV. Drugs used for maintenance therapy during the patient's last follow-up visit

Diagnosis of pemphigus	Prednisone	Prednisone + cytotoxic drug	Prednisone + gold	Prednisone + oxychloroquine	ACTH	Topical treatment only	No treatment	Not known
P. vulgaris	4	1	-	-	-	2	2	-
P. vegetans	-	-	-	-	-	1	-	-
P. foliaceus	8	-	1	-	-	-	-	-
P. erythematodes	8	1	-	2	1	8	1	1
P. NUD	2	-	-	-	-	1	-	-
All patients	22	2	1	2	1	12	3	1

Table V. Causes of death of pemphigus patients, 1969-78

Diagnosis of pemphigus	No. of cases	Age at death	Duration of pemphigus before death (years)	Maintenance therapy	Immediate cause of death (autopsied cases*)
P. vulgaris	2	38	2	No treatment Steroid	*Pemphigus vulgaris *Acute lobular pneumonia with septicaemia
		68	3		
P. vegetans	—	—	—	—	—
P. foliaceus	3	54	9	Steroid	*Pulmonary embolism
		80	7	Steroid	Pneumonia l.d.x.
		89	5	Steroid	Acute pneumonia
P. erythematodes	3	70	8	Steroid	*Mesenteric thrombosis with gangrene of small intestine
		81	2	Local treatment	*Chronic duodenal ulcer with perforation
		88	14	Steroid + cytotoxic drug	*Colitis NUD
P. NUD	—	—	—	—	—
Total	8	Mean 71.0	Range 2-14 Mean 6.3		

and Lynch et al. (14). One explanation for this might be the small (about 1000) Jewish population of Finland. The predominance of pemphigus in Jews is well established (4, 8, 11-13, 16). The series of Pisanti et al. (15) was collected from a Jewish population only.

Ahmed (2) pointed out that in most large series of pemphigus both men and women are equally affected. In this study the male/female ratio was 0.9:1.

Pemphigus is considered to be a disease of middle and old age (1-3, 7, 8, 12, 13, 15, 16). The mean age at onset for all forms of pemphigus was 57½ years. In the present material p.fo. started considerably later than p.vu., p.er. and p.NUD. This is in contradiction of the study by Beutner & Chorzelski (3). They reported that p.fo. and p.er. were found in a significantly higher proportion of cases in the 2½-20 year age group. The only patient under 20 years in the present series was a 9-year-old girl with p.er. The second youngest patient of the whole series was 33 years old and also had p.er.

P.er. was the most common form of pemphigus, comprising half of the cases; p.vu. and p.fo. together accounted for 41%. This is in contrast to

many other studies on pemphigus in which p.vu. is the most common form of the disease (2, 3, 6-8, 13, 16, 17).

Because the systems used to record the initial lesions varied in the different Finnish central hospitals, reliable evaluation of the initial extent of pemphigus lesions on the sole basis of case records was difficult. However, extensive initial lesions were estimated to be present in 27% of the cases. The initial involvement of oral mucosa in early pemphigus, especially in p.vu., is well established (1, 2, 4, 8, 15-17). In the present study, initial oral lesions were found in 75% of patients with p.vu. and p.NUD, whereas not a single patient with other forms of pemphigus had initial oral lesions.

Of the routine blood values, ESR and the relative number of eosinophils differed from normal values more commonly than haemoglobin or the total number of leukocytes. The non-specificity of these values restricts their use as diagnostic aids (1).

The dosage of prednisone used in Finland for the initial treatment of pemphigus, especially for p.vu., is lower than that recommended by Lever & White (13). In the present study the average initial dose of prednisone for p.vu. was 101.1 mg/day, which is

Principal cause of death	Overall mortality	Disease and treatment related mortality
Pemphigus vulgaris	2/9= 22.2%	2/9= 22.2%
Multifocal necrosis of spinal medulla	3/9= 33.3%	-
Gangrene of left foot	-	-
Generalized cerebrovascular ischaemia	-	-
Mesenteric thrombosis with gangrene of small intestine	3/22= 13.6%	1/22= 4.5%
Chronic duodenal ulcer with perforation	-	-
Myeloid aplasia	-	-
	8/44= 18.2%	3/44= 6.8%

lower than that recommended for milder cases by Lever & White (13).

In the present series a dose of more than 50 mg of prednisone or its equivalent was needed in 10 cases for 0-2 weeks, in 3 cases for 3-5 weeks, and in 3 cases for 9-11 weeks. However, Lever & White (13) suggested that the initial high dose should be continued until the lesions have healed completely (6-8 weeks).

An interesting feature of the present study was that 33% and 36% of the patients with p.fo. and p.er., respectively, were treated without initial prednisone, which indicates the milder nature of p.fo. and p.er. compared with p.vu.

The drug most widely used for maintenance therapy was prednisone, or one of its derivatives (50% of the cases). In a few Finnish central hospitals prednisone was combined with either cytotoxic drugs or gold therapy. The combination of prednisone and other drugs enables a reduction to be made in the dosage of prednisone and avoidance of its side effects (7, 8, 11, 12, 16, 17). Very many patients received maintenance therapy comprising topical treatment only (27%) and 7% of the patients received no treatment whatsoever.

In all forms of pemphigus the mean lowest daily dose of prednisone required to achieve a remission of 6 months was approximately 5 mg. This also applies to p.vu., although the initial dose required to control p.vu. was approximately twice that needed with other forms of pemphigus. This discrepancy between the initial and maintenance doses in different forms of pemphigus is difficult to explain.

The longest average remissions recorded varied with the different forms of the disease, the mean for all forms being 30½ months. An estimation of length of remission based solely on case records is difficult and involves sources of error.

The aim of treatment in pemphigus is to find a balance between the risks caused by the disease on the one hand, and those caused by the side effects of the treatment on the other. Most Finnish central hospitals prefer the occurrence of a certain number of lesions to vigorous systemic treatment. This might also explain the low frequency (18%) of side effects possibly attributable to systemic drug therapy. Most of them were caused by prednisone (or its derivatives). Osteoporosis and candidiasis were the two most common side effects. Common side effects of prednisone have previously been reported as follows: diabetes mellitus (hyperglycaemia), Cushingoid features, candidiasis, and osteoporosis (5, 6, 8, 13, 16, 17).

In the present material one patient had both p.er. and myasthenia gravis. The association of pemphigus with other autoimmune diseases and even with malignancies has already been established (2, 9, 16).

Before the era of corticosteroids, pemphigus was considered a fatal disease and patients died from the widespread skin lesions (4) and secondary disturbances in fluid and electrolyte balance. After corticosteroids and cytotoxic drugs became available, the causes of most deaths were attributable to treatment (5-8, 11-13, 16, 17).

In this study the principal cause of death was shown at autopsy to be p.vu. in 2 cases. One was treated with steroids and the other was on homeopathic drugs only. In one case the principal cause of death was myeloid aplasia, possibly caused by the combination of prednisone and methotrexate. In the 5 other patients who died between 1969 and 1978 the principal and immediate causes of death were probably not attributable to pemphigus or its treatment. Thus 6.8% (3) out of 44 patients died of the disease or its treatment. Mortality rates similar to

those of the present study have been reported (5, 6, 8, 11, 12). The mean age at death of patients who died of pemphigus or its treatment was 64.7 years, compared with a mean age of 74.8 years for those who died from other causes.

The average annual numbers of hospitalization days and admissions for all forms of pemphigus were 16.4 and 0.7, respectively. The more severe character of p.vu. is also reflected in the greater need for hospitalization than for other forms of pemphigus.

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