

REVIEW ARTICLE

Epidemiology of Itch: Adding to the Burden of Skin Morbidity

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Itch is the most frequent symptom in dermatology and has been researched more extensively in recent years. Nevertheless, there are few true epidemiological studies on itch. The aim of this paper is to review the current state of research on the epidemiology of chronic itch in Western and non-Western populations. The electronic databases PubMed, Medline and the Cochrane Library were searched. Conference proceedings and national and international studies were included. It is difficult to compare existing studies due to differing methodology and lack of standardized measures. The symptom of itch is a challenge, not only to clinicians, but also within the structure of regional health systems, and with regards to accessibility to specialized medical doctors in non-Western countries. Published studies show that the symptom of itch is highly prevalent; it should therefore receive adequate attention from physicians and other healthcare providers, including healthcare planners. Key words: community; epidemiology; itch; pruritus; psycho-social factors; skin diseases.

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Although itch is often described as the most frequent symptom in dermatology, there have been very few studies of the incidence, and a limited number of the prevalence, of chronic itch. Prevalence is a measure of those individuals affected by a condition within a specific time period, while incidence is a measure of the number of new individuals who develop a condition within a specific time period. Clinical experience indicates that patients frequently do not consult a doctor for acute itch, but more often do for chronic itch (defined as itch lasting longer than 6 weeks) (1). Most of the studies refer to specific diseases or patient groups, which complicates the comparability and validity of the existing studies.

Focusing on symptoms in dermato-epidemiology provides a new contribution to the assessment of the burden of skin morbidity in the community. The assessment of disease in populations is an important measure in health planning and for the understanding of associations of

disease with environmental factors, to meet demand and to investigate factors of importance in preventing disease in the population (2–4). Individuals presenting to doctors tend to have more severe disease, thus this patient population represents the tip of the iceberg relative to ill-health at the community level (3, 5).

The aim of this paper is to review current knowledge of the distribution of chronic itch in different populations. The electronic databases PubMed, Medline and the Cochrane Library were searched. The search terms used were: itch, itching, and pruritus, plus all of these terms in combination with dermatology, epidemiology, community, psycho-social factors, and skin diseases. Conference proceedings of national and international dermatology/allergy/itch meetings (abstracts of poster and oral presentations) and the reference sections of identified publications were screened manually.

CHRONIC ITCH IN THE COMMUNITY

Studying a symptom such as itch at the community level can provide valuable information on associations with demographic factors, psycho-social factors and, eventually, other diseases in the community. This provides a different perspective from the clinical one, and has the advantage of including information on risk factors for chronic itch that cannot be explored so easily in patient populations.

In 1976, the prevalence of prurigo and allied conditions was reported to be 8.2% according to the study in Lambeth (6). A cross-sectional study in Oslo, Norway (from 2000 to 2001) including a total of 40,888 adults enabled data on the prevalence of itch to be provided for the first time (7). The assessment of variable itch was made as part of a larger questionnaire. The prevalence of itch in this population was 8.4%; this was the most prevalent of all reported skin symptoms. The result refers to reported itch with the grades “quite a lot” and “very much”. In a survey of 18,137 French people presenting with skin diseases and skin problems, 42% stated that they experienced itching. Whether the itch was acute or chronic was not defined (8). A German pilot study of chronic itch in a sample of the general population ($n=200$) showed a point prevalence of 13.9%. In this study, 16.5% had experienced chronic itch within the last 12 months, and the lifetime prevalence of chronic itch was 22.6%. This indicates a possible higher pre-

valence of chronic itch in the general population than reported previously (9).

Socio-demographic factors

Women reported more itch than men (11.9% and 9.6%, respectively) (7). Although gender differences have been little explored in the field of dermatology, the higher level of reported itch among females is seen in other studies (6, 9–11).

Individuals reporting itch were found to be younger in a Norwegian study (7). However, there was no significant difference with respect to age between the patient and non-patient groups in a German pilot study, with a mean age of 63.7 years (9).

Itch is more prevalent among individuals with lower socio-economic status and lower household income (7). As for other health outcomes, the report of itch has strong social determinants (12–14).

Report of itch seems to be associated with ethnic background in Western urban communities (15). In this Oslo study individuals from the Middle East, North Africa and the Indian subcontinent reported significantly more itch than individuals from Western countries. These ethnic differences in the report of itch should be interpreted with caution. "Health and ethnicity" is an emerging research area, and studies have demonstrated increased mortality and morbidity rates among immigrants. Low socio-economic status and different health behaviour and lifestyle among immigrants may be important contributing factors (16–19).

Psycho-social factors

At the community level there is significantly more reporting of itch among depressed people (18% compared with 9% among non-depressed people), and individuals who have experienced many negative life-events, stress and loneliness tend to report more itch (20–22). It could be shown that the psychosocial well-being of patients with skin diseases in primary care is lower than that of the general population (23). A lower psychosocial well-being was significantly related to more physical symptoms such as itch (24). The relationship between internal factors of relatively stable personality traits, external stressors, and the influence of possible mediators (cognitive, behavioural and social factors) on itch was summarized in a review (25). Observations during an itch-inducing lecture showed that itching can be induced by psychological trigger factors (26).

CHRONIC ITCH IN SPECIFIC POPULATIONS

Children

There are no epidemiological studies investigating the prevalence of itch among children. Differential diagnosis

of itch has a great range (27, 28). Congenital ichthyoses, such as lamellar and X-linked ichthyosis, epidermolysis bullosa and linear IgA-dermatosis, are known to cause chronic itch in children, but epidemiological data on their frequency and intensity are missing. Nevertheless, chronic itch is the dominating symptom of atopic dermatitis (AD) and an essential outcome measure of this highly prevalent childhood dermatitis. Providing an overall estimate of frequency of AD is difficult, as studies differ in measures of disease frequency, instruments for recording AD and ages of subjects. The overall cumulative prevalence of AD is between 5% and 22% in developed countries. Incidence figures for AD suggest approximately 50 cases per 1000 in the first year of life, falling to approximately 5 new cases per 1000 per year for the remainder of childhood (29). The German Atopic Dermatitis Intervention Study (GADIS), which included 823 children and adolescents, showed that age-related educational programmes are effective in the long-term treatment of AD, and revealed significant correlations between the severity of AD and itch intensity, as well as itch and sleeplessness. The coping and itching behaviour of children aged 8–12 years and adolescents aged 13–18 years had higher significant correlations with the itch compared with the parents' answers (30). A Norwegian cross-sectional questionnaire-based population study involving 4744 adolescents in Oslo revealed an itch prevalence of 8.8%. Itch was associated with mental distress, gender, sociodemographic factors, asthma, rhinoconjunctivitis and eczema. Mental distress and eczema were the variables in the study that contributed most to the distribution of itch at the population level among adolescents (31).

Itching of mild to moderate severity in acne was found to occur in 13.8% of subjects in a Polish study of 108 teenagers with acne (mean age 15.8 years), in which 36.1% of subjects had a history of itching. Itching episodes lasted less than 10 min; 37.7% experienced itch less than once a month and 24.5% several times a week; and 31.5% reported that they had medical treatment to reduce itch (32). Another study on itch in acne, carried out in Singapore, supports these findings (33). Out of 120 acne patients aged 12–40 years, 70% reported itch. Of these, 43.3% reported itching episodes of at least once a week. This clinical association is not restricted to Caucasian teenagers; 85.8% were Chinese, 8.3% Malay, 3.3% Indian and 2.5% other ethnicity (33).

There are no studies of the systemic causes of chronic itch among children. It must be assumed that systemic causes in children are based largely on genetic or systemic diseases, e.g. hepatobiliary diseases, such as biliary atresia or hypoplasia, Alagille syndrome (absence of interlobular bile ducts), familial hyperbilirubinaemia syndromes, such as Byler disease (intrahepatic cholestasis) and haemolytic icterus. Uraemic itch occurs in terminal renal insufficiency caused by polycystic

kidney disease. In Germany, the frequency is reported to be 9% in paediatric dialysis patients (34). In a small Turkish study 22.2% of children on peritoneal dialysis treatment experienced itch (35). In both studies itch is described as mild. Haematological pruritus may be due to iron deficiency, Hodgkin's disease, acute lymphatic leukaemia (ALL) or polycythaemia vera. Itch can occur in malignant diseases and tumours of the central nervous system, such as brainstem gliomas.

Drug-induced itch with no specific skin symptoms appears to be rare in children. Common medications associated with itch in adults play a minor role in children due to limited use of such treatments among children. Chloroquine-induced itch occurred in 12.8% of treated children in Kenya (36). Twenty-five percent of children over 12 years of age were experiencing itch during tumour pain therapy with morphines (μ -opioids). Of those children, almost 10% were affected (37, 38). Anti-malarials and morphines usually induce acute itching that lasts hours to days, but epidemiological data about their long-term use, especially in tumour pain therapy, are missing.

Pregnancy

There are no epidemiological studies assessing the prevalence of chronic itch in pregnancy. Itch is the leading dermatological symptom in pregnancy, estimated to occur in approximately 18% of all pregnancies (39). Itch is the leading symptom of the specific dermatoses of pregnancy (polymorphic eruption of pregnancy (PEP), pemphigoid gestationis (PG), intrahepatic cholestasis of pregnancy (ICP) and atopic eruption of pregnancy (AEP)), but may also occur in other dermatoses coinciding by chance with pregnancy or in pre-existing dermatoses (28, 40). PEP is one of the most common gestational dermatoses, affecting approximately one in 160 pregnancies. While PG, PEP and ICP characteristically present in late pregnancy, AEP starts before the third trimester in 75% of cases (40).

A French prospective study of 3192 pregnant women revealed that 1.6% had pruritus (41). Seventeen cases (0.5%) had pruritus gravidarum, 2 cases were unrelated to pregnancy (one scabies, one exfoliative dermatitis), and all other cases were pregnancy-specific dermatoses. The prevalence of pruritus in pregnancy was 4.6% in an Indian study of 500 pregnant women, but with the exception of 4 cases of pruritus gravidarum (0.8%) all experienced specific dermatosis of pregnancy (42).

ICP is characterized by severe itch with no primary skin lesions, but secondary skin lesions occur due to scratching. It is more prevalent among native Indians in Chile (27.6%) and Bolivia (13.8%) depending on ethnic predisposition and dietary factors (43, 44). ICP has decreased in both countries, e.g. to 14% in Chile. ICP is more common in women of advanced maternal

age, multiple gestationis, personal history of cholestasis on oral contraceptives and during winter months (43, 44). Scandinavian and Baltic countries are also more affected (1–2%). In Western Europe and North America ICP is observed in 0.4–1% of pregnancies (43, 44).

Elderly people

Only a small number of studies have investigated itch in elderly people. They are characterized by selection bias and differing end-points (pruritic skin disease or itch). An American study investigated 68 elderly people, aged between 50 and 91 years. Of the complaints recorded, itch was the most frequent, accounting for 29% of all complaints and for 2 of the 3 cutaneous complaints subjectively graded as severe (45). A Turkish study detected that itch ranks first within the distribution of skin diseases when investigating 4099 elderly patients. In this study 11.5% reported itch. Women were more affected (12.0%) than men (11.2%). According to the age group, patients older than 85 years showed the highest prevalence (19.5%). When examining seasonal variations, itch was found to be among the 5 most frequent diagnoses in all seasons, being most frequent in winter (12.8%) and autumn (12.7%) (46). In a Thai study, pruritic diseases were the most common (41%) identifying xerosis (which was for the authors identical with senescent itch) as the most frequent one (38.9%) in a total of 149 elderly patients (47). The burden of chronic itch among elderly people represents a growing challenge due to the changing demographic distribution.

CHRONIC ITCH IN SPECIFIC DISEASES

Dermatological diseases

A study in primary care of 492 patients with dermatological problems as their primary complaint showed that 50% reported fatigue and itch, which was experienced as relatively severe by 25%. Pain was reported less frequently (23%) and, on average, was less intense (24). In 132 German patients consulting the dermatology department of a university hospital for chronic itch, 57% experienced dermatoses (48). Eighty-one out of 84 Ugandan patients with chronic itch who were consulting a dermatology department had a skin disease (48).

In AD, chronic itch is considered a key symptom, and the diagnosis of AD cannot be made in the absence of this symptom. A clinical study of 100 Chinese patients with AD showed daily itching in 87%. Itching was most frequent at night (65%). The peak itch intensity was rated as nearly twice as strong as the itch of a mosquito bite (49). In a web-based survey 91% of a total of 304 individuals with AD reported itching at least once

daily, and 68% reported at least 5 episodes per day (50). Participants reported a mean itch intensity of 8.3 out of 10 for a typical episode of itch. Ninety-eight percent of individuals described their pruritus as “annoying”, “bothersome”, “unpleasant” or “bothering”. Pain and heat sensations significantly correlated with itch frequency, being reported by 59% (pain) and 53% (heat), respectively (50). There are no epidemiological studies investigating the prevalence and course of itch in AD in different age groups (also see the section on “Chronic itch in specific populations: children”, above).

Among 82 inpatients with psoriasis, 67% reported moderate or severe itch (51). According to a questionnaire of 17,488 members of the American Psoriasis Foundation, itching was the second most frequent symptom experienced by 79% of the psoriasis patients interviewed (52). In a study in Singapore with 101 gravely affected psoriasis patients 84% report generalized itch, 77% of the patients reporting daily occurrence (53). Out of 100 psoriasis patients, itching was found in 80%, with a significantly higher disease severity measured by Psoriasis Area and Severity Index (PASI) in pruritic psoriasis patients compared with non-pruritic psoriasis patients (54). In 81% itching was limited to psoriatic lesions, and in 19% it also involved non-lesional skin (55). All patients who experienced severe or extremely severe stress within the month before psoriasis exacerbation experienced itch (55). In a study of 93 hospitalized women with psoriasis, those patients with vulvar discomfort had psoriatic lesions on the vulva significantly more often than women without discomfort (56). In 80 patients with chronic plaque psoriasis 80% confirmed itching most commonly located on the lower leg (56%) and scalp (47%). Major aggravating factors were stress (67%) and drying of the skin (80%), whereas sun, sleep and holidays relieved itching (57). These results lead to the conclusion that itch in psoriasis should not be underestimated, and this symptom should be considered in therapy planning.

Chronic idiopathic urticaria is characterized predominantly by itch, estimated to occur in 100% of cases. One study in Singapore showed that 68% of patients experience daily itching, dominating during the evening and night, on the arms, back and legs. Seventy-six percent found their itch bothersome, 66% annoying and 14% complained of depression (58). A study of 41 patients with chronic idiopathic urticaria and 44 with psoriasis investigated the relationship between negative emotions and itch. The results showed that depression was the only significant predictor in psoriasis, explaining 12% of variance, and that anger was the only significant predictor in chronic idiopathic urticaria, explaining 19% of variance (59).

Infestations such as scabies, pediculosis and fleas, and insect bite reactions, occur with itch that is usually not chronic. Bacterial skin infections, such as folliculitis, impetigo and intertrigo, may present with itch, as well as fungal infections such as tinea and candidiasis, but

usually these skin diseases do not account for chronic itch. There are no epidemiological data on frequency and distribution of chronic itch in these skin diseases.

Erythroderma is a rare skin disease caused by, for example, AD, psoriasis, drugs, pre-lymphomatous disease or malignancy. A clinical study of 97 cases identified itch as the most common finding (97%), followed by fever (33.6%), lymphadenopathy (21.3%) and oedema (14.4%) (60).

A small questionnaire-based survey of 26 patients with adult dermatomyositis showed that, except for 4 patients, all experienced moderate itching even though the muscle disease was not active at the time of the survey (61). Further studies are needed to examine the prevalence of chronic itch in this population.

Itching is common in scars, being a consequence of physical, chemical stimuli and nerve regeneration. Post-burn itch is considered a variant of scar itch, but may also be a consequence of morphine therapy and psychological factors. Leg or arm wounds are particularly affected (62, 63). According to a Dutch study itch may follow 3 months post-burn in up to 87% of patients (64). Significant predictors of itching at all time-points were deep dermal injury and early post-traumatic stress symptoms. The most significant decrease was seen during the first year of post-burn. It decreased to 70% at one year post-burn and to 67% at 2 years post-burn (64).

Itching and burning may be present in patients with mild to moderate chronic venous insufficiency even before skin signs are present. Out of 100 patients, 66 reported itch, 47 reported itch and burning and 44 reported itch and pain (65). No correlation was noted between the severity of these symptoms and the degree of venous insufficiency. Ninety-seven percent of the patients described itch as more frequent during the evening and night (65).

Infectious diseases

Viral infections, such as herpes simplex, varicella, herpes zoster, and viral exanthemas can present with itching, which is usually not chronic even when the immune system is impaired. Mild or moderate itch usually accompanies herpes zoster and post-herpetic neuralgia (PHN). Among 188 patients with PHN, 58% reported itch (66). According to a Turkish study chronic itch in herpes zoster may occur in 4% of patients, termed post-herpetic itch (67). This is more likely to occur after shingles on the head, face and neck. In a study of 113 patients with varicella, 4.5% still reported itch 3 months later (66).

Itching in HIV infection is an important cause of discomfort and morbidity (68, 69). It presents in patients with advanced HIV disease, patients with CD4 counts less than 50 cells/ μ l and appears to be a cutaneous marker of disease progression (69). In a significant number of HIV patients itching has no detectable cutaneous or systemic cause (69). A descriptive study in 200 Nigerian newly

diagnosed HIV patients showed that 13% experienced itch as a major symptom (70). HIV patients are prone to develop pruritic skin diseases including pruritic papular eruption (PPE) and eosinophilic pustular folliculitis. Itching is described to be the only symptom experienced in PPE (71, 72). PPE is the most common cutaneous manifestation in HIV-infected patients, with a prevalence that varies between 11% and 46% according to the geographical region (72). Systemic causes, other than HIV itself, are relatively uncommon. Itch may be due to a complication of HIV, such as Norwegian scabies, increased carriage of *Staphylococcus aureus* and overgrowth of *Demodex* (69). In a study of Ugandan dermatology patients, 28% were shown to have chronic itch due to prurigo, 71.4% of them were HIV positive (73). This is in accordance with earlier observations showing a high association between prurigo and HIV. In 2002, 88% of the HIV-tested prurigo patients were positive (73). There are no true epidemiological studies on frequency and distribution of chronic itch in HIV infections. Due to widespread use of highly active antiretroviral therapy (HAART) since the mid-1990s, cutaneous manifestations in HIV, including chronic itch, will evolve (74).

Scabies is a pruritic skin disease that usually causes acute itch, but it needs to be recognized in chronic itch of patients with impaired immune system or when pretreated with, for example, topical cortisone. Cutaneous onchocerciasis is a common problem in many areas in Africa, even in those without high levels of onchocercal blindness (75). A multi-country cross-sectional study in 7 African centres showed that 42% of the population aged >20 years suffered from itch. There was a strong correlation between the prevalence of itch and the level of endemicity as measured by the prevalence of nodules in the examined population (5459 subjects). The presence of onchocercal reactive skin lesions, such as acute papular onchodermatitis, chronic papular onchodermatitis and/or lichenified onchodermatitis, was the most important risk factor for itching, followed by palpable onchocercal nodules (75).

Internal diseases

Chronic itching can be a key symptom of systemic disease. When 43 cases of generalized itch were followed up, 7 cases (16%) had an underlying systemic disease (76). Seventeen out of 34 (50%) inpatients admitted for investigation and treatment of generalized itch had a more (11 cases) or less probable (6 cases) relation to systemic disease (50%) (77). Among 74 patients with itching, 18 (24.3%) had a systemic disease (78). In a retrospective study of 44 cases of generalized itch, 13 (30%) had a systemic disease that is believed to be associated with generalized itch (79). Out of 50 patients seen in a university outpatient clinic for dermatology, 11 (22%) had a systemic disease (80). In 7 of these 11

patients, itching preceded the diagnosis of the systemic disease, and in 4 patients the systemic disease, that was causing the itching, was diagnosed before the onset of itch (80). According to a French study investigating 95 patients with generalized itching, 38 cases (40%) had an underlying systemic aetiology (81). Toxocariasis, a parasitic disease, was identified in 8 cases (8.4%), being the most frequently found systemic disease. In 132 German patients with chronic itch as a leading symptom, 47 patients (36%) had an underlying systemic disease (48). In 84 Ugandan patients, none of the patients had a systemic disease and itching was caused mainly by skin diseases, even in HIV patients (48). In a German retrospective study of underlying diseases in 263 patients with chronic itch, 13.3% had an underlying systemic disease. In addition, 24.7%, especially elderly patients, had many cofactors, suggesting multifactorial origin of chronic itch (82).

Uraemic disease.

Itch in dialysis patients is a major challenge. Decades ago up to 85% of haemodialysis (HD) patients suffered from uraemic itch, but improved HD technology and effectivity has decreased the prevalence during recent years (83, 84). Worldwide variation of the prevalence of uraemic itch ranges from 10% to 77%. Some studies measure lifetime prevalence, explaining higher numbers than those asking for period prevalence or current symptoms (85). The Observational Dialysis Outcomes and Practise Patterns Study (DOPPS) collecting data from more than 29,000 HD patients in 12 countries showed that 42% of HD patients experience moderate to extreme itch during the time period 2002 to 2003 (86). The percentage of dialysis unit patients reporting uraemic itch varied from 70% in some dialysis units to 5–10% in other dialysis units. Regional differences need to be taken into account. Prevalence differences were found between countries, ranging from 38% in France, 45% in Japan and the USA, 48% in UK, 49% in Germany to 55% in Italy (86, 87). In other studies, the prevalence of uraemic itch was assessed as 66–74.3% in Israel (88, 89) and 50.2% in Turkey (90). The quality of most studies is restricted by a lack of defining the prevalence period and differing time periods. Regional life expectancy, the population's proportion of elderly people, the healthcare system and access to certain therapies, such as HD, also limit the comparability of different studies (48). According to a German cross-sectional survey of 1420 nephrologists, the prevalence of uraemic itch may be underestimated by nephrologists. Large variation in the reported prevalence of uraemic itch and the undulating pattern of itch after dialysis may impede its recognition (91).

Hepatic disease.

Itching is described to be a symptom of cholestasis in 80–100% of cases (92). It has been shown to be the pre-

senting symptom of primary biliary cirrhosis (PBC) in 25–70% of patients, being experienced by at least 70% of patients by 10 years after diagnosis (92–94). Itch was found in 69.3% of 49 PBC patients in a case-control study (95). Itching was noted in 15% of hepatitis-C virus positive (HCV) patients compared with controls (4%) and 15% in a prospective study comprising 1614 patients with chronic HCV (96, 97). Itch was the only symptom that was significantly more frequent in the HCV-positive group (96). Distinct epidemiological studies about hepatic itch are missing.

Haematological disease. Chronic itching can be an important symptom in Hodgkin's disease, appearing without any specific skin lesions on the body years in advance of any other disease manifestations. It is estimated that up to 30% of the patients with Hodgkin's disease, up to 10% of patients with non-Hodgkin's lymphoma, and up to 5% of leukaemia patients have chronic itch, although no distinct epidemiological studies exist (98–100). According to a retrospective analysis of a tumour registry database over a 5-year period, searching 1049 patients with Hodgkin's disease and an appointment at dermatology clinics, eczema and itching were identified as the most common cutaneous manifestations (101). Itch was commonly associated with staphylococcal colonization. The selection of patients in this study may be biased, as it was limited to those patients whose skin findings merited referral to the dermatology clinic. Adult onset of itch or eczema should be evaluated for possible Hodgkin's disease (101). Itching in cutaneous T-cell lymphoma and mycosis fungoides is usually present with cutaneous lesions, but has occasionally been reported to precede the disease for years (102).

A retrospective cohort study including 397 patients with polycythaemia vera showed that 48% of patients had a documented history of itching (103). Itch at diagnosis was present in 17% and absent in 17%. In 36% of patients who did not have any itching at diagnosis, it developed subsequently. At diagnosis, the presence of itch was found to be significantly associated with decreased blood cell mean corpuscular volume and a higher leucocyte count (103).

An association of iron deficiency and itching has long been recognized (104, 105). A Finnish study of 23,289 men and 19,912 women showed that 13.6% of men and 7.4% of women with iron deficiency anaemia experienced itching. The difference from non-anaemic subjects was significant in men and women even when adjusted for age (106).

Malignant diseases.

Itch is described to be a relatively rare symptom in malignancies, but may be experienced as worse than pain (107, 108). Various different aetiological mechanisms have been observed, ranging from direct tumour inva-

sion of the skin, or distant metastases, to paraneoplastic inflammatory skin diseases and paraneoplastic phenomena. It may be caused by nerve compression, tumour growth, bile duct compression, cholestasis, side-effects of therapy and xerosis cutis. Toxic substances and necrotic tumour cells have also been postulated as possible eliciting factors for itch in cancer patients (27, 109). It is also possible that unknown mechanisms or metabolites released by the cancer tissue contribute to the origin and perception of chronic itch.

One prospective study investigated 34 patients with itch and diagnosed or suspected malignancy in 26% (77). Two patients had Hodgkin's disease, 2 visceral malignancies, 2 mycosis fungoides, one malignant lymphoma, one myeloma and one metastatic thyroid carcinoma (77). In a 3-year prospective study of 74 patients 3% had malignancies (one lung carcinoma, one carcinoma of unknown location (78)). Retrospective studies revealed malignant disease in 11% (79), 6% (80), 7% (48) and 2% of chronic itch cases (82). One study of 3 cancer cases showed that all cancer patients developed itching between 10 months and 2 years before the diagnosis of cancer was made (80). The carcinoid syndrome is characterized by flushing and erythema of the head, neck and upper trunk. It is caused by a tumour of the intestine producing neuroendocrine mediators, especially serotonin. This may lead to generalized pruritus with or without a rash, but there is no epidemiological data about this.

It is usually believed that paraneoplastic itch disappears or diminishes after tumour resection. Relapse of itch may constitute the only sign of reactivation and progression of the carcinoma, and as such is an important sign (107). So far, there is no clear evidence for these criteria according to clinical studies. One explanation for this circumstance is that itch is mostly not recorded as a symptom in cancer studies, especially in non-dermatological fields. It is so far not clear if all the discussed mechanisms depend on progression of the carcinoma and metastasis. The presence of itch for months or longer before the discovery of the underlying carcinoma suggests that some cancers may remain small and localized for long periods of time (107). The diversity of studies and the differing criteria used to select patients for study limit any conclusion as to whether generalized itch is statistically significantly associated with the presence of cancer (110, 111). Yet, the demographic situation, especially of the Western population, with an increasing proportion of elderly people, increases the possibility of cancer. This fact should be considered when diagnosing patients with chronic itch.

Endocrine disease.

Diabetes mellitus is the most common endocrine disease, and is accompanied by dermatological diseases and cutaneous manifestations in up to 70% of patients (112–114).

Generalized itching may occur as a presenting symptom of diabetes, but it is not significantly more frequent than in non-diabetic patients. It was found to affect 2.7% of a diabetic population (113). Itch was the second most common manifestation in a study from Kuwait, found in 49% of diabetic patients, and in an Indian study in 15.6% of diabetic patients (114, 115). Itch confined to the scalp was reported to be caused by diabetes, and all patients experienced complete relief of itching when control of the underlying diabetes was achieved (116).

Severe generalized itch may be a presenting symptom in hyperthyroidism, especially in thyrotoxicosis (117). The cause is not known, but it is probably explained by hormones in the skin. Chronic urticaria may be caused by the effects of thyroid autoimmunity. Localized or generalized itch may be seen in hypothyroidism, but is not reported as a frequent complication. It needs to be considered that, in hypothyroidism, the skin is dry, which can lead to pruritic asteatotic eczema.

Parathyroid gland activity is frequently increased in chronic renal failure, and most patients with end-stage renal failure develop secondary hyperparathyroidism. This has been suggested to be a cause of uraemic itch. Complete or partial relief of itch after parathyroidectomy was observed in patients (118–120), but the circulating parathyroid hormone (PTH) level alone does not explain itch. Itch is not always present in uraemic patients with hyperparathyroidism. It was shown that levels of PTH did not correlate with itch (121, 122) and not all patients with itch had elevated PTH activity. Others found significantly higher serum levels of PTH in patients with itch compared with patients without itch (123). In summary, there is no clear evidence for any role of PTH in different forms of itch such as uraemic itch.

Pre-menstrual itch related to recurrent cholestasis induced by oral contraceptives or other hormonal treatment is well recognized (124). Generalized itch related to menses and sensitivity to intradermal oestrogen has been described (125). Episodic itch is an occasional symptom in perimenopausal women and can be treated with hormone replacement therapy.

Neurological diseases

Mild to severe itch may accompany post-herpetic neuralgia (see Infectious diseases). Brachioradial itch and notalgia paraesthetica are variants of neuropathic itch. There is no information about their frequency and ethnic distribution. Chronic itch may occur in multiple sclerosis, polyneuropathy and following a stroke, but no epidemiological data are available.

Psychiatric diseases

In a community-based study involving 316 patients with a history of a major dermatological or medical disorder, 69.3% experienced itch during the previous

month. The total number of major life events experienced over the previous 6 months correlated with the severity of the individual cutaneous symptoms and with the total cutaneous symptom severity score (126).

In 31 patients with psychogenic excoriations, 58% had major depressive symptoms and 45.2% had obsessive compulsive disorder, which differed significantly from a control group of 31 patients with chronic urticaria (127).

A study of a consecutive sample of 109 inpatients with chronic itch showed that more than 70% had a psychiatric comorbidity (128). The most frequent diagnosis was “psychological impact on or psychosomatic cofactors in itch” (46.8%). Patients with prurigo nodularis (PN) were similar to those with psoriasis, with 18% cases of anxiety and 22% cases of depression, when 94 PN patients were compared with 91 psoriasis patients (129).

Out of 111 patients hospitalized in a mental health centre of an Israeli university hospital 32% reported itching (130). Out of 40 patients with depression 17.5% experienced itching during the depressive episode in a Polish pilot study. There was no predilection site for itching (131).

Genital and anal itch

Vulvar itching may occur in normal appearing skin and as a symptom of an underlying vulvar disorder (28). There is no clear and precise terminology. Primary or essential itch may describe itch without any visibly detectable disease, but may also be used for lichen simplex chronicus, which can follow chronic scratching. Some term itch according to the affected region (vulvar itch, scrotal itch, anal itch). Itching was the single most frequent presenting symptom, occurring in 70% of patients consulting a clinic for vulvar disease (132). “Dermatitis” was found in 25% of patients (133). In 50 women with vulval pruritus, 52% had at least one positive patch-test reaction to allergens such as cosmetics, preservatives and topical medications (134). Contact dermatitis should be considered in patients with genital itch.

Some dermatoses are not generally pruritic, e.g. psoriasis, unless they occur in warm and moist areas, such as the anogenital region. Out of 93 women with psoriasis 44.1% experienced vulvar discomfort, including 19.4% with itch, 10.8% with burning and 14% with both itching and burning sensations. Psoriatic lesions were present on the vulva in 23.7% of subjects. There was no significant correlation between burning/itching intensity and global psoriasis severity (56).

Localized itch, especially in the genital and perianal areas, is significantly more common in diabetic women and is significantly associated with poor diabetes control (113). Vulvar itching was significantly more common in diabetic women (18.4%) than in controls (5.6%). In some cases this may be due to predisposition to candidiasis or dermatophyte infections. A prospective study

in 42 women with pruritus vulvae and 42 asymptomatic controls did not provide evidence to support the routine determination of iron status in patients presenting with pruritus vulvae (135).

A total of 126 patients with perianal dermatitis were prospectively studied over a 4-year period (136). Anal itch was diagnosed in 5.6% of cases. As other diagnoses, e.g. AD, intertrigo, contact dermatitis, are also pruritic skin diseases it is most likely that the term "pruritus ani" resembled cases without any visible skin disease.

DRUG-INDUCED ITCH

In a prospective study of hospitalized patients, itch without any skin lesions occurred in 5% of drug-induced cutaneous side-effects (137). Drug-induced itch without any skin lesions can be caused by hydroxyethyl-starch (HES) in patients treated with HES for, e.g. tinnitus, acute hearing loss, or circulation-maintaining therapy in operative and intensive care. Various studies with differing methodology and study design have been published, estimating that 12–42% of patients treated with HES develop itching (138). In approximately two-thirds of cases HES-induced itching is generalized (138). According to a questionnaire survey in 253 patients discharged from intensive care units, 12.6% subjects who had received HES reported itch (139). The limit of HES to induce itching is 200 g HES. The duration depends on the cumulative dose, usually persisting for an average of 15 months (12–24 months after HES deposits in the tissue have been reduced).

Itching is a frequent side-effect following morphine treatment, but this occurs mostly as acute itch. Epidemiological studies of long-term treatment with morphines for treatment of chronic pain, e.g. in cancer patients, are missing. Anti-malarial drugs, such as chloroquine for, e.g. lupus erythematoses or malaria treatment, are prescribed very frequently worldwide. They induced non-aquagenic itching in 64.5% (140) and 75% (141) of treated patients, usually occurring 24–36 h after drug ingestion, resembling the time between the first and the second dose (36, 141–143). Chloroquine-induced itch occurs less frequently in children (36). Most studies do not document the duration exactly, but most studies describe itch remitting spontaneously within hours and days (36, 142, 143). Aquagenic itch in anti-malarial drug therapy starts after water contact, lasting for 10 min at high intensity, followed by a low intensity for hours without visible skin changes (142). Drug-induced itch during pregnancy may occur as acute chloroquine-induced itch for malaria therapy, affecting 64.5% within 24 h after drug onset and rated as severe by 60% of those affected (140). There are no epidemiological studies about itching in long-term treatment with anti-malarial drugs, including chronic drug-induced itch during pregnancy. All this may be due to: (i) remission

of itching within hours to days (142); and (ii) prompt drug removal after initiation of itch.

CHRONIC ITCH OF UNDETERMINED ORIGIN

Itch of undetermined origin is the term suggested by the International Forum for the Study of Itch (IFSI) when no underlying cause can be found for chronic itch (1). In the literature it has been mentioned as "itch or pruritus of unknown origin", "idiopathic itch/pruritus" or itch without any detectable skin or systemic disease.

The cause of itch was unknown in 13/43 (30%) cases of generalized itch (76). In 34 inpatients admitted for investigation and treatment of generalized itch, 3 had no aetiological factor (8.8%) (77). Analysing 74 problem cases of itching revealed 10 unexplained cases (13.5%) (78). Out of 132 German patients with chronic itching as a leading symptom, the cause of itch remained unclear in 10 patients (7.6%) in spite of intensive diagnostic investigations (48). In 3/84 Ugandan patients (3.6%) the cause of chronic itch was unknown (48). In a German retrospective study of underlying diseases in 263 patients with chronic itch no disease was found in 44.5% of patients. 55.6% of them, especially elderly patients, had many cofactors contributing to chronic itch, suggesting its multifactorial origin (82).

In a study in Singapore of 75 patients with generalized idiopathic pruritus, the legs, arms and back were the most frequently involved body parts, with a predominance of symptoms occurring in the evening and at night. Patients most frequently reported the itch as unbearable, bothersome and annoying (144).

CHRONIC ITCH: WORLDWIDE VARIATIONS

There are few epidemiological studies related to itch and ethnicity among adults. One such study describes German and Uganda patients with itch (48). Direct access to a specialist such as a dermatologist is not available in many countries, depending on the regional healthcare system. This explains the different referral patterns and different access to specialists.

In a Danish acute outpatient dermatological clinic "pruritus, and prurigo" were among the most prevalent diagnoses, accounting for 2.5% of all referred patients, but when considering all diagnoses one may assume that itch was an accompanying symptom in more than 50% of referred cases (145). Out of 740 patients admitted to a medical ward in Lahore, Pakistan, 8.1% experienced itching; 5.4% experienced itching caused by a skin disease and 2.7% caused by internal disease (146).

The BEACH programme is a continuous national Australian study of general practice activity, giving an overview of consultations in general practice. There were 2871 encounters with general practice in BEACH between April 1998 and March 2003 in which patients

described itch as one of the reasons for the encounter (147). The most common diagnosis was "contact/allergic dermatitis" (31%). At 14% of encounters the itch remained undiagnosed, being described by the general practitioner as "pruritus" (12%) or "rash" (2%).

Pruritic papular eruption (PPE) is a substantial cause of HIV-related morbidity in Sub-Saharan Africa. The prevalence of PPE varies from 12% to 46% depending on the geographical region. More than half of HIV-infected patients in some countries, including Uganda, may report the eruption of PPE as their initial disease manifestation (71, 72). In one study none of the Ugandan itch patients had an underlying systemic disease and in all HIV patients, itching was caused by dermatoses (48). It is likely that Ugandan patients with severe systemic diseases, such as renal failure, do not have a survival period that allows the initiation of itch, such as uraemic itch, or access to certain therapies such as haemodialysis. The lack of systemic itch reported in Uganda may be explained by characteristics of the Ugandan healthcare system, such as limited resources for healthcare (see www.health.go.ug) and lack of dermatology care (73).

CONCLUSION

The symptom of chronic itch represents a worldwide burden in the community as well as in specific populations. The causes of chronic itch appear to vary depending on age, ethnicity, characteristics of the regional healthcare system and the study population. Chronic itch is often ignored as a disease symptom in clinical studies. Research is complicated because the causes of chronic itch are frequently multifactorial, especially in elderly people. Making comparisons of existing studies is difficult due to differing methodology and a lack of standardized measures. All of these factors may explain why epidemiological research on itch has been disregarded for a long time. The symptom of itch is a challenge for clinicians, the structure of the regional healthcare system and the accessibility to specialized doctors, especially in non-Western countries. The study of chronic itch in the general and diseased population adds to the description of the burden of skin morbidity and should receive attention from physicians and other healthcare providers including healthcare planners.

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