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Research article

Distal Sensory Peripheral Neuropathy: An Undervalued Determinant of Wellbeing

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Introduction

Peripheral neuropathy (PN) is a significant, frequently debilitating complication of HIV infection and diabetes caused by damage to the sensory and motor peripheral nerves. In persons with HIV infection (PWH), neuropathy is thought to result from highly active antiretroviral therapy (HAART) neurotoxicity, particularly stavudine (d4T), dideoxycytidine (ddC), and didanosine (ddI), effects of HIV, or both [1]. Advanced age, taller height (as a proxy for longer neuronal axons), comorbid diabetes, and treatment with nucleotide reverse transcriptase inhibitors (NRTI), increased PN risk [2]. Among patients with diabetes, neuropathy is likely the culmination of multiple chronic insults to the nervous system, including hyperglycemia, microvascular insufficiency, oxidative stress, and autoimmunity [1,3,4]. Risk increases with advancing age and duration of diabetes, poor glycemic control, high body mass index (BMI), and comorbid conditions such as hypertension. While the prevalence of PN varies according to the types of criteria used for diagnosis, population demographics, stage of disease, and other variables, database reviews and meta-analyses estimate that between 30% and 70% of PWH and 10% and 90% diabetes cases are complicated by PN at any given time [4]. The most common type of PN among patients with HIV or diabetes is distal sensory peripheral neuropathy (DSPN), also called distal symmetric polyneuropathy, characterized by

progressive dysfunction of length-dependent sensory peripheral nerves [1,4-9]. Damage to large- and small-fiber neural networks cause a range of symptoms starting in the toes and feet, such as tingling, prickling, and discomfort, that increase over time in a symmetric, bilateral "stocking-glove" distribution involving the legs, hands, and arms. Symptoms may be accompanied by pain, either at disease onset or later in the course, typically described as burning, aching, shooting, or electrical [1].

DSPN is progressive and challenging to treat and has been consistently associated with reduced quality of life (QoL) [1]. Symptoms may start as minor annoyances and evolve over months to years into the main focus of patients' attention and disability [1,10]. In PWH, the presence of distal sensory paresthesias predicts the development of worsening symptoms and pain. As symptoms progress, patients may struggle to stand, walk, drive, sleep and lose the ability to perform basic activities of daily living (ADL) [11]. Loss of sensation or balance may lead to falls, injuries, and infections of affected limbs. Temperature sensation thresholds may shift, affecting sweating and increasing risk for burns. Physical symptoms and disabilities, social and work challenges, the stress of deteriorating QoL, and the threat of loss of independence may contribute to feelings of hopelessness and depression [1,12].

Painful peripheral neuropathies have been underdiagnosed for decades despite an enormous, multifaceted burden on patients' lives [5]. It is not altogether clear why; however a lack of awareness among patients and providers, frustrations inherent in diagnosis and managing a currently incurable disease, prioritization by providers attention to life-threatening complications, and scarcity of clinical time and resources are some hypotheses [2, 4, 7]. Firstly, patients may not mention their symptoms if not directly asked or may downplay the impact of their symptoms on their lives. In addition, they may harbor a belief that their symptoms are not severe enough to bring up or that their provider does not want to hear about them. And that belief may be somewhat founded. Providers may not ask about and assess for DSPN symptoms and signs to save time, focusing their attention on other primary pathology and more acute complications they perceive as more serious, more easily measurable, or more amenable to treatment. Providers may lack awareness of the burden borne by patients with DSPN or be reticent to discuss worsening symptoms, especially with patients who may be struggling with depression [13].

This is unfortunate, as early diagnosis is the goal, and diagnosing and managing neurologic symptoms is associated with improved wellbeing and health-related quality of life (HRQoL) [7,10]. In one study, PWH with PN (PWH-PN) who reported more engagement with their providers and a higher perceived "controllability" of their symptoms were more involved in their self-care. Additionally, they engaged in more effective self-care activities and had improved overall QoL. Although specific FDA-approved pharmacologic treatments are lacking, other pharmacologic and non-pharmacologic modalities are available that provide relief and enhance wellbeing for DSPN sufferers [14]. See the "Assist" discussion below.

The patient experience of DSPN is variable and complex. Actual descriptions offer valuable insights that cannot be gained from standard data-driven research into the immediate, real-world understanding of the disease. While evaluating patients for two non-pharmacological RCTs for moderate to severe neuropathic pain secondary to HIV (Clinical Trials Identifier: NCT03855111) and Type2 diabetes (NCT05104047) that are unresponsive to medical therapies, patients would report on their neuropathy symptoms and would often comment on the impact of DSP had on their lives [15]. Here we present candid comments, quotations, and background information from the medical literature for context, organized by four interrelated themes that emerged upon review: their experience of their DSPN symptoms, the impact of their symptoms on ADL, the motivation to stay independent, and strategies for coping. Both studies were approved by our Institutional Review Board and registered in ClinicalTrials.gov. Patient initials are fictitious.

The Patient Experience

Symptoms

In the early stages of DSPN, patients report experiencing symmetric bilateral paresthesias in the toes and/or feet as "pins and needles" sensation, tingling, prickling, tenderness, heaviness, restlessness, aching, burning, tightening, electric shock sensation, or numbness. These sensations may be accompanied by

pain, which may arise spontaneously or occur in response to sensory stimuli (which are innocuous to unaffected persons), such as the light touch of socks or bedsheets [1, 2, 15]. Pain associated with PN has been described as aching, burning, searing, shooting, jabbing, tingling, "being stabbed with a knife," or "walking on needles." Feet may be described as feeling like they are "on fire" or "squeezed into an ill-fitting shoe" [15]. For many patients, the paresthesias come first and predict the development of pain in later years [15,16]. Patient FG said, "I would feel such absolute intense aching and burning pain in my feet that basically immobilized me from walking [1,11]."

Another patient noticed that changes in the weather triggered his intermittent pain. "When it rains, I know it. I know it before the weatherman. So whenever I feel the pain in my legs, I know it is about to rain."

Pain or increased sensation with a light touch, i.e., hyperalgesia, may cause DSPN sufferers to alter the way they dress, opting for looser styles. They may avoid wearing socks and shoes or wear pants that do not brush sensitive ankles. A patient in our clinic wore overalls almost exclusively so that her legs, swollen from neuropathy, were unrestricted.

Patients may limit standing, walking, and all weight-bearing activities to avoid feeling pain in the soles of their feet. Stepping to avoid feeling pain often alters the normal gait, which may be insecure, wide, or high-stepping. Patients may be embarrassed and worry that, to an unwitting observer, their antalgic (ie., pain-avoiding) gait gives the appearance of being intoxicated [1,16]. For some patients, symptoms are worse at night and exacerbated by contact with sheets which interferes with sleep [1].

Patient AR said he experiences shooting pain in his feet intermittently during the days, stating, "Sometimes I'm walking, and I have to stop in my tracks to recuperate and let the pain subside." AR said his pain is at its worst at night, and he has trouble falling asleep. "I just lay in bed with shooting pain in my legs."

As symptoms progress, pain intensity and distribution increase, following a "stocking-glove distribution" starting in the big toe and feet, moving into the ankles, distal legs, proximal legs, and then the hands, wrists, and arms [1]. Although mainly a sensory neuropathy, motor symptoms including cramps and muscular weakness may be present in severe cases [1]. Pain may become chronic, constant, and debilitating, and activities of daily living increasingly difficult [2]. Patients may experience fatigue, difficulty concentrating, and altered sweating [1].

Daily Living

Patients with DSPN symptoms may struggle to perform domestic, work, and leisure tasks that the average person takes for granted. Due to paresthesias, pain, numbness, and struggles with balance, activities involving standing, walking, getting out of bed, and exercising may be challenging. They may require a cane to walk and watch their feet climb stairs to avoid falling. Patients may start to economize their steps around the house, batching tasks together to minimize the need to stand up and move around. They find it challenging to mop the floor, clean the house, and hold on to things [15].

Getting outside and taking a walk may be difficult. Due to foot

pain, they may have to limit exercise on rowing machines or other apparatuses involving a foot strap etc [15].

AR, a patient with diabetes and DSPN, who walks with a cane, stated, "Sleeping, driving, and walking are some of the normal tasks that I can't do as well as I used to. In addition, the shooting pains in my legs and feet prevent me from driving safely. I can't feel the gas or brake pedal."

Many patients may cut back on their social interactions to avoid explaining their invisible disability and their limitations to others. Many patients with DSPN are unable to work [5].

Independence

Several patients told us that they are currently dependent on others for transportation and other basic needs or fear they will soon be. The prospect of losing independence can be a source of tremendous distress, triggering feelings of inadequacy, shame, depression, and hopelessness [5,15].

FG, a patient with HIV and painful DSPN said, "When my neuropathy was at its worst, I was unable to take the train to commute into the city. I could barely get out of bed. I was in a terrible place mentally."

His depression, he said, was made worse by what he perceived as a lack of interest on the part of his primary care doctor. He said, "It is tough to be in this much pain. I know there is no cure for this yet, but I hope some new treatments are available for PN down the line. We need help."

Other patients report pushing through the pain to remain independent. For example, patient LA said, "I can do most of the activities I would like to, but there is much more pain involved. It's not always easy to do my routine or get out of bed, but I do not want to feel dependent on anyone else."

Coping

"Illness representation," a construct that describes how patients think about and makes sense of their illness, influences coping styles, and maybe predictive of self-care behaviors and quality of life outcomes. Effective coping strategies reduce stress; they may also reduce physical pain, increase treatment adherence, and improve other determinants of wellbeing [14,17].

An essential domain within the illness representation model is patients' perception of having some semblance of "control" over their destiny. This is consistent with our observation that patients whose statements indicated an internal locus of control (vs. an external locus of control or feeling victimized) were motivated and proactive about their self-care, more hopeful about their futures, and generally seemed more optimistic [14]. Ways of coping reported by our patients included: staying focused on finding effective pain relief, thinking positively and taking life day by day, harnessing their motivation to live independently, and finding supportive environments and people—including their medical team—where they felt validated and respected.

Patient FG, for example, spoke to the power of perseverance and pain relief. Essentially bedridden by pain and depression at the start of therapy, FG achieved pain reduction to manageable levels, resumed his usual routine, and found renewed hope for his future within nine months of starting treatment. But, he stat-

ed, "You have to find a treatment that helps reduce the pain and keep fighting."

Feeling allied with their medical team is also helpful to patients, especially those lacking in social support or caretaking, struggling with current or imminent homelessness, or facing multiple health-related and personal challenges. The study of a PWH-PN cohort mentioned above showed that engagement with their provider (and a feeling of control) was significantly associated with more frequent self-care activities [14]. Engaging with patients may involve inquiring about DSPN symptoms, helping them find solutions, or simply listening to them share their experience, all of which engenders trust and empowers patients to succeed [18].

RL, a middle-aged patient with DSPN secondary to HIV, reported that his healthcare clinic and staff helped him cope. "It's a welcoming environment. I feel like they listen." Conversely, feeling alone in their predicament engenders despair. Patient FG reported feeling "alone" and "ignored" by his medical team. "My pain was unbearable, and frankly, my doctor was not helpful. It was a dark time in my life."

Focusing on Symptoms and Quality of Life

Diagnosing and managing PN has been shown to improve patients' quality of life significantly. Providers optimize their delivery of care to patients with diabetes and HIV/AIDS when they stay Aware of the potential for DSPN, Ask their patients about symptoms and the impact of symptoms, Assess patients' feet and peripheral nervous systems, and Assist patients in finding pain relief and tools to maintain their QoL [10].

Be Aware

The main goal of this manuscript is to elevate QoL's status in the evaluation and management of patients with DSPN and encourage the valuation of QoL to the same degree as patients value it. In addition, we encourage providers to be aware of the signs and symptoms of DSPN in the evaluation of at-risk patients, become curious about patients' experience of their symptoms and daily functioning, and stay current on established and emerging options for DSPN management.

Ask

It is important not to presume that patients will necessarily volunteer information about how they are doing or that a lack of complaint indicates an absence of PN symptoms. A complete history and review of systems should include neurological symptoms of the feet, recognizing that patients with early distal peripheral neurologic symptoms may not recognize them as such or mention their symptoms without being specifically asked. Start with open-ended questions about what is bothering them.

Then ask about PN symptoms specifically. For example, have they experienced numbness, changes in sensation, difficulty feeling hot or cold, tingling, pins, needles, burning, aching, or pain in their toes, feet, legs, hands, or arms? Have they had recent injuries, accidents, burns, falls, or infections? Are they having any difficulty with their balance, walking, driving, sleeping, dressing, or doing what they usually do?

For patients with known DSPN, ask how their symptoms affect their life, how they are feeling in general, and how they are coping; validate their experience. Listen to their responses, and make it clear that how they are doing matters and that you are an advocate for their wellbeing.

Structured reporting instruments, such as the Gracely Pain Scale (GPS), Sensory Peripheral Neuropathy Screen (SPNS), NIH Patient-Reported outcomes Measurement Information System (PROMIS), and Body Pain Maps may help quantify and monitor patient symptoms [19].

Assess

Patients may have signs of DSPN, such as decreased vibratory sensation or diminished ankle reflexes, before developing symptoms. Electrophysiologic evidence of neuropathy (reduced nerve conduction velocity and amplitude) may be present in up to two-thirds of PWH [1,7,20]. Thus, regular foot examinations and neurologic sensory assessments are appropriate in at-risk patients, irrespective of the presence or absence of symptoms [21]. Patients at increased risk for DSPN include prediabetes, diabetes, HIV infection, especially those older, tall, or treated with nucleoside analog reverse transcriptase inhibitors or anti-Tb agents [1]. Early detection is the goal [22]. Incorporate examination of bare feet into routine clinic visits. For example, the Semmes-Weinstein monofilament examination for assessing pressure sensation takes less than one minute per foot to perform. A tuning fork may be used to check for a high vibratory threshold, an essential indicator of subclinical PN [23]. Assessments for abnormal proprioception, temperature, pinprick sensation, and deep tendon reflexes are easy and quick to perform [1,19,16,20,23,24].

Instruments for screening and monitoring positive neuropathic signs include the Michigan Neuropathy Screening Instrument (MNSI), the Diabetic Neuropathy Examination, and others.

Assist

Assist DSPN patients in identifying therapies and resources that will improve their QoL, including analgesic and antiepileptic medications, marijuana prescriptions, complementary and alternative medicine (CAM) therapies, and innovative treatments available through clinical trials. Surveys show that CAM therapies are widely used to treat neuropathic pain, and many patients reported significant relief [19,26,27]. Providers play critical roles in identifying and mitigating comorbid neuropathogenic factors, such as hyperglycemia, hypertension, dyslipidemia, obesity, smoking, and vitamin deficiencies [26, 27]. Additionally, making needed referrals (e.g., occupational therapy, podiatry, neurology, mental health, and pain management); and providing resources eg: Foundation for Peripheral Neuropathy and other advocacy groups where patients can receive support. Providers can provide in-office education, counseling, and support around foot care and inspections, proper footwear, fall prevention, and other topics [19, 23,25]

Summary

Peripheral neuropathy and painful peripheral neuropathy are prevalent among patients with HIV and diabetes and present significant challenges. In the absence of disease-modifying therapies, raising the importance of patients' symptoms and lived

experience in clinical settings is critical to improving QoL. Providers play a central role in alleviating suffering by observing symptoms and signs, diagnosing PN early, and partnering with their patients to find pain and symptom relief and resources for ongoing support.

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Conflicts of Interest

"The authors declare no conflict of interest."

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