Common Neuropathic Itch Syndromes

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Published Version</td>
<td>10.2340/00015555-1318</td>
</tr>
<tr>
<td>Citable link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:34627161">http://nrs.harvard.edu/urn-3:HUL.InstRepos:34627161</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>
Patients with chronic itch are diagnosed and treated by dermatologists. However, itch is a neural sensation and some forms of chronic itch are the presenting symptoms of neurological diseases. Dermatologists need some familiarity with the most common neuropathic itch syndromes to initiate diagnostic testing and to know when to refer to a neurologist. This review summarizes current knowledge, admittedly incomplete, on neuropathic itch caused by diseases of the brain, spinal cord, cranial or spinal nerve-roots, and peripheral nerves.

Key words: itch; pruritus; diagnosis; herpes zoster; radiculopathy; peripheral nerve.

(Accepted December 24, 2011.)


Anne Louise Oaklander, M.D., Ph.D., Nerve Injury Unit, Departments of Neurology and Pathology (Neuropathology), Massachusetts General Hospital, 275 Charles St./Warren 310, Boston, MA 02114, USA. E-mail: aoaklander@partners.org

The sensation of itch – pruritus in medical terminology – can only be perceived by a few tissues, specifically the skin and superficial mucous membranes such as the conjunctiva. So chronic itch complaints are the province of dermatologists, and indeed they most often signal cutaneous injury or inflammation. However, substantial numbers of patients who complain of disabling chronic itch have no apparent cause in the skin. Many of these patients have systemic or medical causes of itch such as drug reactions, allergic or hypersensitivity syndromes, metabolic or endocrine disorders, or toxins associated with kidney or liver dysfunction. Itch is most likely a small-fiber-mediated protective (nocifensive) sensation like pain. It is hypothesized to have evolved to protect against small clinging threats such as insects and plant spines that would not be effectively removed by the withdrawal response associated with sensing pain. A close evolutionary relationship is evident in the considerable micro- and macro-anatomical overlap between itch and pain neurons (1, 2).

There is recent recognition that neurological disorders are an additional cause of focal or generalized pruritus. Dermatologists are increasingly aware of this, but many neurologists are not and are ill-prepared to treat such patients. Neuropathic itch remains unmentioned in most neurology textbooks and training curricula, and the visible cutaneous stigmata of neuropathic itch still are unnoticed by most neurologists despite their importance for localization. Patients with chronic itch should first be evaluated by dermatologists, but if no dermatological or systemic causes are identified, consider the possibility of neurological causes.

Twycross et al. (3) classified itch according to the origin of the itch-transmitting action potentials. Cutaneous or pruritoceptive itch is caused by pruritogens activating cutaneous nerve endings bearing pruritogenic receptors. In contrast, neuropathic itch is defined by diseased or malfunctioning pruritic neurons firing action potentials without pruritogenic stimuli (an abnormal stimulus-response curve). They also recognized neurogenic itch caused by pruritogens acting in the central nervous system (e.g., intrathecal morphine), although it is uncertain how often this circumstance otherwise arises. This manuscript summarizes the best known neuropathic itch syndromes to help dermatologists include them in their differential diagnoses, initiate appropriate diagnostic evaluations, and know when to refer to a neurologist.

ANATOMY AND PHYSIOLOGY OF ITCH

The sensation of pruritus is carried primarily by a subset of the unmyelinated C-fibers often classified as pain-fibers (nociceptors). Different C-fibers deploy different receptors and ion-channels to equip them to respond to different sensory stimuli. The C-fibers that activate after local histamine administration to produce itch perceptions in the brain are mechanically insensitive afferents (MIAs) with unusually slow conduction velocities and large receptive fields (1). Some also respond to heat stimuli, perhaps explaining why heat worsens many itch sensations and cooling abolishes itch (1). Some laboratories report involvement of the A-delta thinly myelinated nociceptors in itch sensation as well. For clinicians the overlap between itch and pain neurons means that the same neurological diseases that can cause neuropathic pain can also cause neuropathic itch in some patients. However there are differences. Most treatments effective for neuropathic pain are not clearly effective for itch. Most notably, opioid pain relievers often cause or worsen itch.

The cell bodies of itch neurons are located in the peripheral nervous system (PNS) just outside the central
nervous system (CNS), for instance in the trigeminal (Gasserian) ganglion that subserves facial sensation, and in the dorsal root ganglia of spinal nerves. These ganglia also send central axons inwards into the spinal cord or brain to trigger the central itch-processing neurons that lead to conscious and unconscious itch perceptions, and the emotions, actions and decisions that these evoke. Nociceptive afferent neurons have other functions besides pain. These evolutionarily primitive nerve cells have a larger goal – maintaining homeostasis and optimal functioning of tissues and organs. Pain and itch sensations, which protect against actual or threatened danger, merely serve that larger goal. These same peripheral neurons, known collectively as “small-fibers” also have important efferent and trophic activities. They innervate and influence all of the body’s organs and tissues, except hair and nails, innervating and regulating the small blood vessels, the internal organs, and the immune response. In the past such regulatory functions were attributed to the subset of small-fibers whose cell bodies are in the autonomic rather than somatic ganglia, but multiple lines of evidence increasingly blur the distinction between autonomic and somatic afferent neurons. Many structures including blood vessels and sweat glands have overlapping innervation by somatic neurons. Many structures including blood vessels and sweat glands have overlapping innervation by somatic neurons. Peripheral structures have become ectopic – uncoupled from their usual peripheral stimuli. Many sensory receptors are over-expressed on the ends of regenerating axons, a potential cause of the itching that often accompanies scar formation. They may also be over-expressed in the bulbous neuromas that can form at the distal ends of transected nerves to contribute to phantom itch perceived in an amputated limb or other missing body part.

Transmission of itch signals into and within the central nervous system

Once transduced, it is not entirely clear how the action potentials of pruritoceptive neurons travel from the skin towards the CNS. Current experimental evidence supports both the existence of distinct itch neurons that are insensitive to pain (labeled-line theory) (1) and also of neurons that can signal either itch or pain by using different firing patterns (signal-selectivity theory). Furthermore, several lines of evidence demonstrate that itch and pain neurons intersect or intercommunicate. For instance, pain often inhibits itch and opioid pain relievers can cause pruritus. And noxious temperature changes, both cold and hot, modulate itch perception (for better and for worse, respectively) (12). In the dorsal horn, the first sensory relay within the CNS – or the equivalent spinal nucleus of the trigeminal nerve – spinthalamic-tract neurons receive incoming action potentials from the central axon of primary afferent itch-transducing neurons (2). They transmit itch signals rostrally towards the brain, but there is considerable signal modulation before that happens. Murine knockout studies of the atonal-related transcription factor Bhlhb5 have identified dorsal-horn inhibitory interneurons that tonically inhibit itch signals (13). Spinal cord lesions that perturb this circuitry can cause neuropathic itch in humans and rodent models, as discussed below (14, 15).

Much less is known about central than peripheral itch pathways. In fact, individual patients with the clinical syndromes described below have proven very useful in identifying the brain’s anatomical pathways involved in itch. The brain’s itch processing centers have only been preliminarily identified. Positron emission tomography studies implicate the primary but not secondary somatosensory cortex in processing histamine-induced itch in normal adults (16, 17). Other brain areas implicated include the periaqueductal gray and cingulate...
gyrus (17). The secondary somatosensory cortex and insula have also been implicated in electrically induced acute itch (18).

CLINICAL PRESENTATIONS OF NEUROPATHIC ITCH

Syndromes of the face, head, and neck

Preliminary evidence suggests that itch, like the other body senses, is not equally distributed along the body surface. Neuropathic itch may be more likely to develop on the face, head and neck than lower on the body. The best evidence for this comes from postherpetic itch (PHI) after shingles, where data from several independent groups confirm that shingles affecting the head or neck is more likely to cause PHI than shingles on the torso (19). Despite its proximity to the brain, neuropathic itch of the face, head, and neck is more likely to be caused by lesions of peripheral rather than central neurons. Although any kind of lesion can cause this type of pruritus, two peripheral diseases, post-herpetic itch after shingles and severe trigeminal nerve-root injuries, and one type of brain lesion, strokes affecting the central trigeminal pathways, are the best known causes and are discussed below.

One extraordinary patient helped bring PHI to general medical awareness, a woman with intractable PHI of the V1 dermatome above and around her eye who gradually and unintentionally scratched through her skull and meninges into her brain (20–22). Skin biopsies and sensory testing demonstrated that her painless self-injurious scratching occurred in the context of profound cutaneous denervation caused by her earlier zoster. The ensuing dermatomal loss of protective pain sensation made her scratching painless even as it penetrated through her skull to cause an epidural abscess and ultimately, neurological disability including hemiparesis, seizures and personality changes from frontal-lobe injury. That patient had no dementia or psychiatric contributors to her scratching.

This type of facial neuropathic itch that progresses to scratching-induced ulcers is a condition known to dermatologists as the trigeminal trophic syndrome (TTS). Alternate names in the literature include trigeminal neuropathy with nasal ulceration, trigeminal neurotrophic ulceration, and trophic ulceration of the ala nasi (23). In order for TTS to develop, patients must have not only intractable neuropathic itch but also profound cutaneous deafferentation that makes the scratching painless. They have lost the usual “brake” that stops scratching before it causes injury. Neither dementia nor psychiatric disturbance (e.g. obsessive-compulsive disorder) are required for TTS to develop. In fact, the one patient that I know of with co-existing severe PHI and severe obsessive-compulsive disorder was careful not to scratch too much and he had no significant injury. In contrast, the reflexive scratching that goes on during sleep or during periods of inattentiveness universally contributes to TTS. Experience with other TTS patients shows that dementia can contribute to this dangerous mix and some patients with decades of neuropathic itch only lose control of their scratching once they become demented (23). Furthermore, some patients (and even their non-dermatology doctors) may not realize that their skin lesions are caused by their scratching. Instead they believe the reverse, that the lesions cause the scratching. The dermatological custom of multiple complex names for the skin changes caused by excessive scratching (e.g. prurigo nodularis, lichenification, macular amyloidosis) can obscure the real diagnosis, which is chronic itch. Why some patients with cutaneous deafferentation develop neuropathic itch, whereas others develop neuropathic pain, or pain and itch together is entirely unknown at present.

TTS was characterized in the early 20th century when neurosurgeons began to transect the roots of the trigeminal ganglion (trigeminal rhizotomy) in futile attempts to treat the debilitating pain of trigeminal neuralgia. Surgery was the only treatment option before effective medications were developed in the mid-20th century (24). It took a while to notice that some patients developed ulcers on or to the side of their nostrils after such procedures. These were originally attributed to loss of trophic factors carried by the transected nerves, hence the name. TTS was later attributed to psychiatric causes with psychosexual explanations proffered during the Freudian era. In addition to trigeminal rhizotomy and trigeminal shingles (Fig. 1), there are rare cases

![Fig. 1. Trigeminal trophic syndrome (TTS) – neuropathic facial itch and self-induced injury from painless scratching. This man has mild TTS caused by post-herpetic itch in the right ophthalmic division of the trigeminal nerve. This was treated with a lidocaine patch.](image-url)
of TTS from other types of trigeminal injury as well as many mild cases that do not proceed to ulceration. These can be caused by any type of illness or injury affecting the trigeminal ganglion and its peripheral and central pathways.

The most common brain lesion causing neuropathic itch is cerebral infarction, particularly strokes that affect the lateral medulla to cause Wallenberg’s syndrome or slightly higher strokes in the lateral pons where itch signals likely ascend (25–28). Central lesions, most often verteobasilar stroke, are said to cause about 1/5 of cases of TTS (29). Central itch has also been described in multiple sclerosis (30, 31), tumors within and immediately outside the brain (32, 33), and infections and autoimmune disorders (34), as well as other conditions (29). As with other types of neurological dysfunctions, the location of a lesion, not its etiology, determines which neurological symptoms it will evoke. Facial itch or scratching that extends beyond the territory of one individual branch of the trigeminal nerve is more likely to have a cause within the ganglion or brain rather than in its peripheral nerve root or major branches.

**Syndromes caused by intramedullary lesions within the spinal cord**

Various intramedullary lesions have been shown to cause neuropathic itch in both humans and animals, attesting to the importance of the spinal cord as an itch-modulating center. Spinal itch has been associated with syringomyelia, tumor, spinal multiple sclerosis, and the Brown-Séquard syndrome after traumatic injury (31, 35–37). Several investigators have described an association between intramedullary cavernous hemangiomas of the spinal cord and chronic neuropathic itch in the corresponding dermatome (14, 38, 39). I hypothesized that the preferred anatomical localization of these hemangiomas in the dorsal regions of the upper spinal cord, as well as histological features such as gliosis and hemosiderin deposition after hemorrhage, make them particularly pruritogenic (14). The term gliosis refers to local proliferation of astrocytes, how the CNS forms scars at the site of prior injuries. We also linked this type of intramedullary itch to a rodent model of spinal-cord injury, where micro-injection of an excitotoxin causes cell death in the deep dorsal horn (14). The severe truncal dermatomal scratching that these rats develop was formerly interpreted as modeling neuropathic pain, but we suggested it better modeled intramedullary itch. Study of cutaneous innervation in these rats revealed profound deafferentation in their itchy skin, implying that the small spinal-cord injections cause retrograde degeneration of primary afferent (peripheral) sensory neurons as well as of intrinsic spinal neurons (15). Thus intramedullary itch may not be purely central.

**Syndromes caused by spinal nerve-root injury (radiculopathy)**

The term “radiculopathy” refers to a pattern of focal or regional neurological dysfunction caused by injury or illness affecting one single nerve root, or less often a few adjacent nerve roots. The symptoms are perceived in the tissues innervated by the damaged nerve root. For sensory problems, the specific areas of skin innervated by each specific nerve-root (the dermatomes) were mapped out in the 19th century mostly by correlating the locations of shingles eruptions with the single dorsal root ganglion involved (Fig. 2). Radiculopathies are almost always unilateral, on the side of the damaged nerve root. The dermatological disorders known as “brachioradial pruritis” (focal itch on the shoulders or arms) and “notalgia paresthetica” (itch lower on the torso) are most often caused by underlying radiculopathy from spinal osteoarthritis (40, 41).

Because of the characteristic location of brachioradial pruritus on the dorsolateral arms, and because it worsens during the warm months, sun exposure has also been suggested to contribute (42). However, worsening with heat is a nonspecific characteristic of itch likely reflecting co-localization of itch and heat receptors on the same primary afferent C-fibers (1). Some of these patients who lack spinal pathology likely have

---

**Fig. 2.** This figure reproduced with permission from Head and Campbell's landmark 1900 monograph is one of the earliest depictions of the sensory dermatomes (58). In Part II, "The Bearing of the Distribution of the Eruption in Herpes Zoster on Sensory Localization," Head and Campbell cross referenced their observations and hand drawings of some 450 patients’ acute shingles rashes with the later autopsies of those patients who died, often of advanced syphilis or tuberculosis. This permitted them to create one of the earliest and still-accurate representations of the pattern of human peripheral sensory dermatomes (59). At that time, the abbreviation D (for “dorsal”) was used to refer to the thoracic dermatomes.

Acta Derm Venereol 92
informative nomenclature such as “left C-s nerve root.” At a minimum, the mechanistic unity of brachioradial pruritus and nostalgia paresthetica should be reflected in the nomenclature. Itch from spinal radiculopathy is less common on the lower torso and legs than on the shoulders and arms, perhaps similar to the pattern observed with PHI (19).

The other common cause of radicular pruritus is shingles. Herpes zoster is most common in middle-aged and older patients but also seen occasionally in the young. If patients report a history of prior shingles or have cutaneous scars consistent with prior zoster, PHI can be diagnosed without additional diagnostic testing. The incidence of neuropathic itch after shingles has been reported to be as high as 36% (19). However, if there is no history or evidence of prior zoster, the physician should determine the approximate spinal-root level and request radiologic imaging preferably using magnetic resonance imaging, which is most sensitive. Imaging is important not only to detect spinal radiculopathy and determine if surgery is indicated, but also to exclude other rare causes of spinal radiculopathy such as tumor (e.g. Schwannoma, metastasis), vascular malformations, and cysts that may require surgery. Also, radicular symptoms are sometimes the major presenting complaint of an intrinsic spinal cord lesion, as discussed above. If spinal imaging is non-diagnostic, the physician should consider the possibility of undiagnosed shingles (zoster sine herpete) or forgotten shingles. Other infections, inflammations, and nerve impingements can also cause spinal radiculopathy. Truncal diabetic radiculitis is the most common in developed countries, and leprosy should be considered in patients from tropical regions. Electrodagnostic testing (electromyography and nerve conduction testing; EMG/NCS) with a request for recording electrical activity of the paraspinal muscles can help confirm non-compressive radiculopathies. Diabetic radiculitis is caused by microvascular dysfunction within nerve roots that cause hypoxia, inflammation and even infarction with degeneration of distal axons. Some of these patients benefit from a short course of corticosteroids so this diagnosis is worth considering.

 Syndromes caused by small-fiber polyneuropathies

The most common cause for otherwise unexplained chronic itch that affects both feet, feet and legs, hands and legs, or bilateral widespread areas throughout the body is small-fiber polyneuropathy (SFPN). SFPN refers to the type of polyneuropathy that exclusively or predominantly affects the small-fibers discussed above (45). Its characteristic sensory symptoms usually begin in the toes and feet, the areas innervated by the longest axons in the body, which most often degenerate under adverse conditions. Symptoms can then progress proximally in a “stocking-glove” distribution with increasing duration or severity of the polyneuropathy. Classic symptoms include paresthesias, dysesthesias, and/or neuropathic pain sometimes accompanied by impaired pain and temperature perception (numbness). Distal weakness will only develop if the large myelinated fibers are affected as well. Often, diminished or absent deep-tendon reflexes, particularly of the distal-most Achilles tendon reflex is a sign of motor involvement. Itch is under-recognized as a presenting symptom of SFPN.

The American Academy of Neurology currently recommends two diagnostic tests for SFPN, one being distal-leg skin biopsy immunohistochemically labeled against PGP9.5 to permit evaluation of epidermal small fibers (46). These must be fixed in special fixatives so paraffin-embedded biopsies fixed for dermatopathological examination cannot be used for this test (45). The other is autonomic function testing, also available at select teaching hospitals (46). This includes various measurements of different small-fiber functions, including sweat production induced by intradermal acetylcholine administration. If SFPN is diagnosed, it is important to look for treatable causes, as treating these is potentially curative. In developed countries, symmetric diabetic polyneuropathy, and perhaps even impaired glucose tolerance, is the most common cause. Tests that provide the highest yield of abnormality are blood glucose, serum \( \text{B}_{12} \) levels with metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis to look for hematogenous malignancies or monoclonal gammopathies (47).

TREATMENT OPTIONS

The best option is to diagnose and definitively treat the underlying neurological disorder, so dermatologists should consider neurological consultation for patients with recalcitrant itches of unclear etiology. However, treating symptoms is also important, because definitive diagnoses and disease-modifying treatments may not be found. There are neither high-quality clinical treatment trials for neuropathic itch nor U.S. FDA-approved treatments. Unfortunately, neuropathic itch does not usually respond to antihistamines, which is one way to recognize these disorders. The importance of behavioral therapies, including physical barriers to scratching, should not be underestimated, and should always be considered in patients with self-injury from scratching. Occasional patients with nerve compression or irritation from muscle or connective tissue may be able to treat their itch by reconfiguring these structures with stretching or exercise (44). Injections
of botulinum toxin to weaken impinging muscles may also be worth considering if the site of muscle-nerve interaction is precisely localized and the muscle can safely be weakened.

**Topical and intracutaneous treatments**

Topical local anesthetics are often effective for even the most severe forms of neuropathic itch (20), and should always be considered. The benefit of the other major topical therapy for neuropathic disorders, topical capsaicin, now available in concentrated 8% patches, is unknown. Because topical capsaicin causes distal axonal degeneration (48), potentially worsening causal nerve damage, it should not be prescribed lightly. Furthermore it is not approved for diabetic polyneuropathy. The U.S. FDA is currently reviewing an indication for HIV-associated polyneuropathy, but cost and practicality of application to large areas of skin are unclear at present. One case report found efficacy of topical tacrolimus for TTS, but as it was co-administered with gabapentin, the relative contributions of each are uncertain (49).

Several case reports and small series find efficacy for subcutaneous injection of botulinum toxin type A for focal neuropathic itch presenting as brachioradial pruritus or notalgia paresthetica (50). Independent of its effects at the neuromuscular junction to weaken muscles (see above), botulinum toxins also affect C-fibers to reduce their secretions that potentiate neurogenic inflammation and apparently also itch (51). This anti-pruritic effect is likely analogous to the relief of neuropathic pain demonstrated after subcutaneous injection of botulinum toxin type A into focal neuralgic areas (52).

**Oral medications**

These are largely untested for neuropathic itch. There are case reports of efficacy for various agents, but no clinical trials. These include pimozide and carbamazepine for TTS (53, 54), and gabapentin for brachioradial pruritus (55). Systemic local anesthetics and analogs such as mexiletine are untested but worth considering as they decrease neuronal action potentials, particularly in unmyelinated axons (39). Anti-epileptic drugs are another class of medication with similar effects to consider.

**Invasive treatments**

None have been studied prospectively, but clinical experience suggests that local-anesthetic nerve blocks will not treat chronic neuropathic itch, e.g. notalgia paresthetica, because they provide only transient relief of symptoms. There is no evidence that nerve blocks given early during the course of an illness such as shingles reduce risk or severity of later postherpetic itch. Such blocks can have diagnostic utility, for instance to con-
trigeminal or spinal nerve roots associated with focal radial itch. Neurologists or spine surgeon may be more willing to engage with patients with neuropathic itch if the causative lesion has already been identified.

ACKNOWLEDGEMENT

Funding: Supported in part by the NIH (NINDS K24 NS059892).

Disclosures: Dr. Oaklander receives research support from the National Institutes of Health, the Department of Defense, and several family foundations. She serves on the editorial boards of PAIN, Neurology Today, and Pain Research Forum. She is a member of the Scientific Advisory Board of the RSD Syndrome Association.

REFERENCES


36. Kinsella LJ, Carney-Godley K, Feldmann E. Lichen simplex chronicus as the initial manifestation of intramedul...