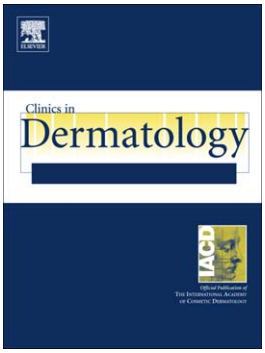

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Causes, Pathophysiology, and Treatment of Pruritus in the Mature Patient

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Abstract

Chronic itch is a common and debilitating health condition in the elderly. There are several common causes of itch in the elderly population, such as skin xerosis, immunosenescence, and neuropathic changes. In addition, skin diseases, such as seborrheic dermatitis and stasis dermatitis, systemic conditions (end-stage renal disease and diabetes), or psychogenic derailments, such as depression, anxiety, and dementia, can all serve as triggers of pruritus. Polypharmacy, a common occurrence among the elderly population, may also serve as a cause of itch that may or may not be accompanied by dermatitis. Such medications, as thiazides and calcium channel blockers, have been found to have a connection with pruritus in the advance aging population.

Determining the exact trigger for pruritus in the elderly may be challenging, especially, because itch can be idiopathic in many cases. The role of treatments should not only take into account elimination of various underlying cutaneous, systemic, or psychogenic conditions associated with itch, but also focus on the skin changes that are characteristic of the aging process. Development of such treatment options can be guided by elucidation of the mechanisms underlying the pathophysiology of itch in the geriatric population.

KEY WORDS: Elderly itch, pruritus, geriatric itch, skin aging, systemic diseases, cutaneous conditions, treatment.

Introduction

Chronic itch is defined as itch that lasts for more than 6 weeks [1]. The prevalence of chronic itch in the elderly patients is reported to range from 7% to 45.9% in various countries [2, 3]. In a recent study conducted in a geriatric Hispanic population, itch prevalence was estimated at 25% [2]. The mean itch intensity was reported in a numeric rating scale ranging from zero to ten, as 6 ± 2.1, which is considered moderate to severe [2]. A large retrospective analysis we conducted in chronic itch patients demonstrated that older patients above 65 years of age rate their itch intensity higher than younger patients [4].

Chronic pruritus is considered to be a common health problem in the elderly population, and negatively impacts the quality of life in the affected individuals [2, 5]. In addition, chronic itch has a deleterious effect on the quality of life of elderly patients and can be compared to common ailments, such as pain, constipation, and sexual dysfunction [3]. Causes of chronic itch in the elderly can be a result of multiple conditions, including (1) aging process itself (immunosenescence, xerosis), (2) skin conditions (psoriasis, eczematous dermatitis, skin cancer), (3) systemic conditions (liver insufficiency, end stage renal disease, HIV), and (4) neuropathic and psychogenic causes. Assessing chronic itch in an elderly patient may be challenging, and in some instances, requires laboratory tests and imaging studies to make a correct diagnosis. Given the polypharmacy and other comorbidities in the elderly, treatment can be a challenge in this population [6].

Pathophysiology of Chronic Itch

Research conducted in recent years made it possible to better understand the neural mechanisms underlying itch. It is known that the itch sensation mainly emanates from the upper levels of the skin due to inflammation and interactions between immune cells, keratinocytes, and nerve fibers [7]. The itch sensation is mostly transmitted by unmylienated C-fibers. These are pruritus-specific nerves and are mainly histamine-independent [8]. In the dorsal horn, these C fibers synapse with the second order projections. The thalamus then receives the itch signal that ascends via the contralateral spinothalamic tract. Itch is transmitted from the thalamus to several areas of the brain responsible for sensation, evaluative processes, reward, emotion, and memory [8]. Patients affected by chronic itch may experience a component of peripheral or central neural

hypersensitization, including alloknesis and hyperknesis, which play a role in itch perception [8, 9]. Due to a variety of interactions that contribute to development of itch sensation on the cell, tissue, and organ levels, the pathophysiology of itch is complex, and there are many etiologies with different mechanisms.

Aging Changes that Predispose to Itch

Three different mechanisms have been proposed as common causes of itch in the elderly:

1. xerosis (dry skin)
2. immunologic changes
3. neuropathic/neural changes.

Xerosis, or dry skin, is one of the most common causes of pruritus in the elderly. The prevalence of xerosis in patients with chronic itch in one study was found to be as high as 69% [2]. Xerosis can present with or without itch. Typically, there is no dermatitis present in xerosis; however, the patient's scratching to alleviate itch my lead to secondary lesions [10]. The exact mechanism of chronic itch in xerosis has not been elucidated; however, multiple causes of skin xerosis can be related to chronic itch. The development of xerosis in the elderly is believed to be a result of a combination of multiple factors, such as:

1. defective desquamation
2. changed function of proteases
3. changes in surface lipids
4. changes in pH
5. decreased estrogen levels [5, 10, 11].

1. **Defective Desquamation**. The process of desquamation involves multiple key components [10]. The corneodesmosomes in the elderly patients suffering from xerosis do not undergo the same breakdown process compared to the normal skin [10].

2. **Changed function of proteases**. The process of defective desquamation in xerosis mentioned above may be linked to ineffective proteolysis of the corneodesmosomes [12]. On study showed that there are different proteases that accomplish various tasks in the

process of desquamation [13]. Proteases are known to activate C nerve fibers via the PAR 2 (Proteinase activating receptor 2) to transmit itch [7].

3. **Change in surface lipids**. The desquamation process of the skin is also dependent on the lipids in the stratum corneum [10, 14]. The total amount of lipid contained in the aged skin seems to be decreased; however, there are no definitive reports explaining the exact mechanism of influence of the lipid components on xerosis involving the elderly [14,15].

4. **Changes in pH**. With the aging process, the pH of skin becomes more alkaline. This change in skin pH may alter the enzymatic activity in the upper layers of the epidermis, which in turn can lead to dry skin and activate proteases to induce chronic itch. In addition, chronic itch is thought to be influenced by changes in pH, because it leads to increase in the serine protease activity; this in turn leads to activation of protease-activated receptor 2 (PAR2). This may explain why it is important to consider interventions to lower skin pH in the elderly suffering from xerosis [16].

5. **Decreased estrogen levels**. Skin alterations predisposing to dryness (and possibly itch) have been associated with decreased amounts of estrogen in postmenopausal women. The two categories into which these skin alterations can be divided are epidermal and dermal. Epidermal changes consist of thinning of the epidermis, lowered hydration, increased TEWL, and alterations in the composition of lipids. Dermal changes include decreased glycosaminoglycans and loss of collagen [17]. While it is believed that many of these alterations can have an association with itch, more research studies have to be done to elucidate the exact mechanism of how decreased estrogen levels influence chronic itch [18].

Immunologic changes. As the aging continues, the immune system undergoes a process of senescence [19]. Such processes as immunologic auto-reactivity can be attributed to the state of immunosenescence. A recent report of several elderly patients suffering from chronic idiopathic pruritus showed evidence of immune dysregulation, such as “T and B cell lymphopenia, eosinophilia, and hypogammaglobulinemia” [20]. The authors suggest that with the progression of immunosenescence the protective effects of Th1 cells are diminishing, which contributes to

higher influence of Th2-driven allergic reactions [20]. This loss of immunologic balance increases susceptibility of elderly to chronic itch [20]. The dysregulation of T cells seen with aging may be associated with the loss of self-tolerance and resulting increase in auto-immune events [21]. Additionally, Langerhans cells found in the aging epidermal layer of the skin not only decrease in number but tend to have fewer dendrites. This finding might suggest a barrier to the trapping of antibodies.

Neural dysfunction. Chronic itch can represent a result of the damage to nerves responsible for detecting, transmitting, or processing itch [22, 23]. Lesions in either peripheral or central nervous system could potentially lead to chronic neuropathic itch [22]. Several forms of neuropathic itch have been described in the elderly population:

- Brachioradial pruritus
- Notalgia paraesthetica
- Multilevel Symmetric Neuropathic Pruritus (MSNP)
- Shingles and post herpetic neuralgia
- Post stroke itch
- Diabetes mellitus
- Trigeminal trophic syndrome.

Additionally, age-related neuropathy may manifest as delayed appearance of such features as pain, swelling after scratching, and erythema, thus predisposing elderly patients with itch to significant self-inflicted cutaneous damage. Another explanation that has not been confirmed is a decay in neural inhibitory fibers to itch; thus, predisposing the elderly to chronic itch.

Brachioradial pruritus is a type of neuropathic itch that commonly involves the dorsolateral arm. It appears either unilaterally or bilaterally; however, it may also involve the neck, back, shoulder, upper part of the arm, and chest [24]. Patients commonly perceive not only itch, but also burning, tingling, or stinging sensations. It is suggested that the reason for neuropathic itch in this condition is largely due to cervical spinal stenosis and C5 –C8 compression [25]. Interestingly enough, sun exposure might be another potentially exacerbating factor [24]. There are several possible age-related confounders regarding these suggested theories, so additional studies have to be conducted to elucidate the etiology of this phenomenon [9, 24].

Notalgia paraesthetica (NP) represents another type of neuropathic itch that mainly affects middle- to-older age individuals. A retrospective study was conducted in which characteristics of individuals affected by NP were evaluated. According to the results, 73.8% of patients were older than 40 years old at the onset of their disease [26]. Individuals suffering from NP typically experience unilateral pruritus between their shoulder blades [26]. The researchers also came to a conclusion that half of the pruritic dermatomes were located within T1-T5, with T2, T4, and T5, being the most commonly involved [26]. As with brachioradial pruritus, the etiology of NP is not fully clear. There are some theories suggesting that damage to spinal nerve or other spinal abnormalities, such as dorsal rami compression, could be a possible explanation of the cause of neuropathic pruritus [9, 26]. Another theory is that damage to peripheral nerves is the etiology underlying NP [26].

Multilevel Symmetric Neuropathic Pruritus (MSNP) is a term suggested to describe "generalized, symmetric, neuropathic pruritus." [27] This is a theory involving an association between pruritus and the neural system, suggesting that nerve dysfunction is involved in the pathogenesis of itch [27]. The investigators of this study reported that based on the imaging findings, nerve impingement may contribute to this dysregulation. This finding further supports the contribution of the neuropathic aspect to development of pruritus.

Shingles is the result of the varicella zoster virus reactivation in older age (cause of chicken pox during childhood). The eruption is mainly self-limited and is present for up to 2 weeks [28]. Post herpetic neuralgia, a common bothersome neuropathic painful complication associated with shingles, also has a high prevalence of itch [29]. It is believed that post-herpetic itch shares a similar pathophysiology with PHN, where neurons involved in itch sensation become damaged [22].

Post stroke itch. Stroke is a common health problem affecting the elderly [30]. A study conducted described nine patients, who began to experience itch mainly on the affected side three to six weeks after a stroke [31]. In these patients, either the internal capsule or middle cerebral artery were affected by the stroke; five of the lesions involved deep brain structures,

such as the thalamus and subcortical areas [31]. If the lateral medulla is the specific location of the damage, this condition is termed Wallenberg syndrome; the typical presentation of the patients includes a combination of itching, painful thermoalgic hypoaesthesia and contralateral trigeminal hypoaesthesia, cerebellar dysfunction, nausea, and vomiting [9].

Diabetes Mellitus (DM) is commonly seen as a cause of pruritus in the elderly patients. While it is a systemic ailment, it can also be categorized as a form of neuropathic itch [32, 33]. Small fiber polyneuropathy is one of the suggested mechanisms underlying pruritus in diabetic patients [22]. Truncal pruritus of unknown origin is more frequently seen in patients having diabetes compared to healthy controls; this finding suggests a possible association with diabetic polyneuropathy [33]. Another common problem that disproportionately affects elderly patients with diabetes is scalp itch [2]. There is a theory that small fiber neuropathy is related to the development of scalp itch in geriatric diabetic patients [34]; furthermore, itchy scalp may represent one of the first symptoms in the elderly patient of diabetes, and the diagnosis of DM should be considered [2].

Trigeminal trophic syndrome is a rare neuropathic pruritic condition caused mainly by trigeminal nerve damage (which can be a result of surgery or stroke in the trigeminal nuclei). There can be central or peripheral causes. This diagnosis might be considered in elderly patients presenting with chronic itch in an area innervated by the trigeminal nerve [22].

Cutaneous Causes

Chronic itch in the elderly patients has been associated with a variety of skin ailments. Cutaneous conditions can be the primary cause of itch, or can influence the perception of itch in the elderly [2]. For this reason, it is very important to concentrate on any skin rash leading to pruritus in the elderly population.

1. **Seborrheic dermatitis (SD)** is seen with a very high prevalence in the elderly patients. It is caused by an abnormal inflammatory process affecting areas of skin that are rich in lipid. Among these areas are eyebrows, zones around the nose and ears, scalp, axillae, parts of the chest and back, and the groin. SD presents as erythematous patches or red-

brown papules with a greasy yellow colored scale. This condition seems to more commonly afflict patients with underlying neurological conditions, such as Parkinson's disease or other CNS problems, both of which are frequently seen in the elderly [28].

2. **Contact dermatitis (CD)** is an inflammatory skin reaction caused by a direct interaction with a particular substance. It can lead to chronic itch in the geriatric population [2]. Contact dermatitis can be divided into two types: Irritant and allergic [35]. Irritant Contact Dermatitis (ICD) is encountered more frequently than Allergic Contact Dermatitis (ACD). The pathogenesis between ICD and ACD differs. ICD results from a non-specific inflammatory reaction; neither prior sensitization, nor genetic predisposition to allergy are required. On the other hand, ACD represents an immune reaction to a particular substance, and is mediated by memory T cells [35]. Differentiating ACD from ICD clinically may be challenging. Lesions may represent different parts of the spectrum, ranging from acute (erythema, popular/vesicular rash) to subacute (scaling, serous exudate) to chronic (hyperkeratosis, fissures, lichenification) signs [35]. Patients are diagnosed based on the history, symptom distribution, and patch test [35]. Possible theories regarding the etiology of CD have been suggested, and include skin changes related to aging (such as alterations in epidermal lipids), impaired barrier function, and increased time required for restoration of epidermal barrier [35, 36]. As mentioned previously, the common elderly ailment, xerosis, can promote the exposure to irritants and allergens [35]. A decrease in Langerhans cells, as well as pro-inflammatory cytokines have been implicated in the immune system of the elderly patients, which may lead to decreased inflammatory response; therefore, result interpretation of the patch testing in the elderly may be influenced by the slower reactivity onset, as well as decreased reaction intensity. For this reason, special attention should be given, when evaluating the results in the older patients [35]. Other predisposing factors commonly found in the elderly population include stasis dermatitis, extremity ulcers, implanted devices, denture or hearing aid material, incontinence, and ostomies [35].

3. **Nummular dermatitis** has a high prevalence in the elderly [28]. The presentation of this condition varies, ranging from erythemic patches with vesicles to dry scaly patches;

however, lesions typically have the shape of a coin and are 1 to 5 cm in diameter [28]. Intense pruritus usually accompanies the lesions. The pathophysiology of these lesions is largely unknown. One study investigating nummular dermatitis in conjunction with the innervation of the skin showed that the skin within these lesions tends to have less epidermal nerve fibers compared to healthy skin. This finding suggests involvement of nerve damage or other inflammatory markers as a potential cause of itch [37].

4. **Lichen simplex chronicus (LSC)** is characterized by lichenification that results from continuous scratching. It represents a common cause of chronic itch in the elderly [2]. Areas commonly affected by LSC include the genital area (particularly the scrotum in men and the vulva in women), as well as the scalp, neck, arms, ankles and shins [28]. While the pathophysiology of this disease is not entirely clear, it has been suggested to be related to neuropathic processes or dry skin. Additionally, LSC has been associated with depression [38, 39]. For this reason, it is important to make a correct diagnosis in patients, who present with LSC, and to assess them for depression.

5. **Stasis Dermatitis** and varicose veins are frequently seen in geriatric population and represent a consequence of a malfunctioning venous drainage from the lower limbs [40]. This can lead to chronic itch, and therefore should be investigated as a cause of chronic pruritus in the lower extremities of elderly patients [2].

6. **Psoriasis** represents a common skin disease found in the elderly population [41–43]. Psoriatic lesions can be seen at locations of trauma in the elderly patients, such as around eyeglasses or hearing aids, a phenomenon known as Koebnerization [43]. It is believed that development of psoriasis is associated with a dysregulation of the immune system and cytokine activation [43]. Psoriasis can be related to a variety of comorbid conditions, such as psoriatic arthritis, cardiovascular disease, and metabolic syndrome [42]. The most common symptom seen in elderly patients affected by psoriasis is pruritus [44]. While the exact mechanism of itch pathophysiology in psoriasis remains unclear, various cytokines and neuropeptides have been suggested to be of significance. These include nerve growth factor, substance P, neurokinin A, and cytokines like TNF-alpha, Interleukin-2,

Interleukin-23, and Interleukin-17 [45, 46]. Polypharmacy, as mentioned earlier, is a common problem affecting the elderly population. It is known that some medications may incite psoriasis [42]. Several of these medications related to exacerbation of this condition include ACE inhibitors, beta-blockers, anti-malarials, lithium, as well as a sudden cessation of glucocorticoids [43].

7. **Transient acantholytic dermatosis or Grover disease (GD),** is most commonly observed in elderly Caucasian men. It presents as intensely pruritic papules found on the trunk and proximal extremities. GD has been associated with multiple factors, such as exposure to sunlight, high temperatures, sweat, malignancies, and skin infection reaction. While tumor necrosis factor alpha (TNF- α) and other mediators of inflammation have been associated with pruritus in these individuals, the exact etiology has yet to be determined [47].

8. **Scabies** typically presents in form of pruritic papular or vesicular dermatitis involving the intertriginous areas, hands, wrists, elbows, and feet [48]. Long term elderly care facilities are known to be the places of outbreaks [48]. A retrospective study evaluating an outbreak that happened in a nursing home found that the average time between the onset of symptoms and diagnosis was 38 days [48]. The contributing factor to delayed diagnosis might have been the fact that the majority of patients had no pruritic complaints, while others had a papulo-squamous eruption [48]. Decreased itch complaints may have been associated with dementia, being bedridden with contractures, and immune changes related to age [48]. In addition to the above findings, epidermal tissue is more flat and has less undulations in the skin of elderly individuals. The researchers hypothesize that this change may contribute to greater and faster skin coverage by the mite, and may aid in explaining the finding of elderly patients having more widespread scabies lesions [48].

9. **Skin Cancers** are commonly noted in the Caucasian elderly population. The most common skin cancer in patients is basal cell carcinoma, followed by squamous skin carcinoma. One prospective study suggests that these cutaneous cancers may be

accompanied by pruritus and pain. The authors made an observation that superficial lesions (such as basal cell carcinoma) are preferably associated with itch, whereas deeper lesions (like squamous cell carcinoma) are rather associated with pain. Another association was found between the level of inflammation and the severity of pruritus or pain – Moderate to marked inflammation corresponded to more itch or pain. Additionally, the presence of neutrophils and eosinophils was found in the context of greater pruritus and pain [49].

10. **Cutaneous T-cell lymphoma (CTCL)** is a neoplasm involving T-cells that grows within the skin. It is most commonly seen in patients over 50 years of age. One of symptoms often present in CTCL patients is severe pruritus [50]. Two of the most commonly seen types of CTCL are mycosis fungoides and Sezary syndrome. Mycosis fungoides with plaques, tumors and folliculotropic cause severe itch. In Sezary syndrome, generalized pruritic erythroderma is seen, and abnormal T cells can also be found in the peripheral blood and lymph nodes; this condition is thought to be more aggressive [51]. One possible theory on the etiology of chronic itch in these patients suggests the involvement of Interleukin-31 [51].

11. **Bullous pemphigoid (BP)** is an autoimmune condition that has been found to be in association with pruritus in the elderly population [21]. The pathophysiology of this disease is believed to involve an IgG autoantibody that binds particular antigens found in the basal membrane; typically, this binding then results in the appearance of a blister [21]. BP does not always present with bullous lesions but may represent an atypical variant without bullae. According to several reports, such an atypical presentation without any skin lesions, but only consisting of pruritus can be found in the elderly [21]. While there are multiple ways in which BP can clinically present in the patients, all of the types are associated with itch [21]. Due to the fact that pruritus might be the only manifestation of BP in the elderly patients, the diagnostic workup including serology to detect IgG autoantibodies, as well as skin biopsies should be considered.

Systemic Causes

The presentation of chronic itch in systemic conditions may or may not involve a primary eruption. Among several systemic maladies associated with chronic itch in the elderly population are chronic kidney disease, pruritus related to cholestasis, thyroid dysfunction, malignancy, HIV as well as some medications.

1. **Chronic kidney disease** (**CKD**) pruritus is found in a large number of patients afflicted by advanced kidney disease, including those receiving the dialysis treatment. Itch can be present in up to 70% of those on dialysis. Based on the observations that both the incidence and prevalence of chronic renal disease are on the rise, and dialysis is a commonly used treatment option in the elderly, therefore it is expected the number of patients with chronic itch would increase [52, 53]. The presentation of the patients is typically characterized by localized or generalized itch which is most frequently found on the back areas. The occurrence of symptoms may be daily (or less frequently) and often worsen during the night time [53]. The sleep quality may suffer which in turn negatively impacts the quality of life of the patients suffering from CKD-associated itch [53]. Both neuropathic damage and alterations in the immune system have been suggested as possible players in the pathophysiology of this condition. A study compared MRIs of end-stage renal disease patients compared to those of the healthy patients [54]. The results pointed to a possible involvement of central neuropathy in the development of CKD-associated itch, as several particular brain areas (S1, SPL, precuneus, insula, and ACC) have been shown to be activated in patients with chronic kidney disease [54]. In addition, the authors made an observation of increased density of the grey matter in several limbic system components, such as nucleus accumbens, amygdala, and hippocampus, as well as in the brainstem [54]. Other explanation for, uremic itch is thought to be related to increased levels of various immune molecules, such as high-sensitivity C-reactive protein, Interleukin-2, and Interleukin-6 [55]. In a cross-sectional study, investagators presented a correlation between uremic itch and increased levels of Interleukin-31(cytokine implicated in itch involvement in other pruritic cutaneous conditions, including atopic and allergic contact dermatitis) [55]. There is a need for additional studies to better understand the immune system and its potential involvement in the development of CKD-associated itch [55]. Other potential players in the

pathophysiology of CKD-associated pruritus are opiodergic system imbalances (particularly, increased u-opioid receptor activity), anemia, hyperparathyroidism, increased levels of histamine, and alterations in calcium phosphate balance [53].

2. **Cholestatic pruritus**. Patients afflicted by hepatobiliary diseases commonly experience pruritus which has a negative impact on their life quality. According to the reports, prevalence of pruritus in this disease is in the range from 15 to 69%, and depends on the type of underlying condition. Autotaxin and lysophosphatidic acid have been suggested to play a role in the pathophysiology of cholestatic pruritus [56, 57].

3. **HIV**. Chronic pruritus is commonly experienced by patients affected by HIV and is likely to be present at some point during the course of this disease. The importance of HIV consideration is on the rise among the elderly due to the prolonged life expectancy of HIV-infected individuals, and the fact that new cases of HIV have been detected in people 65 years of age and older. Underlying cutaneous conditions, such as xerosis, seborrheic dermatitis, or superficial fungal infection, are typical presentations of chronic pruritus in this population. The exact mechanism of itch in this patient group has not yet been elucidated; however, it is very important to get a better understanding of the processes underlying itch development to provide patients with appropriate treatments. Because polypharmacy is a common problem in the elderly population, careful consideration should be devoted to prescription of medications to take into account drug interactions and adverse effects [58, 59].

4. **Thyroid dysfunction (TD)**, in particular hyperthyroidism, is thought to be associated with chronic pruritus. One study showed an increased occurrence of itch in the patients with thyroid dysfunction when compared to healthy individuals. There was no report regarding the prevalence or incidence of chronic itch in the elderly patients affected by thyroid disease, which can be pursued in further research studies [60]; moreover, identifying the influence of thyroid hormones on pruritus in the elderly would be very valuable in further understanding the pathophysiology of these processes [57].

5. **Malignancy**. The risk of developing cancer is increased with advancing age [61]. One study evaluating patients recently diagnosed with malignancy showed that 5.9% of the individuals experienced generalized itch. Paraneoplastic itch is defined by The Special Interest Group (SIG) of the International Forum on the Study of Itch (IFSI) as "the sensation of itch as a systemic (not local) reaction to the presence of a tumor or a hematologic malignancy neither induced by the local presence of cancer cells nor by tumor therapy." [62, 63] Specific or non-specific cutaneous eruptions may be associated with itch [64]. Different types of cancers can be associated with paraneoplastic itch. Fett et al. demonstrated that in a cohort study, individuals suffering from chronic itch had a greater incidence of occult hematologic or bile duct malignancy when compared to general population [65]. Other cancers, including lymphoma and polycythemia vera, are associated with pruritus [62]. There are numerous suggestions as to what pathways might be underlying this condition, however the exact mechanism of pathogenesis involving paraneoplastic itch is still largely unclear.

6. **Medications.** Owing to the fact that chronic diseases are commonly found in the elderly, the presence of polypharmacy is a frequent occurrence in this patient population [6]. There are numerous medications that have been found in association with itch. Some of these agents include MU opioids, anti-hypertensives such as ACE inhibitors, anti-diabetics, hypolipaemics, chemotherapeutics, antibiotics, anti-epileptics, psychotropic drugs, and cytostatics [63, 66]. The newer targeted anti-cancer biologics such as EGFR inhibitors (cetuximab, erlotinib, panitumumab), a RAF kinase inhibitor (vemurafenib), and a monoclonal antibody (ipilimumab) have pruritus as a side effect [67]. An additional example of the relationship between pharmacologic agents and itch may be a possible connection between calcium channel blockers and chronic eczematous eruptions in people of advanced age [68]. Because many of these medications are commonly used in the elderly, and taking into consideration the high likelihood of polypharmacy in this population, medication-induced itch should be on the list of differential diagnoses when encountering an elderly patient with chronic itch.

Psychogenic Causes

Various psychologic abnormalities have been associated with psychogenic itch. While the prevalence of psychogenic pruritus affecting the elderly population remains unknown, an assumption can be made that increased life expectancy in people diagnosed with mental disorders, as well as high numbers of mental disorders in the elderly, may affect the number of older patients experiencing psychogenic itch. Typically, patients experience an increased urge to scratch or pick at normal skin. Those patients affected by severe dementia can pick at their skin which leads to worsening of itch scratch cycle. Additionally, such factors as stress or anxiety, might cause the exacerbation of pruritus in several cutaneous conditions, including psoriasis, lichen simplex chronicus, and nummular dermatitis. A psychiatric consultation might be considered when evaluating an elderly patient with normal skin after systemic conditions have been excluded [23].

Work-up

It is paramount to obtain a detailed medical history, review of systems, and medication list, as well as a thorough physical examination when evaluating an elderly patient with a complaint of itch. Certain cases require additional studies, such as skin biopsies, laboratory studies, and imaging in order to make a correct diagnosis [8]. **Figure 1** illustrates a suggested work-up algorithm for elderly presenting with chronic itch.

History of present illness should include details regarding several itch characteristics useful in determining a correct diagnosis. These include itch duration (acute vs. chronic), intensity (using the visual analogue scale or numerical rating scales [VAS-NRS]), location (localized vs. generalized), timing (when itch is at its worst—morning vs. day vs. night), as well as alleviating and aggravating factors. It is important to evaluate itch intensity (VAS, NRS, or VRS) on a scale from 0 (least intense) to 10 (most intense) during every visit, as it is used for monitoring the treatment response [69]. In an elderly patient presenting with an itch of new onset (within the past 6 months), paraneoplastic itch should be considered as a part of differential diagnosis. Additionally, a thorough past medical and social history should be obtained when talking to the patient, because this information may provide valuable clues useful in determining the cause of chronic pruritus.

Multiple systemic conditions, including diabetes mellitus, renal and hepatic diseases, HIV, or a history of neck/spine trauma, can be important factors predisposing an older patient to chronic

pruritus. Asking patients about their use of alcohol, drugs, and sexual habits as a part of social history may help determine a particular disease possibly underlying chronic pruritus. Another important part of the social history involves inquiries regarding the living arrangements (such as nursing homes, which would make scabies a possible itch etiology), and if other family members or people in patient's surrounding also experience itch. Multiple conditions involving chronic itch mentioned above are responsible for sleep disturbances. These should be addressed during the evaluation, and questions regarding patient's sleep hygiene might be necessary to obtain a better understanding of the underlying condition.

Physical examination should be performed, partially in attempt to evaluate the cause of itch as being cutaneous or not. In order to determine a correct diagnosis, it is important to clarify whether the patient has a primary or secondary eruption. While primary lesions are caused by the same abnormality that is responsible for itch, secondary lesions result from repetitive scratching of the itch (and are not related to the pathologic process that gave rise to itch). If a suspicion of systemic malignancy is entertained as a causative agent for itch, lymph nodes should be evaluated during the physical exam [8].

In a case when there are no identifiable characteristic skin lesions, taking a biopsy might be useful in obtaining a diagnosis. The use of immunohistochemistry and immunofluorescence may aid in identifying a variety of cutaneous diseases in particular [21].

Additionally, laboratory studies (such as complete blood count, iron studies, blood urea and creatinine, liver function tests, thyroid function tests, erythrocyte sedimentation rate, and serum immunoglobulins) can be used to gauge for systemic conditions underlying itch [57]. Specific screening tests might be ordered when a diagnosis of paraneoplastic itch is considered [65].

A decision to order imaging studies should be made based on specific cases. Magnetic resonance imaging may be helpful when addressing itch found in a particular dermatome, or that is a likely result of possible spinal degeneration. When paraneoplastic itch is one of the differential diagnoses, a chest x-ray and/or CT scan of chest and abdomen should be ordered.

Psychiatric assessment can be done once aging-related, cutaneous, and systemic causes of pruritus have been ruled out.

Treatment

Based on the information presented above, there are multiple causes responsible for development of pruritus in the elderly population. In case of an apparent underlying condition, treating this condition would be an initial step in attempt to alleviate the itch [8, 57]. Given the factors of polypharmacy, physical impairments, and comorbidities associated with the aging process, it is necessary to develop an individualized treatment plan for elderly patients which would take into consideration their state of health [57]. Currently, there are a variety of treatments, including topical and systemic medications, as well as psychological therapies that might help to achieve this goal. **Table 1** provides an overview of medications used for treatment of chronic itch.

1. Topical Therapy

There are a variety of topical treatments used for relieving chronic itch in the elderly.

- The use of **topical moisturizers/emollients** is very common in treatment of xerosis and mild localized itch [8].
- **Humectants** (such as urea and glycerin) applied topically are capable of retaining water and replenishing some of the lipids around keratinocytes in the stratum corneum. The effects have been shown to be of benefit in a variety of itchy conditions, including xerosis [7, 70].
- **Oatmeal** is another agent used as a remedy for pruritus. The beneficial effects are thought to be due to a decrease in several anti-inflammatory mediators, including TNF-alpha, nuclear factor kappa B, IL-8, and histamine [7].
- **Salicylic acid** applied topically has some keratolytic and emollient effects and is thought to counteract thickening of the skin induced by scratching. Local desensitization of the itch fibers might be underlying its antipruritic effect. Some studies have demonstrated its effect on decreasing itch in the LSC patients [71].
- Topical **menthol** has been used in order to control itch, which is most likely due to its cooling effect; this property is believed to be mediated by transient receptor channels, particularly TRPM8, TRPA1, TRPV3 [8, 72].
- Topical **Capsaicin** has a role in modifying itch by binding to the TRPV1 ion channel on the C fibers and depleting pruritogenic neuropeptides (such as Substance P) from the nerve fibers [73]. Due to the fact that an intense sensation of burning and redness is frequently observed during the treatment initiation, use of topical anesthetics (EMLA) before the application of capsaicin may be helpful [73].

- Topical **steroids** aid in decreasing itch due to their anti-inflammatory effects. Because potent formulations are known to cause skin thinning (which is already an issue in the elderly), care should be taken to not exacerbate thinning with chronic steroid use [57].
- Topical **calcineurin inhibitors** (TCI) include tacrolimus and pimecrolimus [8]. Their role in itch treatment is believed to be related to their effect on the regulation of T-cells, decreased release of inflammatory cytokines, and over-activation of TRPV1 in the nerve fibers of the skin.
- Topical **anesthetics** can also play a role in controlling pruritus. Pramoxine (1% or 2% cream) acts by stabilizing the neuronal membrane. The combination of lidocaine and prilocaine (EMLA ®) has been used for notalgia paresthetica and as pretreatment for capsaicin [8, 74, 75].
- Topical **strontium** 4 % can be used for itch relief, although the exact mechanism is still not clear. It is believed to affect the depolarization of C-type nerve fibers, and has been shown to have an antipruritic effect on histamine-induced itch [76]. A recent double-blind, vehicle-controlled trial showed the beneficial effect of strontium on non-histaminergic pruritus induced by cowhage in humans [77].
- Topical **amitriptyline** and **ketamine** combination has been used for treatment of localized neuropathic pruritus. Amitriptyline has antihistaminic and anticholinergic properties, whereas the mechanism of itch reduction caused by ketamine is not well understood. It is thought that topical combination of these medications leads to the local inhibition of sensitized A- and C-fibers. It has been employed for treatment in BRP, NP, and post-herpetic itch as well [78].
- In some instances, the effect of topical medications can be further enhanced by using **occlusive bandaging** [57]. This aids in better delivery of the medication, and additionally prevents further potentially damaging scratching [57]. One example is using the “wet pajama” treatment: An emollient is applied to pruritic skin; then damp cotton pajamas are put onto the skin, and an additional dry set of pajamas is placed on top. The patient wears these layers during the night [8].

2. Systemic Treatments

Prescription of systemic medications should be done with great care in order to evaluate possible drug-drug interactions, side effects, polypharmacy, as well as comorbid conditions and cognitive state of the elderly patient.

- **Antihistamines,** even though often used as first line agents for chronic itch, have a modest impact on chronic pruritus (except urticaria). First-generation antihistamines (hydroxyzine and diphenydramine) are commonly used for nocturnal itch, and second-generation antihistamines (cetirizine, fexofenadine, loratadine) are employed in chronic urticaria. There is a variety of side effects associated with this class of drug [8, 57].
- **Gabapentin** and **pregabalin** (both analogues of Gamma-aminobutyric Acid, GABA), aid in treatment of chronic pruritus and can benefit patients with itch related to CKD [8].
- Systemic **immunosuppressants** (cyclosporine, methotrexate, azathioprine, glucocorticoids, and mycophenolate mofetil) can help managing chronic itch in the elderly with skin inflammation, and the choice of the agent is based on the individual's cause of pruritus [7]. The authors often use mycophenolate mofetil for itch associated with Grover disease.
- **Thalidomide** acts as an immunosuppresive anti-inflammatory agent and neurotoxic agent and decreases itch mostly by modifying TNF-α secretion and neurotoxic effects on central and peripheral nerve depressant. It has been used in treating prurigo nodularis and uremic itch [76, 79].
- **Mirtazapine** is an SSRI antidepressant used in treatment of nocturnal itch. Combining mirtazapine with either gabapentin or pregabalin has been found lessen itch in a case series of patients with cutaneous T-cell lymphoma [8, 80].
- The **selective serotonin-reuptake inhibitors** (SSRIs) such as fluvoxamine and paroxetine may relieve itch by increasing serotonin. High levels of serotonin can potentially suppress T cells, thus decreasing inflammatory substances involved in itch [81]. Several studies have shown effects of SSRIs on reducing pruritus in patients with atopic dermatitis, systemic lymphoma/ solid carcinomas [82], chronic liver disease [83].
- **Tricyclic anti-depressants** (Amitryptiline and Doxepin) decrease itch by antagonizing H1 receptors and having anticholinergic properties [8]. These agents may be used to treat nocturnal and psychogenic itch [5].

- **Aprepitant** is an oral selective neurokinin – 1 receptor antagonist (NKR1-antagonist). It blocks the effects of an itch mediator (Substance P) which works by binding to the Neurokinin-1 receptor. Aprepitant was found to have some effect in decreasing itch in patients with drug-induced, paraneoplastic, and brachioradial pruritus, as well as CTCL [84, 85].
- Systemic use of **Naltrexone** (a mu-opioid receptor antagonist) was described to relieve itch in patients with cholestasis and atopic dermatitis in randomized controlled trials. However, its prescription in elderly can be limited due to a variety of side effects [86].
- **Butorphanol** (a kappa-opioid agonists and mu-opioid antagonist) used intranasally has shown some effect in decreasing itch [87]. It can also be used in cases of intractable itch.
- **Nalfurafine** (a kappa-opioid agonist) has been shown to be helpful in patients with uremic pruritus. It is only approved in Japan for severe pruritus in hemodialysis patients [88].

3. Phototherapy

Ultraviolet A radiation (**UVA**), ultraviolet B radiation (**UVB**) and narrow-band ultraviolet B radiation (**NBUVB**) alone, or in combination, have been employed to relieve numerous skin conditions associated with increased itch in the elderly, as well as to manage pruritus caused by chronic kidney disease [8]. The initiation of phototheraphy of both UVB and NBUVB may be associated with itch due to erythema resulting from photo irradiation. This side effect should decrease after 1 to 2 weeks of phototherapy [89]; however, long term treatment in patients with skin affected by sun damage or history of skin cancers should be done very cautiously.

4. Behavioral Treatments

The treatment options mentioned above may be supplemented by psychological methods. Working on coping mechanisms, such as **habit reversal** and **relaxation**, as well as undergoing **cognitive behavioral therapy** can be useful in breaking the itch-scratch cycle and enabling better sleep. More studies have to be conducted to better understand influence of behavioral interventions on itch [8, 90].

Conclusions

Chronic itch in the elderly population can be caused by a variety of cutaneous, systemic neuropathic and psychogenic factors. Understanding the pathophysiology of chronic itch in the aging population is paramount in developing specialized treatments and avoiding polypharmacy.

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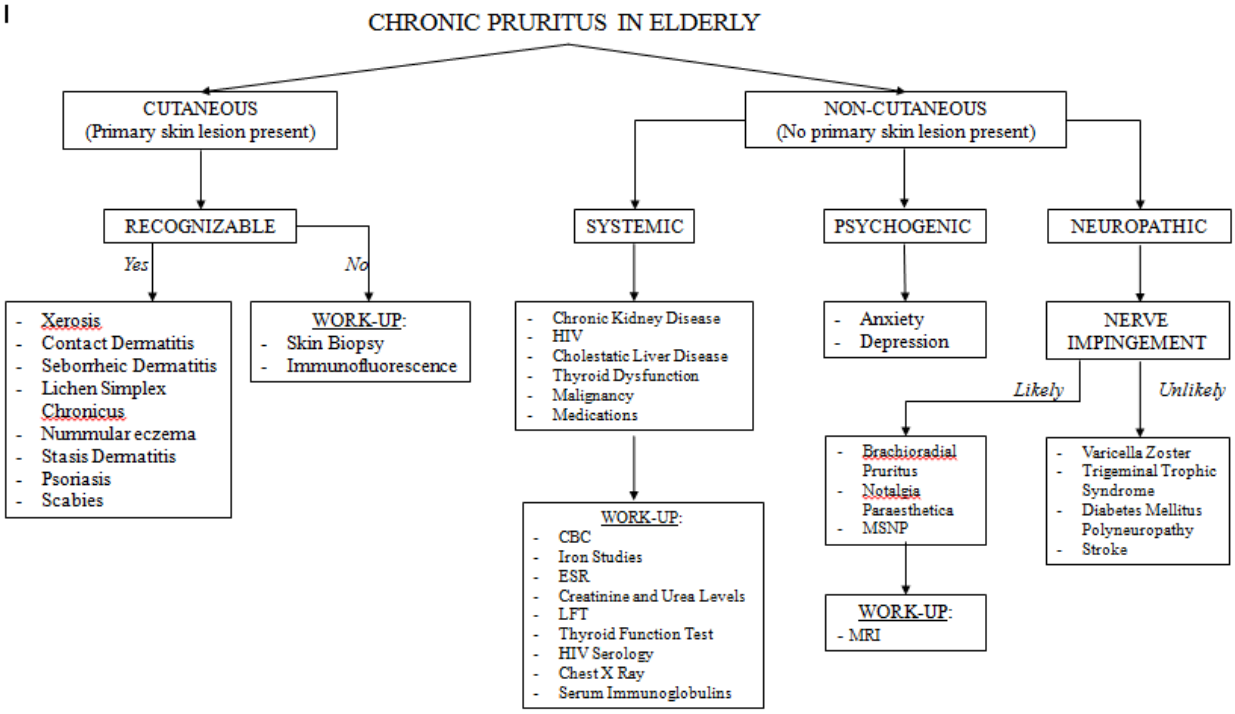

Figure 1. Workup suggested in evaluating elderly patients presenting with chronic itch.

Abbreviations: MSNP, Multilevel Symmetric Neuropathic Pruritus