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Pruritus in elderly patients: review of literature

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ABSTRACT

Pruritus is the most common symptom reported by dermatology patients, including the geriatric patient population. Due to population ageing, pruritus will be an increasingly common reason for medical consultations. Pruritus can involve both previously affected and unaffected skin, occurring as the only manifestation of the disease. Chronic pruritus lasting more than six weeks has a significant impact on patients' quality of life, often resulting in sleep disorders and depressive-anxiety disorders. Mechanisms responsible for pruritus in the elderly include abnormal dermal-epidermal barrier, age-related changes in the immune system, and central and peripheral neuropathy. Xerosis is considered the most common cause of pruritus in geriatric patients. Chronic pruritus occurs in the course of many dermatological conditions, as well as Internal diseases, and neurological or psychiatric disorders. The treatment of chronic pruritus in elderly patients may sometimes be a therapeutic challenge due to comorbidities or the complexity of the mechanisms leading to its onset. Each patient needs an individual and often multidisciplinary approach, taking into account comorbidities and polypragmasia. In addition to emollient skincare — which is the basis of skin care — and topical anti-inflammatory preparations for inflammatory skin disorders, biologics are increasingly being used in the treatment of pruritus, as well as drugs with antidepressant and antiepileptic effects.

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Keywords: senile pruritus, immunosenescence, xerosis, pruritus treatment, quality of life

INTRODUCTION

Pruritus is the most common symptom reported by dermatology patients. Pruritus can involve both previously affected and unaffected skin, occurring as the only manifestation of the disease. Pruritus is also associated with internal diseases such as inter alia, chronic kidney disease (CKD) and cirrhosis, or neurological/psychiatric diseases. Chronic pruritus, which is defined as an unpleasant sensation resulting in the scratch reflex that lasts for more than six weeks, is often the cause of sleep disorders, depression or anxiety disorders, significantly affecting patients' quality of life [1]. Chronic pruritus is also one of the most common symptoms in geriatric patients [2]. It represents a significant health problem among people aged 65 years and older. Studies on the impact of pruritus on patients' quality of life and the relationship between pruritus and chronic pain have shown that most patients would prefer to live a shorter life and be free of symptoms rather than live longer and struggle with chronic pruritus, as the detrimental impact of chronic pruritus is comparable to that of chronic pain [3, 4].

EPIDEMIOLOGY

According to a study by Matterne et al. [5], the lifetime risk of chronic pruritus was estimated to be approximately 23%, with an estimated prevalence of 13.9%. The prevalence of pruritus is thought to increase with age. A survey of employees at 144 German companies found that the prevalence of chronic pruritus increased with age from 12.3% in those between the ages of 16–30 to 20.3% in those aged 61–70 [6]. In studies conducted on other patient populations, the prevalence of pruritus did not differ significantly between the paediatric and adult populations and was above 8% [7] and ranged from approximately 12% to 41% for elderly patients [8]. In addition, pruritus appears to be the most common symptom reported in elderly patients. This is supported, among other things, by a study of 149 Thai patients [9] and 68 patients aged 50–91, in which 83% of those aged 80 and 90 years reported pruritus as the most common symptom [10]. A study conducted in Thailand revealed that 41% of patients suffered from pruritic conditions, of which xerosis was the most common (38.9%) [8]. Other studies of elderly patients found that the prevalence of pruritus ranged from 11 to 78% [2, 11, 12]. Nowadays, there is recognition that chronic pruritus will become a growing health problem due to an ageing population, especially in economically developed countries. The population aged 60 and older is growing at a rate of approximately 3% per year. It is estimated that the number of elderly people in the

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world will be 1.4 trillion in 2030 and 2.1 trillion in 2050 [13]. Consequently, the number of patients with chronic pruritic skin conditions will also increase.

PATHOPHYSIOLOGY

Several mechanisms are responsible for the development of pruritus in the elderly. These mechanisms include abnormal skin-epidermal barrier, age-related changes in the immune system, and central and peripheral neuropathy [14]. In addition, factors such as dermatoses and systemic or psychiatric disorders may cause pruritus in elderly patients [14, 15].

The changes in the immune system that result from ageing are called immunosenescence [16–19]. This process affects both acquired and innate immunity and induces increased autoreactivity of the immune system [20, 21], which may lead to autoimmune disease. Nonbullous pemphigoid, which is manifested by chronic pruritus associated with nonspecific skin lesions and the presence of circulating antibodies, is increasingly becoming the focus of research. In this case, pruritus may be the only symptom of the disease or may precede bullous pemphigoid for many years [22]. The immune system becomes increasingly inefficient with age. There is a several-fold increase in proinflammatory cytokines and acute phase proteins in the bloodstream of the elderly. The consequence is the appearance of chronic inflammation of low intensity. In addition, the function of T and B lymphocytes is significantly impaired. This is related, among other things, to the loss of naive T cells, which leads to a reduced ability of the immune system to respond effectively to infectious agents to which the elderly person has not previously been exposed [23]. It is implied that with the progression of immunosenescence, the balance between two main subclasses of helper T cells — Th1 and Th2 — is altered [24], exhibiting mutual antagonism. As a result of immunosenescence, Th1 lymphocyte-dependent cellular immunity loses importance in favour of defence mechanisms that are dependent on an "allergic" Th2-dependent response [25], making elderly patients more susceptible to chronic pruritus. Elderly patients with chronic pruritus also exhibit immune dysregulation in the form of lymphopenia, eosinophilia or hypogammaglobulinemia [25].

Xerosis, or dry skin, is considered the most common cause of pruritus in the elderly population. Its prevalence is estimated to range from 38% to as high as 85% [26–29]. Many changes in the skin of the elderly are associated with xerosis and include an increase in skin pH and protective function of the epidermal barrier and increased protease activity, reduced activity of sweat and sebaceous glands or reduced oestrogen levels [30]. From approximately 55 years of age, the epidermal pH becomes more alkaline [31, 32]. This affects the activity of the enzymes of the stratum corneum, resulting in reduced production of natural moisturizing factor [33] and ceramides [31, 34] through reduced activity of enzymes that affect their production and reduced secretion of lamellar bodies [35]. As pH increases, serine protease activity also increases, leading to the activation of protease-activated receptors (PARs) that induce pruritus in the skin [33, 35]. Pruritus induced by PAR-2 receptor stimulation is also observed in dermatoses such as atopic dermatitis (AD) [36]. The stratum corneum, as the outermost part of the epidermis, acts as a barrier against external factors and protects against transepidermal water loss (TEWL) [37]. As the skin ages, the normal process of exfoliation can be disrupted, leading to the appearance of dry skin [38, 39]. A link has been suggested between xerosis/pruritus and an acquired abnormality of keratinization and a reduced amount of water in the stratum corneum [39]. The intercellular lipid matrix is one of the components of the stratum corneum that determines epidermal barrier function [40]. The matrix consists of ceramides, cholesterol and free fatty acids [40]. On the other hand, lipids of the matrix originate from the lamellar bodies of the stratum granulosum (granular layer) [41]. In older and elderly patients, there is a reduced secretion of lipids of the lamellar bodies into the intercellular spaces, which is also affected by the aforementioned alkalinization of skin pH. These abnormalities significantly impair the epidermal barrier, leading to an increased risk of developing allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD) [42]. Therefore, special caution is recommended in terms of the use of topical anti-inflammatory preparations in geriatric patients [43]. In addition, when the epidermal barrier is impaired, proinflammatory cytokines are released to repair it, which leads to dermatitis [20]. Other factors that lead to xerosis include the aforementioned reduced activity of the sweat and sebaceous glands [44, 45] and endocrine disorders, mainly those related to reduced oestrogen levels in women with age [46].

Chronic pruritus may also be associated with neuropathic changes, resulting from damage to the central and peripheral nervous systems acquired with age [20, 21, 47]. In the elderly, neuropathic pruritus (NP) is found in several conditions such as shingles, diabetes, radiculopathies, and — in rare cases — neurodegenerative diseases of the central nervous system [48]. In the case of shingles, which is the most common viral skin infection in the geriatric population [11, 49], the prevalence of pruritus that persists after the disease — postherpetic pruritus — is 36% [50], while activation of pruritus-inducing neurons in the affected dermatomes is cited among the causes [51]. Diabetic patients may develop NP as a result of polyneuropathy [52]. A study of pruritus in diabetics revealed that pruritus of the trunk can be a common manifestation of diabetes-induced

peripheral nerve damage [52], while a link with scalp pruritus was established in geriatric patients with diabetes [2]. Brachioradial pruritus (BRP) and *notalgia paresthetica* are two radiculopathies associated with NP in elderly patients. In most cases, BRP affects the upper half of the body, involving the distal parts of the arms and the extensor parts of the forearms on both sides and sometimes can also be found on the proximal parts of the arms, neck, back or chest. In rare cases, BRP can be generalised or affect only one side of the body or the lower limbs. *Notalgia paresthetica* causes topical pruritus of the interscapular region in the T2–T6 dermatomes, which is often associated with pain, a tingling or prickling sensation. The secondary symptoms of pruritus are areas of hyperpigmentation.

CLASSIFICATION OF PRURITUS

The first step in the management of geriatric patients suffering from pruritus requires confirmation of the presence of primary skin lesions. Most patients with chronic pruritus can be diagnosed with inflammatory skin diseases. If no primary skin lesions are found, it may be a case of an invisible dermatosis or metabolic cause of pruritus, especially when the lesions on the skin are very subtle or only lesions secondary to scratching are visible. The IFSI (International Forum for the Study on Itch) classification distinguishes three groups of patients, taking into account the clinical picture of skin symptoms: 1) group 1 — pruritus involving previously affected skin; 2) group 2 — pruritus involving unaltered skin; 3) group 3 — pruritus associated with skin lesions secondary to scratching (neurotic excoriations, lichenification, papules, nodules). In the second stage of pruritus classification, the patient is classified into one of six categories: 1) skin-derived pruritus; 2) systemic pruritus; 3) neurological pruritus; 4) psychogenic pruritus; 5) mixed pruritus; 6) pruritus of unknown cause.

PRURITIC DERMATOSES

In the elderly, many dermatological conditions are associated with chronic pruritus, which shows higher intensity [2]. These include seborrheic dermatitis, contact dermatitis, psoriasis and scabies, among others. Seborrheic dermatitis is marked by erythematous and scaly lesions on the face, chest and scalp. The prevalence of seborrheic dermatitis in the geriatric population is 31% [52], and the associated pruritus is localized [53, 54]. In elderly patients, this dermatosis particularly often presents with Parkinson's disease, depression or anxiety disorders [55]. The increased risk of seborrheic dermatitis in patients with Parkinson's disease may be related to parasympathetic overactivity and increased melanocyte-stimulating hormone levels [56]. It is increasingly believed that seborrheic dermatitis is one of the first symptoms of Parkinson's disease, occurring even before motor dysfunction [57].

A disease whose prevalence is increased in the elderly due to long-term stays in hospitals or nursing homes is scabies [58]. Patients are observed to have scattered papules or erosions, scabs or neurotic excoriations secondary to scratching. These lesions are often very discrete, hence the need for a thorough examination of the patient, taking into account the spaces between the toes, soles, genitalia, nipples or umbilicus. The associated pruritus is very intense and generalised, often with greater intensity at night; however, this should not determine the diagnosis. Patients under immunosuppression resulting from systemic conditions or secondary to treatment with topical or systemic immunosuppressants are at particular risk of developing hyperkeratotic (Norwegian) scabies [59].

Chronic prurigo is a dermatosis that occurs in all age groups but is more commonly diagnosed in middle-aged women. It presents with chronic pruritus and lesions secondary to chronic scratching, for example, scratch marks and scars. Moreover, due to the complex clinical picture of chronic prurigo, several subtypes of the disease are distinguished according to predominant skin lesions observed: nodular prurigo, papular prurigo, plaque prurigo, umbilicated prurigo and linear prurigo [60]. Skin eruptions are usually located symmetrically on the distal parts of the limbs, buttocks or trunk. Intense pruritus is a characteristic symptom of the disease; however, some patients also experience burning or stabbing pain [61].

Contact dermatitis — both allergic and irritant — is also common in the elderly population; its prevalence ranges from 33% to 64% [62]. This is most likely related to immunosenescence and abnormal epidermal barrier function [63]. The development of contact dermatitis in the elderly is most common on the lower limbs.

Nummular eczema, considered a type of contact eczema, is an inflammatory dermatosis characterised by severe pruritus and the presence of round erythematous plaques, within which exfoliation is visible in the chronic phase. The peak incidence is between the ages of 50 and 70, occurring more often in men [52]. Some researchers consider frothy nummular eczema to be a variant of AD that appears in late life [64].

Psoriasis as a chronic inflammatory dermatosis is another condition prevalent in the geriatric population [65]. Pruritus is the most common symptom among this group of patients [66] and is often observed in the genital area [67, 68], hence the need for careful evaluation of genital involvement.

Grover's disease, a transient acantholytic dermatosis, is more commonly seen in elderly men. Numerous papular and papulovesicular eruptions are found mainly on the

trunk and proximal parts of the limbs. Its primary symptom, however, is pruritus. Causes of the occurrence of the disease in the elderly include immunosenescence [20]. Factors that stimulate the appearance of skin lesions are sunlight and infections [68]. Cases of the disease were described in patients with malignant neoplasms of the kidney, stomach or genitourinary system [69–71].

Intense pruritus also occurs in cutaneous T-cell lymphomas, especially in the advanced stages of the disease. Often, pruritus is the predominant symptom of slow-onset T-cell lymphomas. Its occurrence is associated with increased expression of interleukin-31 (IL-31) [72].

PRURITUS WITHOUT VISIBLE SKIN SYMPTOMS

In the absence of primary skin symptoms, consideration should be given to a metabolic cause of pruritus and pruritus associated with systemic diseases, neurological pruritus and psychogenic pruritus or so-called invisible dermatosis. The most common condition causing pruritus without visible skin symptoms is xerosis, which was discussed earlier. Scabies is sometimes included in this group due to its very discrete skin lesions or lack thereof. A number of drugs responsible for the induction of pruritus, sometimes without visible exanthema, have also been described. This is confirmed by a large study from the 1980s, which found that pruritus without skin rash represented 5% of adverse drug reactions among inpatients [73]. In another study, drug-induced pruritus without visible exanthema was reported in 12.5% of cases [74]. Some of these drugs can cause liver and biliary tract dysfunction and thus generate pruritus. Hydroxyethyl starch may cause pruritus with a delayed onset, without visible skin lesions. Intense pruritus with minimal or no skin lesions was also described in the course of lichen planus, dermatitis herpetiformis, urticaria or bullous pemphigoid.

There are increasing reports of pruritus as a single or early manifestation of various autoimmune conditions such as systemic sclerosis [75] or bullous pemphigoid. The course of bullous pemphigoid traditionally involves intense pruritus and well-tense blisters on an erythematous background [76]. The frequent co-occurrence of psychiatric and neurodegenerative diseases was described [77]. One in five patients with pemphigoid does not have typical blisters, and such a condition is called nonbullous pemphigoid [78], which can develop severe pruritus and a wide spectrum of clinical manifestations resembling other pruritic skin conditions [79–81]. The most common lesions observed are papules or nodules and urticarial lesions [79–81]. Bullae may occur in 10% of patients as the disease progresses [82]. For this reason, the disease is usually diagnosed after a long delay [82]. A study of seven Dutch nursing homes found the prevalence of pemphigoid to be 6%, with more than half of the patients having no previously established diagnosis and presenting no blisters [83]. Nonbullous pemphigoid appears to be an unrecognised cause of pruritus [84], and this is facilitated by its atypical clinical presentation. Indirect and direct immunofluorescence tests should be performed to diagnose the condition, revealing linear deposits of IgG and/or C3 at the dermal-epidermal junction. Occasionally, IgE deposits may be present as the only immunological component or in addition to IgG, along with circulating antibodies [78]. Histopathology is nonspecific and should not determine the diagnosis [79].

Pruritus may be associated with many internal conditions such as CKD or chronic liver disease, as well as endocrine and haematological diseases, which statistically tend to develop with age. Elderly patients are also more likely to develop cancer, and malignancy-associated pruritus is called paraneoplastic pruritus. Pruritus can also occur as an adverse drug reaction. This is facilitated by the phenomenon of polypragmasia in geriatric patients. Drugs with the greatest known pruritogenic potential include calcium channel blockers (particularly popular in elderly patients), angiotensin-converting enzyme inhibitors, thiazides [85], salicylates, opiates and antimalarials [54]. New drugs for melanoma therapy, such as vemurafenib and ipilimumab, may also cause pruritus — according to literature, in 29% [86] and 31% [87] of patients, respectively. Drug-induced pruritus occurs by several mechanisms, including the induction of drug-induced skin rashes, phototoxicity, neuropathies, xerosis or deposits of drugs or their metabolites in the skin [88].

Pruritus may be associated with mental disorders such as depression or be the only symptom present in patients — in both of these situations, it is psychogenic pruritus. In the case of psychiatric conditions, pruritus may be a symptom of these or lead to the development of psychiatric disorders, so it is necessary to determine which disorder appeared first. In patients suspected of psychogenic pruritus, other possible causes of pruritus should be ruled out first. Furthermore, the patient should meet at least three of the seven supporting criteria developed in 2007 by the French Psychodermatology Group [89].

TREATMENT

Selecting an appropriate treatment for pruritus can be problematic due to diagnostic difficulties, comorbidities or the complexity of the mechanisms leading to pruritus. If possible, the primary cause of pruritus should be determined before implementing treatment. In certain cases, such as scabies, paraneoplastic pruritus, CKD-associated pruritus or cholestasis-associated pruritus, treatment of the underlying disease is often sufficient.

The fundamental therapy of pruritus in geriatric patients, regardless of the cause, is the use of emollients and gentle skin care. Patients should avoid high-pH cleansers and those containing alcohol [90]. The most recommended emollients are those with ceramides, cholesterol or free fatty acids in their composition, allowing the regeneration of the epidermal barrier. Preparations containing urea (usually at a concentration of 5–10%), menthol and other cooling agents or topical anaesthetics also reduce the severity of pruritus. Moisturising creams with fragrances and preservatives should be avoided because of the possibility of causing allergic contact dermatitis.

Topical glucocorticosteroids or calcineurin inhibitors should be used in the case of pruritic inflammatory skin conditions. Topical glucocorticosteroids are not antipruritic drugs, however, by reducing inflammation they reduce the associated pruritus. In addition, they bring rapid improvement and stop the vicious circle mechanism of itching-scratching. Topical glucocorticosteroids should be used briefly due to the risk of skin atrophy. Moreover, long-term use can exacerbate pruritus due to inhibition of prostaglandin D2 production [91]. Calcineurin inhibitors such as tacrolimus and pimecrolimus, unlike glucocorticosteroids, do not cause skin atrophy, which is why they are recommended for long-term therapy [92]. They are particularly popular in the treatment of AD, seborrheic dermatitis and contact eczema [93]. Despite much debate, their effect on the risk of developing cutaneous lymphomas or non-melanoma skin cancers was not proven [94–96].

Oral, especially second-generation, antihistamines are considered relatively safe and thus are often used in the treatment of pruritus. First-generation antihistamines (hydroxyzine, diphenhydramine, dimethindene) not only block histamine H1 receptors but also other receptors, including muscarinic or serotonergic receptors. Therefore, they should not be used in elderly patients due to adverse effects such as drowsiness or anticholinergic symptoms. In addition, hydroxyzine (which is heavily used by the elderly) is thought to increase the risk of delirium or dementia in addition to its high anticholinergic activity [97, 98]. Data supporting the efficacy of antihistamines in the treatment of pruritus other than chronic spontaneous urticaria are severely limited [99].

The treatment of choice in patients with multiple chronic diseases and associated pruritus appears to be ultraviolet-B phototherapy and UVA photochemotherapy. It is particularly popular in inflammatory dermatoses such as psoriasis and AD, cutaneous T-cell lymphomas or cholestatic or uremic pruritus [100]. In the case of phototherapy, it is important to be mindful of accelerated ageing and an increased risk of skin cancers.

Immunosuppressive drugs are also used in the treatment of pruritic dermatoses. Cyclosporine is effective in reducing pruritus in AD and chronic urticaria. Methotrexate reduces pruritus sensation in patients with psoriasis, and azathioprine at a dose of 50–200 mg/day was found to be effective in inhibiting pruritus in patients with bullous pemphigoid [101].

Recent studies reveal the antipruritic properties of various biologics. An example is dupilumab — a monoclonal antibody that inhibits IL-4 and IL-13 cytokine-induced responses, which is used in the treatment of AD. When applied subcutaneously every fortnight, dupilumab significantly reduces pruritus and disease activity [102, 103]. Until recently, it was used off-label for the treatment of diseases with severe pruritus, such as nodular prurigo [104, 105], chronic spontaneous urticaria [106], allergic contact dermatitis [107] and pemphigoid [108, 109]. In September 2022, the U.S. Food and Drug Administration (FDA) registered dupilumab for the treatment of patients with nodular prurigo. In December 2022, dupilumab received the same registration in Europe as well. Nemolizumab, a monoclonal anti-IL-31 receptor antibody, which is in final phase III trials in patients with nodular prurigo, also causes reduced pruritus sensation and improved sleep quality [110]. Upadacitinib, abrocitinib, and Janus kinase inhibitors were found to significantly reduce pruritus in AD patients compared to a placebo [111, 112]. Omalizumab (a humanised monoclonal anti-IgE antibody that binds to high-affinity IgE receptor) was found to rapidly and effectively reduce pruritus and the number of skin lesions in chronic spontaneous urticaria [113]. A meta-analysis confirmed the inhibition of blistering and reduction of pruritus in patients with bullous pemphigoid [114]. In cases of pemphigoid refractory to conventional treatment, omalizumab was also used in combination with the previously mentioned dupilumab [115].

Opioid receptor agonists and antagonists are another group of drugs used in various forms of pruritus, especially in cholestasis and uraemia. Difelikefalin is an opioid, a kappa-opioid receptor agonist, which in April 2022 was approved in Europe for the treatment of moderate to severe CKD-associated pruritus in haemodialysis patients [116]. Butorphanol reduces the severity of pruritus in patients with non-Hodgkin's lymphoma or cholestasis. It should be noted, however, that butorphanol has no registration for these indications and is used off-label, including in refractory cases of pruritus [117]. Naloxone and naltrexone — opioid receptor antagonists — are used in the treatment of cholestatic and uremic pruritus [118]; however, opioid-induced pruritus is not an indication of their use. Anxiolytics and/or antidepressants from the selective serotonin reuptake inhibitor (SSRI) group, such as paroxetine at a dose of 20 mg/day

[119] or sertraline, are used in the therapy of psychogenic pruritus. Tricyclic antidepressants (TLPDs) are less commonly used in this context. Antidepressants from both of the aforementioned groups also show a beneficial effect in the treatment of chronic paraneoplastic pruritus, in the course of cholestasis or AD [120]. For NP, capsaicin cream and antiepileptics such as gabapentin and pregabalin [99] are used, which are also reported to be popular for postherpetic neuralgia (PHN) [121]. Gabapentin is also effective in treating CKD-associated pruritus [122, 123]. Particular caution should be exercised in elderly patients due to the numerous adverse effects.

CONCLUSIONS

Pruritus in geriatric patients is a common health problem. Due to population ageing, pruritus will be an increasingly common reason for medical consultations. Therefore, it is essential to understand the pathophysiology and complexity of the mechanisms that lead to its formation. The management of geriatric patients requires an individual and often multidisciplinary approach that takes into account comorbidities and polypragmasia, which can have a limiting effect on therapeutic options. An important diagnostic aspect of pruritus is its occurrence as the only manifestation of the disease, which triggers the need for an in-depth analysis of the problem. In this case, it is always important to be aware of rarer and less typical variants of various dermatoses, in which pruritus may precede the full-blown development of the disease for many years.

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