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CLINICAL REPORT

Underlying Diseases and Co-factors in Patients with Severe Chronic Pruritus: a 3-year Retrospective Study

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Chronic pruritus is a symptom of many diseases, with studies pending investigating its prevalence or incidence. The aim of this study was to describe the characteristics of the underlying diseases in a large number of patients. A total of 263 patients (110 men, 153 women; age range 8–95 years; mean 55.9 years) were included in the study. The following data were collected from patients presenting over a 3-year period: gender, age, history, skin lesions, laboratory, histological and radiological investigations. An underlying dermatosis was identified in 41.8% of patients, a systemic disease including unidentified neoplasms in 13.3% and a neurological disorder in 0.4%. No disease was found in 44.5% of patients. Among the patients in whom no disease was found, 55.6% of the, mainly elderly, patients had an accumulation of many co-factors, suggesting an own subgroup with multifactorial origin for the pruritus. The distribution and type of secondary scratch lesions gave no clue as to the underlying disease. In conclusion, patients with chronic pruritus presenta inhomgeneous collective with different underlying diseases, including malignancy, necessitating thorough investigation. ***Key words: chronic pruritus; itch; prevalence; incidence; prurigo nodularis; atopic dermatitis.***

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Chronic pruritus is a frequent symptom in dermatology, arising from both dermatological and systemic diseases. To date, few studies have quantitatively characterized pruritus at a population level, and the prevalence of this symptom has not yet been determined. It is currently estimated that 8% of patients presenting to general practice have chronic pruritus. A recent representative questionnaire study of a large urban population (Oslo; 18,747 persons participated) revealed that 8.4% of all adults (female:male ratio 1.2:1) experienced chronic pruritus, which was the dominant self-reported skin complaint in this age group (1). Another questionnaire study was performed in over 2000 patients in London, investigating the presence of skin diseases. Prurigo and other pruritic conditions (e.g. lichen simplex, pruritus ani, pruritus vulvae) had the second highest prevalence of 8.2%, with a female:male ratio of 1.6:1 (2) (the highest prevalence was for "eczema"). A recent study of the prevalence of skin diseases in dermatological outpatients in Copenhagen found that 2.5% had pruritus and prurigo (3).

Precise prevalence rates of pruritus in systemic diseases are not known, except for conditions such as renal failure with haemodialysis (4–6). In other diseases, pruritus is a rare, but sporadically occurring, symptom, for example in hyperthyroidism and may not be attributed to the disease in every case. Moreover, no accordance exists among pruritus researchers about whether diseases such as diabetes mellitus are capable of inducing pruritus. Accordingly, there is a debate about the range of investigations necessary in examining patients with chronic pruritus. To resolve this situation, representative studies characterizing the origin of chronic pruritus in large studies are necessary but still missing. Retrospective clinical analysis of single groups of patients (34–132 patients) found that 13–50% of patients with generalized pruritus had a systemic underlying disease (7–13) (Table I). No studies of the prevalence of pruritus in dermatological diseases are yet available, except for psoriasis (14–16). The aim of the present retrospective study was to characterize precisely the underlying diseases in a large number of patients admitted with severe, chronic pruritus to a specialized dermatological department over a 3-year period.

PATIENTS AND METHODS

Study design and data acquisition

This retrospective study collected data from patients at the Department of Dermatology, University of Münster, Germany. Only patients referred with "chronic pruritus" or "prurigo nodularis" by general practitioners or dermatologists between January 2000 and December 2002 were included without preselection. Patients with dermatoses accompanied by acute pruritus were not considered.

Patient data were ascertained via the diagnoses coded during the foregoing inpatient stay. Coding of principal and secondary diagnoses was based upon the International Statistical Classification of Diseases, 10th revision (ICD-10) (17) and the revised German version 2.0 (18), respectively. Patients with "pruritus" and/or "prurigo nodularis" were included and retrieved from the patient data management system. These patients were identified by the ICD-10 codes L28.1 (*prurigo nodularis*), L28.2 (other *prurigo*), L29.8 (other *pruritus*), and L29.9 (*pruritus, not elsewhere classified*) as principal or secondary diagnoses.

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Table I. *Systemic origin of pruritus in the literature and present study*

Author, year (ref.)	No. of patients	Patients with underlying systemic disease, *n* (%)	Type of disease
Rajka, 1966 (7)	34	17 (50)	Metabolic disease, lymphoma, solid cancer
Lyell, 1972 (8)	74	18 (25)	Metabolic disease, drug-induced pruritus, solid cancer
Beare, 1976 (9)	43	7 (16) and 18 (41.9) with known uraemic pruritus	Metabolic disease, lymphoma, solid cancer
Kantor & Lookingbill, 1983 (10)	44	13 (30) confirmed association: 6 (13)	Metabolic disease, haematological disease, solid cancer
Zirwas & Seraly, 2001 (11)	50	11 (22)	Metabolic disease, lymphoma, solid cancer
Afifi et al., 2004 (12)	95	38 (40)	Metabolic disease, parasitosis, haematological disease, lymphoma, solid cancer
Weisshaar et al., 2006 (13)	132	47 (36)	Metabolic disease, lymphoma, solid cancer
Present study	263	35 (13.3)	Metabolic disease, drug-induced pruritus, lymphoma, solid cancer

The accuracy and validity of data coding was checked routinely by specialized physicians in close accordance with the official German coding standards. Since coding of inpatient treatments was not compulsory before 2001 in Germany and, therefore, data derived from before the second half of the year 2001 could not be regarded as providing high-quality coding, all available medical records for patients who had been hospitalized previously were ascertained manually concerning chronic pruritus and prurigo nodularis. The complete sample set obtained in this manner was then analysed individually.

Assessments

According to previous reports on diseases potentially inducing pruritus (19–21), patients were investigated extensively, with the aim of determining any underlying disease that cause chronic pruritus. Data were collected retrospectively as follows:

History. Medical history comprised onset and course of pruritus, presence and onset of skin lesions, known systemic and dermatological diseases and allergies, predisposition for atopic dermatitis, past and actual drug intake, and family history.

Skin examination. Data from skin examination by a dermatologist, including examination for primary skin disease, secondary scratch lesions (linear or round excoriations and ulcerations, lichenification, erosive or crusted, hyperkeratotic, red-livid papules and nodules, hyper- or hypopigmentation, and atrophic scars) and xerotic skin were included. Data from skin biopsy (in the case of presence of skin lesions which could not have been classified on clinical criteria, and performance of an additional skin biopsy) were collected. Concerning the presence or absence of secondary scratch lesions, three clinical groups were defined irrespective of the presence of a skin or systemic disease: (*i*) no scratch lesions; (*ii*) single, acute excoriations only (no papules, nodules); (*iii*) chronic, disseminated scratch lesions of prurigo nodularis: erosive or crusted generalized or localized, hyperkeratotic papules and nodules.

Laboratory investigation. Collected laboratory investigation data comprised electrolytes, erythrocyte sedimentation rate, blood count, differential blood count, total protein, protein electrophoresis, iron metabolism, level of folic acid, zinc and vitamin B12, blood glucose, uric acid, urea, creatinine, liver transaminases, bilirubin, alkaline phosphatase, hepatitis serology, thyroid function test, antibodies against thyroid gland, parathyroid hormone level, total IgE serum level.

Radiological investigation. Results from the following radiological investigations were considered: ultrasound of abdomen and lymph nodes and chest X-rays.

Follow-up. All patients were followed-up retrospectively for at least one year, some of them for 3 years to exclude the development of diseases contributing to pruritus, such as Hodgkin's disease or plasmocytoma, e.g. in the presence of paraproteinaemia, as found in some of the patients.

Statistical analysis

Data were collected and encoded using Microsoft® Excel Version 2000. Statistical analysis was performed with SPSS® for Microsoft® Windows (German Version 14.0). Categorical data were summarized by means of absolute and relative frequencies; continuous data were summarized by arithmetic mean and standard deviation. To detect possible differences between the groups, Fisher's exact test (for categorical data) and Kruskal-Wallis test (for continuous data) were applied as two-tailed tests and $p < 0.05$ was considered statistically significant. Pearson's bivariate correlation was performed on age and number of co-factors in order to discover a significant correlation.

RESULTS

A study population of 263 patients with chronic pruritus hospitalized in the period 2000 to 2002 was analysed. The demographic data are given in Table II. Most patients were adults, with a majority of elderly patients between 60 and 69 years of age (Fig. 1). There were 7 children (2.7%), age range 8–18 years (mean 14.4 years), among the patients.

Diseases underlying chronic pruritus

Collected data were correlated with the history of onset and course of chronic pruritus before being attributed

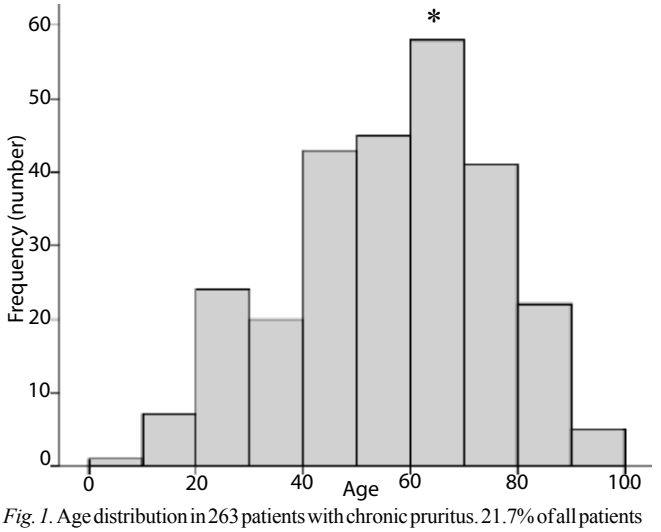

Fig. 1. Age distribution in 263 patients with chronic pruritus. 21.7% of all patients were between 60 and 70 years old (*). The mean age was 55.9 years.

Table II. *Demographic and clinical characteristics in 263 patients with chronic pruritus*

	All patients	Group I: undetermined origin	Group II: dermatological disease	Group III: systemic disease	Group IV: neurological origin	*p*-values
Number of patients, *n* (%)	263 (100)	117 (44.5)	110 (41.8)	35 (13.3)	1 (0.4)	
Sex, *n* (%)						
Male	110 (42.0)	44	47	19	–	0.18
Female	153 (58.0)	73	63	16	1	
Age, years						
Range	8–95	18–91	8–92	20–95	44	0.001
Mean ± SD	55.9±19.0	60.1±16.08	50.3±20.8	59.4±17.80	–	
Age distribution, *n* (%)						
0–19 years	8 (3.0)	2	6	–	–	
20–64 years	168 (63.9)	70	76	21	1	0.14
65–95 years	87 (33.1)	45	28	14	–	
Duration of pruritus, months						
Range	1–804	1–540	1–804	1–300	24	0.96
Mean, years	5.7	5.1	6.6	4.8		
Localization of pruritus						
Generalized	194	82	85	27	–	0.24
Localized	69	35	25	8	1	
Secondary skin lesions, *n* (%)						
No	37 (14.1)	14	17	6	–	
Single lesions	71 (27.0)	13	50	7	1	<0.001
Prurigo	155 (58.9)	90	43	22	–	
Number of co-factors, *n* (%)	156 (100)	100 (64.1)	36 (23.1)	20 (12.8)	–	
Number of patients with co-factors, *n* (%)	109 (100)	65 (55.6)	29 (26.3)	15 (42.9)	–	< 0.01

SD: standard deviation.

as be responsible for the pruritus. When a clear correlation between the onset or severity of pruritus and an identified disease was evident upon history and investigation, patients were grouped to one category of underlying disease. Thereupon, the following groups were defined (Fig. 2):

Group I: "Pruritus of undetermined origin (PUO)". Though extended examination of patients, in 117/263 patients (44.5%) no disease could be attributed to chronic pruritus. A correlation of secondary scratch lesions with underlying diseases revealed that 90 (76.9%) patients with PUO showed prurigo nodularis (Table II, Fig. 3).

Group II: "Pruritus due to dermatological disease". A total of 110 of 263 patients (41.8%) referred to us with severe "chronic pruritus" or "prurigo nodularis" had an underlying skin disease that was responsible for the symptom. Clinical, histological and immunofluorescence investigation revealed several underlying dermatoses (Table III). Most of the patients (57.3%) suffered from atopic dermatitis in a chronic-subacute

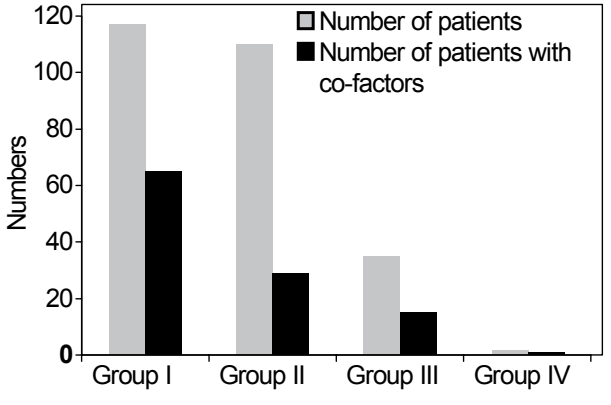

Fig. 2. Total number of patients suffering from pruritus in group I "Pruritus of undetermined origin (PUO)", group II "Pruritus due to dermatological disease", group III "Pruritus due to systemic disease" and group IV "Pruritus due to neurological disease". In three groups, a high number of patients had additional co-factors.

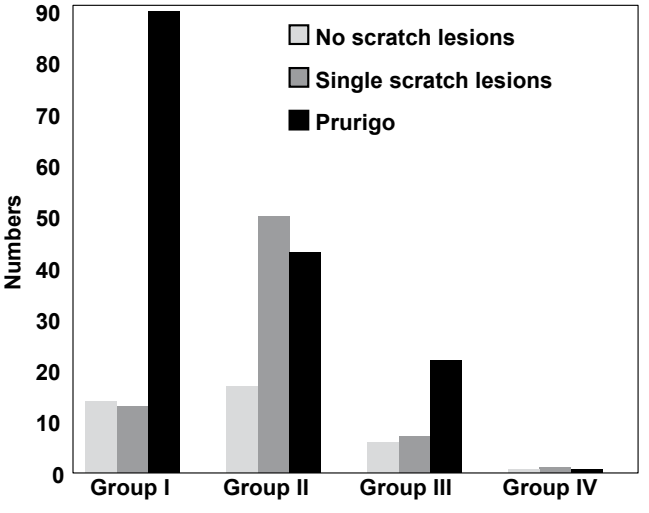

Fig. 3. Presence of secondary scratch lesions in each group.

Table III. *Diagnosis underlying chronic pruritus: group II: dermatological disease*

Diagnosis	*n*
Inflammatory disease (n = 90)	
Atopic dermatitis	63
Urticaria	12
Psoriasis	5
Dry skin	7
Erythema anulare centrifugum	1
Lichen planus	1
Nummular dermatitis	1
Arthropod disease (n = 8)	
Scabies and post-scabious dermatitis	6
Arthropod reaction	2
Autoimmune disease (n = 7)	
Bullous pemphigoid	4
Pemphigus vulgaris	1
Duhring's disease	1
Unclassified autoimmune disease	1
Cutaneous lymphoma (n = 5)	
T-cell lymphoma	3
B-cell lymphoma	2

stage or predisposition for atopic dermatitis. Only a few patients had no additional scratch lesions in addition to skin disease; most showed either single lesions or prurigo (Fig. 3).

Group III: "Pruritus due to systemic disease". In 35 patients (13.3 %), clinical and laboratory investigation revealed an up-to-date unidentified systemic disease, including several neoplasms (Table IV). Most of these patients (62.9%) showed clinically additional prurigo nodularis.

Table IV. Diagnosis underlying chronic pruritus: group III (systemic disease) and group IV (neurological disease)

Diagnosis	*n*
Metabolic disease (n = 23)	
Diabetes mellitus	7
Renal pruritus	5
Vitamin deficiency (folic acid, iron, zinc)	3
Thyroiditis	3
Metabolic syndrome (adipositas, dyslipoproteinaemia, hyperuricaemia, essential hypertonia, diabetes mellitus)	2
Cholestatic pruritus	2
Malnutrition (due to anorexia nervosa)	1
Drug-induced pruritus (n = 7)	
Hydroxyethyl starch, oxacepam, metoprolol, thiazide, amiodarone	7
Neoplasm (n = 5)	
Non-Hodgkin's lymphoma	4
Prostate carcinoma	1
Neurological disease (n = 1)	
Brachioradial pruritus	1

Group IV: "Neurological disease". In one patient (0.4%), a brachioradial pruritus, i.e. localized neuropathic pruritus of both arms, was responsible for the chronic pruritus.

Co-factors of chronic pruritus

In addition to the main disease causing pruritus, many additional pathological findings were revealed in the entire study population, such as internal or dermatological disturbances. These factors were classified in factors with (e.g. hyperuricaemia) and without (e.g.

Table V. *Number of co-factors as found in 262 patients* (several patients with more than one co- factor)*

Groups of co-factors	Sum of factors	Group I: pruritus of undetermined origin *n* (%)	Group II: pruritus due to dermatological disease *n* (%)	Group III: pruritus due to systemic disease *n* (%)
Internal disturbances: 110 co-factors (70.5%)				
Metabolic-endocrine disturbances				
Increased liver transaminases/st.p. Hepatits B (*n*=15), Renal insufficiency (*n*=14), diabetes mellitus (n=13), hypothyroidism (*n*=10), hyperthyreosis (*n*=2)	54	33 (61.1)	17 (31.5)	4 (7.4)
Haematological, lymphoproliferative disease				
Iron deficiency (*n*=17), eosinophilia (*n*=4), IgG-kappa-paraproteinaemia (*n*=4)	25	22 (88)	1 (4)	2 (8)
Allergic diatheses with asthma bronchiale	4	3 (75)	1 (25)	–
Parasital infections				
Oral, vaginale and intestinal candidiasis (*n*=26), gastral Helicobacter pylori infection (*n*=1)	27	16 (59.3)	9 (33.3)	2 (7.4)
Intake of drugs: 4 co-factors (2.6%)				
Furosemid, enalapril, allopurinol, opioids	4	4 (100)	–	–
Dermatological disturbances: 35 co-factors (22.4%)				
Atopic diathesis (*n*=23), dry skin (*n*=4), multiple Type IV sensitization (*n*=4), multiple Type I sensitization (*n*=2), urticarial dermographism (*n*=2)	35	19 (54.2)	8 (22.9)	8 (22.9)
Neurological diseases: 7 co-factors (4.5%)				
Polyneuropathy (*n*=7)	7	3 (42.9)	–	4 (57.1)
Number and percentage of all co-factors	156	100 (64.1)	36 (23.1)	20 (12.8)

*The patient with neurological origin of pruritus had no additional pathological finding.

Table VI. Clinical characteristics of the subgroup with multifactional origin

Patient's age	>65 years
Women preponderance (male:female ratio)	1:1.7
Clear time- and history-related association between pruritus and underlying disease	None
Skin changes present:	
Dry skin	42.2%
Prurigo nodularis	76.9%
Internal disturbance (metabolic-endocrine, haematological) present	69.9%

hypertension) pruritogenic potency. Only factors with pruritogenic potency were considered in regard to the history of pruritus (Table V). However, all these findings did not correlate clearly with the onset of pruritus and may have occurred coincidentally, but might also act as co-factors contributing to worsening or chronification of the symptom. In the whole study population, 156 pathological conditions were found (Table V); in several patients more than one pathological finding was identified. Seventy-two (27.5%) patients had one pathological finding, 28 (10.7%) patients had two, 5 (1.9%) patients had three, 2 (0.7%) patient four and one (0.4%) patient had five co-factors. A total of 155 (58.8%) patients had no co-factor. In the PUO group, the highest number of pathological findings could be evaluated. In 65/117 patients (55.6 %), 100 co-factors (64.1% of all co-factors) were revealed (Table VI).

DISCUSSION

The present study aimed to investigate retrospectively the underlying diseases of patients with severe, chronic pruritus in a dermatological study sample. In total, 263 in-patients with chronic pruritus referred to us in the years 2000–2002 were included. There was a majority of women, with a female:male ratio of 1.4:1. This concerns mainly the patients with unknown or dermatological origin of pruritus, while systemic diseases did not show any gender preponderance. The age distribution and mean age in men (54.6±18.1 years) and women (56.7±19.6 years) were similar and did not differ significantly ($p = 0.38$). Approximately half of the patients who presented were among the older age group, 60–95 years (47.9% of patients), with an average age of 73 years. In contrast, only 2.7% of patients were children with either dermatological or undetermined origin, but no systemic disease.

Patients were referred to the Department of Dermatology by general practitioners as well as by dermatologists. Accordingly, both as-yet unidentified skin and systemic diseases were found to be the origin of chronic pruritus. In 41.8% of these patients, an underlying dermatological disease was responsible for the chronic pruritus. For example, atopic dermatitis, urticaria, psoriasis vulgaris, lichen planus, bullous pemphigoid and mycosis fungoides had not been diagnosed before, in part due to unusual development of the disease, and were found to be in close association with the onset and course of the reported chronic pruritus. Atopic dermatitis in chronic-subacute stages was most common. Despite the fact that many patients in this study had a dermatological origin of pruritus, the composition of pruritic dermatoses should be interpreted with caution. Patients were referred primarily for their severe chronic pruritus independent of skin changes. In a dermatological practice the composition of pruritic skin diseases may be different; this concerns dermatoses with presence of acute and/or chronic pruritus, such as allergic, nummular or dyshidrotic dermatitis.

In addition to dermatoses, skin investigation revealed acute and chronic scratch lesions. Among these were many patients with prurigo nodularis, which is now widely accepted to represent a cutaneous reaction pattern to repeated rubbing or scratching caused by pruritus of different origin (19, 22). Accordingly, we consider skin lesions of prurigo nodularis as secondary scratch lesions and separate it in our evaluation from primary skin diseases. In our study population, prurigo nodularis was found in each diagnosis group, but significantly more often in patients with PUO ($p < 0.001$). However, there was no correlation between the origin of pruritus and the patient's scratching behaviour. For example, in patients with a systemic lymphoma underlying the pruritus, different forms of scratch-associated conditions were observed, such as single scratch lesions, prurigo nodularis, as well as no skin lesions. In summary, the distribution and type of secondary scratch lesions allows no conclusion to be drawn about the underlying disease.

Pruritus as a symptom of a systemic disease is well known, but current epidemiological data are insufficient. The up-to-date published studies found a systemic origin varying from 13–50% of patients with chronic pruritus (Table I). The most recent studies of Afifi et al. (12) and Weisshaar et al. (13) revealed systemic diseases in 36–40% of patients, ranging from toxocariasis to pulmonary cancer. However, these studies and their findings of an associated disease have to be interpreted very carefully. Some studies followed the patients over several years and, with time, systemic diseases developed explaining the high prevalence of systemic diseases (7). However, it remained unclear whether the identified disease is responsible for the chronic pruritus or whether it developed incidentally. This circumstance was taken into account in one study of 44 patients with generalized pruritus who were followed for 6 years. In 13 (30%) of these patients a systemic disease was evaluated; in 6 patients (13%) only this could be strictly attributed to the pruritus (10). Moreover, the authors compared their findings with a psoriasis control group to

demonstrate coincidental associations. Accordingly, we only considered a systemic disease to be responsible for pruritus when a clear relation between onset and course of both pruritus and disease was reported. Systemic diseases were found to be less frequent than dermatological diseases and to be responsible for the pruritus in 35/263 patients. Our result of 13.3% of patients having a systemic origin of pruritus is in accordance with the result of Kantor & Lookingbill (10), which also found a systemic disease in correlation to pruritus in 13% of patients. Among our patients, 5 were identified with unknown lymphoma and visceral neoplasm (prostate-carcinoma, non-Hodgkin's lymphoma). Other patients had pruritus in association with renal disease (renal pruritus), vitamin-deficiency, thyroiditis, metabolic disturbances, liver disease (cholestatic pruritus) and intake of drugs. Interestingly, we also detected an association of chronic, generalized pruritus to insufficiently adjusted diabetes mellitus. These comprised 7 patients (6 men, 1 women; 35–82 years, mean 58 years) with localized (n=4) and generalized (n=3) chronic pruritus. Two had no scratch lesions, one had single scratch lesions and 4 showed prurigo. It is frequently debated whether diabetes mellitus induces pruritus. Recent findings suggest that diabetes mellitus may induce cutaneous sprouting of sensory nerve fibres along with hyper-excitation and pruritus (23, 24).

Regarding the present and previous studies (Table I), all authors reported cases of underlying neoplasm leading to pruritus, such as lymphoma (Hodgkin's and non-Hodgkin's lymphoma) as well as solid cancer (e.g. prostate, lung, breast, gastric, renal and tongue cancer). Some studies therefore focus on this and investigate whether malignancy has a higher prevalence in patients with pruritus than in the general population (25, 26). For example, Paul et al. (25) followed 125 patients with generalized pruritus up for 6 years; 8 patients in this group (6.4%) developed cancer. However, the incidence and types of malignancies did not differ significantly from the value expected for the general population, matched for age and sex. Concerning lymphomas, the incidence was significantly higher than that expected for a similarly matched population. Because of this, we followed our patients for up to 3 years without observation of subsequent development of lymphoma. In summary, patients with chronic itch should be followed-up thoroughly for the development of lymphoma, which may occur years after the beginning of the pruritus.

For most patients in our study (44.5%, i.e. 117/263 patients) no time- or history-related underlying disease was identified as responsible for chronic pruritus. However, in the majority of these patients (65/117 patients, 55.6%) various co-factors without a clear association to history of pruritus were found. These factors have pruritogenic potency and therefore may contribute to the maintenance of the symptom. Among them, metabolic-endocrine or haematological disturbances were most common. Interestingly, the presence of co-factor correlates significantly with age ($p < 0.01$) and concerns mainly elderly patients. Like Kantor & Lookingbill (10), we observed that several patients had more than one underlying disease and combination of kidney disease, liver disease, hypothyroidism and drug intake. In summary, it may be speculated that these patients with an unclear association of only one pruritogenic disease represent an own subgroup with accumulation of several co-factors that finally leads to chronic pruritus of multifactorial origin. These are mainly elderly patients (mean age 63 years) with a preponderance of women (female:male ratio 1.7:1), different internal metabolic or haematological disturbances, and skin changes (Table V). As a consequence, treatment of these patients with anti-pruritic substances (26) exhibits several difficulties such as contraindication due to pre-existing systemic diseases, increased side-effects in elderly patients, or interaction with other drugs.

In conclusion, patients with severe, chronic pruritus present a non-homogeneous group with different underlying diseases, including malignancy. The clinical presentation of scratch lesions does not usually signify its underlying origin. Interestingly, in elderly patients a subgroup seems to exists with a multifactorial origin of pruritus. However, further epidemiological studies characterizing the prevalence of pruritus in certain diseases, as well as investigating the incidence of pruritus in the general population, are needed.

Conflicts of interest: None to declare.

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