EDITORIAL (SEE YAMAOKA ET AL., P. 150)

Barely Scratching the Surface

Itching or pruritus is an unpleasant sensation that evokes the desire or reflex to scratch. Itching in people with diabetes for the most part suggests a skin condition such as psoriasis, eczema, sunburn, athlete's foot, hidradenitis suppurativa, pruritus vulvae from monilial infections, xerosis and diabetic eczema, necrobiosis diabeticorum, allergies to medications, drug eruptions, and many other conditions. Most are inflammatory disorders. In addition, there are generalized medical conditions that need to be excluded such as obstructive jaundice (bilirubin is a skin irritant at high concentrations), polycythemia that can cause generalized itching, myxedema, hypoparathyroidism, uremia, iron deficiency anemia, and malignancy or systemic internal cancers such as lymphoma or Hodgkin's disease (1). When all have been considered and excluded, the question that needs to be answered is, Does the itching derive from a peripheral or a central mechanism?

Sensations associated with scratching

Pain and itch have very different behavioral response patterns. Pain evokes a withdrawal reflex that leads to retraction and is therefore a reaction trying to protect an endangered part of the body. Itch creates a scratch reflex that draws one to the affected skin site (2). It has been hypothesized that motivational aspects of scratching include the frontal brain areas of reward and decision making. These aspects might therefore contribute to the compulsive nature of itch and scratching (2). It is clear, therefore, that itching is not skin-deep.

Unmyelinated nerve fibers for itch and pain both originate in the skin; however, information for them is conveyed centrally in two distinct systems that both use the same peripheral nerve bundle and spinothalamic tract (3). It is surprising, then, that no one has reported on itch as a symptom of neuropathy. In this issue of *Diabetes Care*, Yamaoka et al. (4) report on truncal itching as being a symptom of diabetic neuropathy. A large-scale survey of 2,656 outpatients with diabetes and 499 patients without diabetes was performed. The prevalence of truncal pruritus of unknown origin (TPUO) in diabetic subjects was significantly higher than that in age-matched nondiabetic subjects (11.3 vs. 2.9%; $P = 0.0001$). The prevalence of other forms of pruritus was not different between the two groups. Multiple logistic regression analysis revealed that abnormal sensation and deep tendon areflexia were risk factors for TPUO independent of age, sex, duration of diabetes, and A1C. Only TPUO related to objective measures of neuropathy; the other five categories of itching, such as head and neck pruritus of unknown origin, leg pruritus of unknown origin, pruritus caused by dermatitis, and pruritus due to athlete's foot, did not relate the presence or absence of neuropathy. More importantly, TPUO was found to correlate with symptoms of neuropathy, loss of deep tendon reflexes, and orthostatic hypotension. The authors speculate that this is, therefore, a dysfunction of the autonomic nervous system, but there are no measures of skin blood flow (5), sudorimetry, or small nerve fiber function (6,7,8) that might have solidified this speculation. The authors further postulate that pruritis may be due to an increased mast cell number and histamine content, which has been reported in experimental dry skin in mice (9). A second possibility is that the sensory C-fiber damage by ddiabetic polyneuropathy causes pruritus directly. Superficial skin pain is considered to be caused by abnormal firing of the pain nerve fiber in diabetic polyneuropathy patients (10). Similarly, abnormal firing of the nerve fiber of pruritus may induce TPUO. In fact, hyperplasia of the C-fiber in epidermis has been reported in dermatitis with strong pruritus (11). The unmyelinated C-fiber that transmits pruritus is a similar fiber to the sympathetic nerve ending in the skin. So, a significant association between TPUO and orthostatic intolerance seems to be reasonable. Both of the two etiological factors, dry skin due to sudomotor hypofunction and direct nerve fiber damage by diabetic polyneuropathy, might be involved in TPUO. To know the accurate etiology of TPUO, a skin biopsy and nerve fiber staining with anti-protein gene product 9.5 antibody in patients with TPUO may have helped (12). From the point of view of mechanistic aspects of itching, this report is barely scratching the surface of itching; hereafter, we will probe further than skin-deep. Itch can originate in the peripheral nervous system (dermal or neuropathic) or in the central nervous system (neuropathic, neurogenic, or psychogenic) (13).

Dermal/pruritoceptive

Itch originating in the skin is considered pruritoceptive and can be induced by a variety of stimuli, including mechanical, chemical, thermal, and electrical stimulation. The primary afferent neurons responsible for histamine-induced itch are unmyelinated C-fibers. Two major classes of human C-fiber nociceptors exist: mechano-responsive nociceptors and mechano-insensitive nociceptors. Mechano-responsive nociceptors have been shown in studies to respond to mostly pain, whereas mechano-insensitive receptors respond mostly to itch induced by histamine. Mechanically induced itch without a flare reaction does not involve histamine; therefore, it is possible that pruritoceptive nerve fibers have different classes of fibers (2).

Itch receptors are only found in the epidermis and the epidermal/dermal transition layers. Individual itch powder spicules (mucuna pruriens) cause maximal sensitivity when injected into the basal cell layer or the innermost layer of the epidermis. Surgical removal of those skin layers removes the ability for a patient to perceive itch. Itch is never felt in muscle, joints, or inner organs, which shows that deep tissue does not contain an itch-signaling apparatus (14).

Sensitivity to pruritic stimuli is not evenly distributed across the skin and has a random spot distribution with similar densities to that of pain. The same substances that elicit itch upon intracutaneous injection (injection within the skin) elicit only pain when injected subcutaneously (beneath the skin). Itch is readily abolished in skin areas treated with nociceptor excitotoxin capsaicin but remains unchanged in skin areas that were rendered insensitive to touch by pretreatment with saponins, an anti-inflammatory agent. Although experimentally induced itch can still be perceived under a complete A-fiber conduction block, it is significantly

diminished. Overall, itch sensation is mediated by A-δ and C nociceptors located in the uppermost layer of the skin (15).

Probing the beyond–skin-deep perception

Neuropathic itch can originate at any point along the afferent pathway as a result of damage to the nervous system, including diseases or disorders in the central nervous system or peripheral nervous system (14). Examples of neuropathic itch in origin are notalgia paresthetica, brachioradial pruritis, brain tumors, multiple sclerosis, peripheral neuropathy, and nerve irritation (16).

Neurogenic

Neurogenic itch, which is itch induced centrally but with no neural damage, is often associated with increased accumulation of endogenous opioids and possibly synthetic opioids (14).

Psychogenic

Itch is also associated with some symptoms of psychiatric disorders such as tactile hallucinations, delusions of parasitosis, or obsessive-compulsive disorders (as in OCD-related neurotic scratching) (14). Thus, attributing itch to a peripheral neuropathy requires careful exclusion of central causation.

Interactions between itch and pain: pain inhibits itch

Counter-irritation has often been used to decrease pain perception. It is often used clinically, e.g., the application of capsaicin that induces pain only to desensitize and relieve it. However, it appears that the sensation of itch can be reduced by many painful sensations. Ward et al. (17) reported the effects of noxious and nonnoxious counter stimuli, such as heat, physical vibration, or chemical stimulation on skin, were studied in healthy adults after they had experimentally induced itch (transdermal iontophoresis of histamine) and pain (with topical mustard oil) in their skin. They found that when they induced nonnoxious counter stimuli, the reduction of pain and itch only lasted for up to 20 s. However, when they induced noxious counter stimuli, there was a significant inhibition of itch for an extended period of time but no inhibition of pain. In addition, it was found that brief noxious stimuli created an antiitch state for more than 30 min. These findings show that itch is not a subliminal form of pain and that noxious counterstimulus is likely to act through a central mechanism instead of a peripheral one (17). Thus, noxious heat and scratching have an inhibitory effect on itch (18), but this needs to be demonstrated in diabetic polyneuropathy.

Mediators of itch

There is a long prodromal period of diabetic polyneuropathy in which there are increased levels of inflammatory cytokines (5). Inflammatory mediators, such as bradykinin, serotonin (5-HT), and prostaglandins, that are released during a painful or pruritic inflammatory condition not only activate pruriceptors but also cause acute sensitization of nociceptors. In addition, expression of nerve growth factors (NGFs) can cause structural changes in nociceptors, such as sprouting. NGF is high in injured or inflamed tissue. Increased NGF is also found in atopic dermatitis, a hereditary and noncontagious skin disease with chronic inflammation (19). NGF is known to upregulate neuropeptides, especially substance P. Substance P has been found to have an important role in inducing pain. Substance P may contribute to itch by increasing neuronal sensitization and may affect release of mast cells, which contain many granules rich in histamine, during long-term interaction (2). In those with diabetes, there is a deficiency of NGF and the response to substance P is impaired; again, one is surprised that truncal itching occurs in diabetic polyneuropathy.

Central sensitization

Noxious input to the spinal cord is known to produce central sensitization, which consists of allodynia, exaggeration of pain, and punctate hyperalgesia, which is extreme sensitivity to pain. Two types of mechanical hyperalgesia can occur: *1*) touch that is normally painless in the uninjured surroundings of a cut or tear can trigger painful sensations (touch-evoked hyperalgesia) and 2) a slightly painful pinprick stimulation is perceived as more painful around a focused area of inflammation (punctate hyperalgesia). Touch-evoked hyperalgesia requires continuous firing of primary afferent nociceptors, and punctate hyperalgesia does not require continuous firing, which means it can persist for hours after a trauma and can be stronger than normally experienced. In addition, it was found that in patients with neuropathic pain, histamine iontophoresis resulted in a sensation of burning pain rather than itch, which would be induced in normal healthy patients. This shows that there is spinal hypersensitivity to C-fiber input in chronic pain (2). Perhaps the damage to C-fiber in small fiber neuropathies (5) unbridles the central pruritogenic mechanism causing itching.

Thus, although truncal pruritus may have drawn attention to a possible relationship with diabetic polyneuropathy, this is only scratching the surface of the complex relationship between itching and central and peripheral somatic and autonomic nerve function. The provocative article in this issue of *Diabetes Care* should lead to an interesting probing of the complexities and depths of itching and provide new insights into the relationship between peripheral and central processing of cognitive function in diabetes.

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