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CASE REPORT

Phenotype-Based Therapy for a Patient with Painful Diabetic Neuropathy

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Introduction

The International Association for the Study of Pain (IASP) defines neuropathic pain (NP) as "pain caused by a lesion or disease of the somatosensory nervous system." However, in many patients, there is no clearly identifiable or visible organic pathology that can be specifically targeted, making NP a challenging medical entity to manage. Conventionally, various international bodies recommend treatment based on the level of available evidence. Gabapentinoids and tricyclic antidepressants (TCAs) fall in Tier I, followed by selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), topical lignocaine 5% patches, and neuromodulatory interventions as Tier II or III medications.

There are also other strategies for managing NP, including therapy directed towards the underlying etiology or specific diagnosis. For example, duloxetine is an evidence-supported treatment option for diabetic neuropathy, gabapentinoids are frequently used for radicular neuropathic pain, and sodium-channel blockers may be useful in post-herpetic neuralgia. However, it has been seen that despite having the same diagnosis, not all patients respond similarly to conventional therapy.

Approximately one and a half decades ago, an approach directed towards the underlying pathophysiology and sensory characteristics of neuropathic pain began to receive increasing attention. Etiology, together with the genetic makeup of an individual, environmental factors, and the underlying pathophysiological processes, may manifest as different sensory characteristics, also referred to as the pain phenotype. Therefore, treatment directed towards the predominant sensory phenotype may provide a more individualized approach to neuropathic pain management.

Case Report

We present the case of an 18-year-old male, a known patient with type 1 diabetes mellitus (DM), who was referred to our pain clinic with severe, resistant neuropathic pain in both lower limbs for three months. His symptoms had not responded adequately to high-dose pregabalin (150 mg/day), tramadol, and paracetamol.

The pain had developed gradually over the preceding few months. It was continuous, with no specific aggravating or relieving factors. His Douleur Neuropathique 4 (DN4) score was 4/10,

comprising predominantly of severe burning pain, with a numerical rating scale (NRS) score of 8–10/10 (0 represents no pain and 10 represents the most severe pain imaginable). The severity of the burning sensation was such that the patient constantly immersed his feet in cold water for relief. The burning pain was accompanied by tingling sensations involving the feet and distal legs. Progressive deterioration of symptoms resulted in significant functional impairment. The patient required a wheelchair for ambulation and was unable to sleep adequately at night.

On physical examination, there was a significant decrease in touch sensation, along with allodynia and hyperalgesia to pinprick in a stocking distribution. Motor strength, proprioception, and tendon reflexes were diminished in both lower limbs, with greater involvement on the left side. Nerve conduction studies demonstrated severe distal symmetrical sensorimotor polyneuropathy (DSPN). His glycemic control had shown some improvement, with HbA1c decreasing from 11% to 9.3% during the preceding nine months while receiving insulin therapy. Investigations including erythrocyte sedimentation rate (ESR), rheumatoid factor, thyroid-stimulating hormone (TSH), free T4, folic acid, and vitamin B12 were within normal limits.

The patient was admitted for continuous monitoring of blood glucose levels and control of his debilitating symptoms. Considering the underlying etiology and the predominant pain phenotype —burning pain with paresthesias, hyperalgesia, and allodynia—we initiated oxcarbazepine at 150 mg twice daily and duloxetine at 60 mg once daily and discontinued pregabalin. Vitamin B12 and omega fatty acid supplements were also prescribed, along with tramadol and paracetamol for analgesia.

After one week of treatment, the patient reported a 25% improvement in burning pain and allodynia. Oxcarbazepine was subsequently increased to 300 mg twice daily and duloxetine to 120 mg once daily. After another week of treatment, there was approximately 90% relief in tingling, hyperalgesia, and allodynia, along with a 50% reduction in burning pain.

The patient had significant improvement in the quality of his life and was then able to walk without support. However, during the preceding week, he had experienced an episode of urinary retention requiring catheterization for one day. Following this episode, the dose of duloxetine was reduced to 90 mg orally once daily. He was discharged after two weeks of treatment and was followed up in the pain clinic two months after discharge.

At follow-up, he reported approximately 70% relief in burning pain and 90% relief in the other sensory symptoms.

Discussion

Our experience in managing this patient by taking into consideration the etiology and sensory phenotype of his neuropathic pain was clinically encouraging. Neuropathic pain can exist in several morphological and sensory forms, regardless of its underlying etiology. Researchers have classified neuropathic pain into five dimensions or pain phenotypes: (a) superficial pain, such as burning; (b) deep pain, such as pressing pain, compression, or tightness; (c) paresthesia/dysesthesia, including tingling and sensations elicited by brushing; (d) evoked pain, including hyperalgesia and allodynia; and (e) paroxysmal pain, such as electric-shock-like or sharp pain (1).

This variability in clinical presentation may reflect differences in underlying pathophysiological mechanisms or interactions between etiology, genotype, and environmental influences (2,3). The combination of positive and negative sensory symptoms in an individual patient has been described as a pain fingerprint or sensory profile.

Several tools are available to characterize the sensory phenotype of patients with neuropathic pain. The DN4 questionnaire is a 10-item tool based on symptoms and clinical examination and is useful for diagnosing neuropathic pain if it scores ≥4/10. The Neuropathic Pain Symptom Inventory (NPSI) provides a subjective assessment of different dimensions of the pain phenotype, whereas quantitative sensory testing (QST) provides an objective assessment of stimulus-evoked sensory responses (4,5). QST can also be used during follow-up for sequential assessment of stimulus-evoked sensations over time.

To identify the pain fingerprint of a patient, the neuropathic pain characteristics are predominantly classified as negative or positive phenotypes. Negative neuropathic symptoms resulting from degeneration or dysfunction of sensory fibres include hypoesthesia, hypoalgesia, numbness, and an elevated heat-pain threshold. Damage to the somatosensory system may result in impaired transduction because of terminal atrophy, impaired conduction due to loss of peripheral axons, or impaired transmission due to loss of central terminals and neuronal cell death. Such patients respond to gabapentinoids, transcutaneous electrical nerve stimulation (TENS), visual illusion techniques, and cognitive behavioural therapy, depending on the individual clinical context.

Positive symptoms may be spontaneous or evoked. Spontaneous symptoms can result from partial injury to sensory afferents, which may lead to altered expression or function of nociceptive sodium channels, ectopic activity, and irritable nociceptors. These may manifest as burning pain, paresthesias, or dysesthesias. This phenotype may respond to centrally acting analgesic agents, including TCAs or SNRIs.

Stimulus-evoked positive symptoms may be associated with altered expression or function of receptor and ion-channel proteins, including TRPV1, and may manifest as allodynia or mechanical and thermal hyperalgesia. Such patients may respond to gabapentinoids for evoked pain, with or without antidepressants for centrally mediated pain. In selected patients with peripheral neuropathic pain, topical capsaicin or sodium-channel blockers such as oxcarbazepine may also be considered, although the evidence supporting phenotype-specific selection remains limited.

Based on diagnostic studies, certain symptom clusters appear to predominate in different neuropathic pain etiologies. Diabetic polyneuropathy predominantly presents with sensory loss (83%), mechanical hyperalgesia (75%), and thermal hyperalgesia (34%). Therefore, pregabalin may be considered for patients with prominent negative sensory symptoms or mechanical hyperalgesia, whereas an SNRI such as duloxetine may be particularly useful in patients with prominent spontaneous pain.

The prevalence of chronic neuropathic pain may be as high as 16–26% among patients with diabetes and is associated with metabolic and vascular abnormalities, including glycosylation-related nerve injury, nerve ischemia resulting from microvascular alterations, and changes in voltage-gated sodium-channel expression (7,8). Despite frequent use of combination pharmacotherapy according to individual symptoms and comorbidities, treatment outcomes in painful diabetic neuropathy (PDN) remain modest. Evidence from duloxetine and pregabalin trials suggests that only approximately 47% of patients achieve a 50% reduction in pain intensity (9).

Recent clinical trials have investigated a therapeutic approach to neuropathic pain based on pain phenotype (10–12). Data from the large multinational randomized double-blind COMBO-DN trial (12) were further explored in another study (10), which suggested that NPSI dimensions such as burning pain and paresthesia may show greater improvement with increasing doses of

duloxetine rather than by adding pregabalin. Pregabalin appeared to have greater effects in patients with certain other pain characteristics, including paroxysmal pain.

Previous studies have reported variable efficacy of oxcarbazepine in patients with PDN. Some studies suggest that the presence of an irritable-nociceptor phenotype, characterized by hyperalgesia or allodynia with relative preservation of thermal sensation on QST, may respond to sodium-channel blockers such as oxcarbazepine (13,14).

In the present case, the patient had marked burning pain accompanied by evoked pain in the form of hyperalgesia and allodynia, together with a poor response to pregabalin before presentation to our clinic. These features provided the rationale for initiating treatment with a combination of oxcarbazepine and duloxetine. A clinically significant improvement in symptoms was observed within two to three weeks. The patient's functional status also improved considerably, from wheelchair dependence to independent ambulation.

However, the episode of urinary retention following escalation of duloxetine should be noted as an important clinical event. The dose of duloxetine was therefore reduced, although a definite causal relationship between the medication and urinary retention cannot be established from this single case.

Conclusion

There are currently no universally accepted guidelines for phenotype-based management of neuropathic pain, and the available evidence remains limited. Therefore, firm conclusions regarding the superiority of phenotype-based treatment or the efficacy of a particular drug combination cannot be drawn from a single case.

Nevertheless, this case illustrates the potential value of assessing individual sensory characteristics in addition to considering the underlying etiology when selecting treatment for painful diabetic neuropathy. The presence of prominent burning pain, paresthesias, hyperalgesia, and allodynia, together with inadequate response to pregabalin, guided the selection of duloxetine and oxcarbazepine in this patient and was associated with substantial symptomatic and functional improvement. Further prospective studies are required to determine whether phenotype-guided treatment can consistently improve outcomes and patient satisfaction in painful diabetic neuropathy.

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Declarations

Ethics Approval

Formal institutional ethics committee approval was not required for this single-patient case report, in accordance with standard journal policy for case reports.

Patient Consent

Written informed consent for publication was obtained from the patient (confirmed per Editor-in-Chief directive, 27 Sep 2026).

Conflict of Interest

There is no conflict of interest of any contributing author.

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Author Contributions

Dr Chetna Shamshery: case management and editing of the article. Dr Vineetha G Gopal: basic first write-up of article. Dr Anil Agarwal: editing of the article. Dr Aakanksha Aggarwal: write-up and editing of article.