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United States expert panel consensus on uniform nomenclature and diagnosis for neuropathic pruritus

Shawn G. Kwatra, MD[a,*], Sarina Elmariah, MD, PhD, MPH[b], Sarah Chisolm, MD[c], Nicholas Mollanazar, MD[d], Marlys Fassett, MD, PhD[e], Emily F. Cole, MD[c], Suephy Chen, MD[f], Ethan Lerner, MD, PhD[b], Timothy Berger, MD[e], Gil Yosipovitch, MD[g]

Importance: Neuropathic pruritus is a debilitating condition lacking a uniform approach to nomenclature and diagnosis.
Objective: A panel of dermatologist experts in pruritus was convened to develop definitions, diagnostic recommendations, and treatment guidelines for neuropathic pruritus.
Evidence review: A roundtable discussion of 10 experts was conducted on November 3, 2021, via the Zoom platform. This study follows the Standards for Reporting Qualitative Research reporting guidelines for qualitative studies. A systematic review of prior literature on the definition, scope, diagnostic, and treatment was performed, looking at sources of treatment from 1991 to 2021. Consensus was defined as >70% agreement for acceptance of a definition or recommendation. A draft of evidence was subjected to revision by all participants and was endorsed by all participants.
Findings: The roundtable identified definitions for neuropathic pruritus, which included different forms of the condition based on cause and presentation such as brachioradial pruritus, notalgia paresthetica, and scalp pruritus. Diagnostic and treatment guidelines were also established. Limitations of this process included lack of randomized controlled studies. These recommendations are also based on expert consensus and must be further supported by evidence-based outcomes research.
Conclusions: Neuropathic pruritus contains numerous subtypes, causes, diagnostic methods, and treatment modalities. The recommendations developed by this panel are meant to serve as shared nomenclature for future clinical studies.

Key words: Neuropathic pruritus, Itch, Consensus, Guidelines, Management

Introduction

The Food and Drug Administration has recently approved several therapies for the treatment of various inflammatory dermatoses associated with pruritus, including atopic dermatitis, which are now often manageable[1]. In contrast, therapeutic options and the treatment ladder for patients suffering from neuropathic pruritus, a debilitating condition defined broadly as itch primarily caused by a lesion of or disease affecting the somatosensory nervous system, are unclear[2–4]. Currently, neuropathic pruritus does not have a distinct International Classification of Diseases, 10th Revision code, which results in it being grouped with many other forms of pruritus as L29.8 (other pruritus)[4]. Data regarding the incidence and prevalence, underlying pathophysiology, and detailed case studies on such patients are scarce. The lack of diagnostic methods for this condition leads to it often being mistaken for other causes of pruritus, and there is lack of consensus in nomenclature[5]. The pathway for the identification and development of effective therapeutic agents through clinical trials is therefore unclear. To begin to offset these limitations in advancing the care of patients with neuropathic pruritus, we convened a US expert consensus panel to provide uniform nomenclature and offer guidance on diagnosis and workup.

Methods

For this qualitative study, a roundtable discussion among experts in the United States in the field of pruritus and pruritus management was held to address the disease definition, core symptoms, additional disease features and subtypes, and diagnostic evaluation of patients with neuropathic pruritus. This study follows the Standards for Reporting Qualitative Research reporting guidelines for qualitative studies[6,7].

[a]Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, MD, [b]Department of Dermatology, Massachusetts General Hospital/Harvard Medical School, Boston, MA, [c]Department of Dermatology, Emory University, Atlanta, GA, [d]Department of Dermatology, University of Pennsylvania, Philadelphia, PA, [e]Department of Dermatology, University of California, San Francisco, CA, [f]Department of Dermatology, Duke University School of Medicine, Durham, NC and [g]Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery and Miami Itch Center, University of Miami Miller School of Medicine, Miami, FL

S.G.K. and S.E. contributed equally.

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*Corresponding author. Address: Johns Hopkins University, 1550 Orleans Street, CRBII Suite 207 Baltimore, Maryland 21287. Tel.: +410 955 5933; fax: +410 367 2405. E-mail address: skwatra1@jhmi.edu (S. Kwatra).

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Participants and design

Ten experts in pruritic and inflammatory dermatologic diseases were recruited for discussion in this roundtable, which was conducted on November 3, 2021, via the Zoom platform. Expertise was identified based on current and prior research, clinical expertise, and experience in treatment of this condition, and leadership in dermatologic organizations specializing in inflammatory and pruritic disease. Key topics that were formulated for this roundtable included the definition of neuropathic pruritus, mechanisms of diagnosis and risk stratification, and treatment strategies.

For the evaluation of existing information on neuropathic pruritus, a systematic review of prior literature on the definition, scope, diagnostic, and treatment was performed using articles from 1991 to 2021, as well as additional literature identified by the panel. Near-consensus was defined as between 70% and 85% concordance, whereas full consensus was defined as greater than 85% agreement for acceptance of a definition or recommendation. A draft of evidence was subjected to revision by all participants and was endorsed by all participants.

Results

The demographics of the 10 participants included a population that was 50% female (5/10 participants) and 70% Caucasian (7/10 participants). Sites of practice included academic facilities, including the Johns Hopkins University, Massachusetts General Hospital, Emory University, University of Pennsylvania, University of California San Francisco, Duke University, and University of Miami. Consensus on each definition and recommendation was achieved with 100% agreement. Table 1 identifies key findings determined by the consensus panel.

Table 1

Neuropathic pruritus definition, terminology, and suggested workup by expert panel consensus.

Definition	• Pruritus primarily initiated or caused by a lesion or disease to the somatosensory nervous system.
Core symptoms	• Normal skin or skin with only secondary skin changes or signs of excoriation. • Pruritus prototypically favors a localized distribution, sometimes with dermatomal involvement that may also affect multiple body sites and be generalized secondary to neural sensitization.
Additional features	• Associated dysesthesias (pain, stinging, burning, tingling), paroxysmal or persistent nature, suboptimal response to therapy, and lack of features of systemic Th2 polarization [nonelevated blood eosinophils and/or immunoglobulin (Ig)E].
Subtypes	• Brachioradial pruritus • Notalgia paresthetica • Multilevel symmetric pruritus • Scalp pruritus • Postherpetic neuralgia • Small fiber neuropathy • Secondary to syndromes affecting central nerves (eg, poststroke pruritus, brain tumors, Creutzfeldt-Jakob disease, trigeminal trophic syndrome, multiple sclerosis, etc.) • Peripheral nerve damage with mixed etiology (postsurgical, scar)

Definition

Neuropathic pruritus is defined as itch primarily caused by a lesion of or disease affecting the somatosensory nervous system. This definition of neuropathic pruritus is consistent with the current terminology for neuropathic pain[8]. The core findings of neuropathic pruritus include the presence of normal skin or skin with only secondary changes or signs of excoriation, which serves as an initial differentiator from primary inflammatory dermatoses[9]. Itch in neuropathic pruritus classically favors a localized distribution (eg, the scalp, arms in brachioradial pruritus, unilateral areas of the back in notalgia paresthetica, or limited anatomic areas previously affected by zoster in postherpetic neuralgia). Neuropathic pruritus may also present as a generalized process due to the phenomenon of central sensitization, in which limited nerve damage leads to heightened neurotransmitter release and hyperexcitable spinal neurons[10,11]. Neuropathic itch has a significant impact on the sleep and quality of life of patients, even when it is localized[12].

Numerous subtypes were identified, with various underlying causes. Brachioradial pruritus, involving the proximal lateral forearm often in middle-aged women, is thought to be secondary to ultraviolet radiation and/or cervical spine dysesthesia[13]. Notalgia paresthetica, a unilateral pruritic condition with dermatomal distribution presenting on the upper back with no associated rash, is associated with cutaneous nerve damage[14]. However, occasionally, notalgia paresthetica can be bilateral[15]. Scalp pruritus is another localized neuropathic pruritus secondary to aberrant function of the trigeminal nerve, although there have been proposed functions of scalp flora in exacerbating pruritus[16,17]. It is not clear whether scalp pruritus is a separate pathologic process from scalp dysesthesia or burning scalp syndrome, which often presents with burning and tingling but may also present with pruritus[18]. Multilevel symmetric pruritus has been described in numerous case series as symmetric, well-delineated dermatitis of the upper and lower extremities, trunk, and back, which is often associated with moderate to severe degenerative disk disease[19]. Small fiber neuropathies may also be associated with chronic itch or chronic pain[20,21]. Central nerve and peripheral nerve damage secondary to illness, syndromes, or surgery can also elucidate pruritus[21]. Common examples include poststroke, postherpetic, or postsurgical pruritus and multiple sclerosis[22–25].

Diagnostic workup

The diagnostic workup of neuropathic pruritus is not currently standardized due to a lack of understanding of disease pathophysiology. Diagnostic testing may be performed based on patient history and review of systems (Table 1). Systemic causes of pruritus must be considered for these patients, requiring screening for renal, liver, and thyroid function, elevated fasting glucose, or low B_{12}[26,27]. Age-appropriate cancer screening would also be recommended. Similarly, infectious causes can contribute to pruritus, including hepatitis B or C infection or HIV infection[28]. As the pathogenesis of neuropathic pruritus does not often include type 2 inflammation or immunologic causes, screening for elevated type 2 markers such as eosinophils and serum IgE may help in confirming the diagnosis, such as in atopic disease[29]. For localized pruritus, radiologic examination of targeted areas may be appropriate to identify spinal degeneration[30]. These may include magnetic resonance imaging

or computed tomography to determine the presence of nerve root compression or spinal cord abnormalities in the peripheral nervous system[8]. Findings of nerve impingement, herniation, or stenosis are often clearly associated with the location of pruritus in brachioradial pruritus; however, this correlation may not be as evident for other conditions such as notalgia paresthetica[31]. In addition, these imaging modalities may help identify evidence of space-occupying lesions, demyelinating disease, or infectious disease[8]. These findings may warrant further evaluation by a neurologist or neurosurgeon.

In addition, brachioradial pruritus is a localized pruritic condition with a specific diagnostic technique known as the "ice pack test," which involves significant improvement of the pruritus after the placement of an ice pack in the affected area[32]. Finally, evaluation of quantitative sensory testing may be recommended for the evaluation of small fiber neuropathy[33]. If other diagnoses are being considered, skin biopsy can be performed to further stratify differential diagnoses. Biopsy is usually performed at the site of pruritus; if there are multiple, then distal extremities may be considered due to length-dependent loss of nerve fibers, which can be seen in axonal polyneuropathy. Control biopsies from nonaffected regions are also usually taken. Specimens should be fixed and cut into 50 μm sections. Immunohistochemistry or immunofluorescence may be used to quantify intraepidermal nerve fiber density with the PGP9.5 stain for the diagnosis of small fiber neuropathy[34–36]. Histology and direct immunofluorescence can also be performed to identify alternative primary skin conditions, including examining for inflammatory infiltrates, such as in atopic dermatitis and antibody deposition[8].

Treatments

Treatment for neuropathic pruritus is anecdotal and based on limited reports, although treatment of the underlying etiology is often the first step if possible[32]. Table 2 features several topical, systemic, and procedural therapeutics utilized by the authors in the management of neuropathic pruritus patients with variable success. Topical medications may work for a short time to relieve pruritus by various mechanisms, including anesthesia via lidocaine and pramoxine, topical ketamine and amitriptyline, peripheral nervous system activation via capsaicin, antihistamine, and antiserotonin/norepinephrine properties such as doxepin[37]. These treatments are often more effective for localized conditions such as brachioradial pruritus, scalp dysesthesia, or notalgia paresthetica[38]. Systemic agents that have been used in pruritus include gabapentinoids (which are most often used for notalgia paresthetica), which are used in many forms of chronic pruritus. Dosing of gabapentin may begin at low dose at 100 to 300 mg per day, depending on the patient age, tolerance, renal function, and increase to doses achieving efficacy[39]. Case reports have identified that stopping gabapentin may be associated with rebound pruritus, which must be considered for patients not otherwise tolerating the medication[40]. Additional options include antidepressants, opioid axis modulators including Kappa opioids, mu antagonists, and cannabinoids[41–43]. Several studies have identified naltrexone as an effective agent for different forms of chronic pruritus, which can be administered at 50 mg daily[44,45]. Dronabinol can be started at 2.5 mg 3 times per day and can be titrated up to 7.5 mg 3 times per day[43]. It is appropriate to start with low doses of these medications and titrate as tolerated by the patient. Procedural therapies are more poorly understood, but options include physical therapy, intralesional botulinum toxin, and transcutaneous electrical nerve stimulation[33].

Discussion

This consensus panel discussion on the definition, diagnosis, and treatment of neuropathic pruritus highlights an unmet need for further evaluation of this condition. Many diagnostic and treatment modalities for this debilitating pruritic condition are supported only by limited case reports, suggesting a need for more thorough study of the condition. Limitations of this process included a lack of randomized controlled studies. These recommendations are also based on expert consensus and must be further supported by evidence-based outcomes research.

Further development of studies examining the pathophysiology of neuropathic pruritus is greatly needed, as well as clinical trials for treatment approaches to the condition. In addition, these findings may assist in the streamlining of International Classification of Diseases coding, using the diagnostic criteria mentioned within this paper. The diagnostic and treatment methods developed by this panel are meant to serve as shared nomenclature moving forward for future clinical and translational studies of neuropathic pruritus and to accelerate the development of novel therapeutics (Table 3).

Table 2

Diagnostic workup of neuropathic pruritus.

Localized	Diffuse
• Consider targeted radiologic examination for brachioradial pruritus and notalgia parasthetica. • If possible, brachioradial pruritus, consider ice pack test to determine whether the placement of ice pack relieves pruritus. • If suggestive, consider a skin biopsy.	• Consider screening for systemic factors that may contribute to itch, including renal and liver function testing, thyroid function tests, iron panel, fasting glucose or hemoglobin A1C. • If suggested by clinical history or review of systems, consider screening Vitamin B_{12}, HIV, hepatitis B and C testing, and complete age-appropriate cancer screening. • Consider screening for malignancies, including serum protein electrophoresis (SPEP) or chest x-ray if indicated in history. • May check complete blood count with eosinophils and serum IgE, both markers of Th2 polarization; if within normal limits, supports a primary nonimmunologic origin of pruritus. • Perform or refer for a neurological examination to rule out central cause of pruritus (eg, multiple sclerosis, other neurodegenerative disorders) or for consideration of quantitative sensory testing/investigate small fiber neuropathy. • If suggestive, consider a skin biopsy to rule out other diagnoses.

Table 3

Therapeutic options for patients with neuropathic pruritus.

Topical agents	Systemic agents	Procedural therapies
• Anesthetics (pramoxine, lidocaine, etc.) • Capsaicin cream/patch • Coolants (menthol, camphor) • Tricyclic antidepressants (eg, doxepin) • Multiclass compounded medications (eg, amitriptyline-ketamine-lidocaine) • For brachioradial pruritus, ice pack may relieve pruritus	• Gabapentinoids (gabapentin/pregabalin) • Antidepressants (selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inibitors, tricyclic antidepressants, doxepin) • Kappa/mu opioid axis modulators (naltrexone, naloxone, butorphanol) • Cannabinoids (dronabinol)	• Physical therapy • Intralesional botulinum neurotoxin • CT-guided nerve root injections • Transcutaneous electrical nerve stimulation • Acupuncture • Exploratory procedures include dorsal root ganglion stimulation

This is largely based on expert opinion as there are currently no Food and Drug Administration–approved therapies for neuropathic pruritus and limited evidence for these therapies other than case reports and uncontrolled retrospective studies.

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Data availability statement

There are no data to disclose.

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