Strategies for the diagnosis and treatment of neuropathic pain secondary to diabetic peripheral sensory polyneuropathy

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Abstract

This article proposes a strategy for the diagnosis and treatment of neuropathic pain due to diabetic peripheral sensory neuropathy, based on 15 years of experience in French pain-management centres and on the available literature. In the diabetic patient with chronic pain in the lower limbs, the first step in the diagnostic process is to identify the neuropathic origin of the pain. The second step is to evaluate the patient’s medical history and make a rigorous baseline assessment of the neuropathic pain symptoms to determine an effective pain-management strategy. In the third step, adequate and well-tolerated treatment directed towards a variety of painful symptoms is selected, taking into account other co-morbidities such as anxiety and depression. This report reports on the clinical aspects of neuropathic pain exhibited by patients with diabetic sensory polyneuropathy, and the key factors in their diagnosis and treatment, based on the results of meta-analyses and on a recent expert consensus.

Keywords: Diabetic polyneuropathy; Neuropathic pain; Antidepressants; Antiepileptics; Review

Mots clés : Polyneuropathie diabétique ; Douleur neuropathique ; Antidépresseurs ; Antépileptiques ; Revue générale

1. Introduction

Patients with diabetes suffer from a number of painful conditions during the course of the disease, among which neuropathic pain is one of the most common and disabling [1,2]. The clinical presentation of neuropathic pain secondary to diabetic peripheral sensory polyneuropathy is disconcerting and often misleading. Pain symptoms usually occur in association with neuropathic lesions, but they follow an unpredictable pattern of evolution as they develop independently of the severity of the neuropathy and can persist over years [2].

During the past 10 years, increasing scientific interest in pain syndromes has helped practitioners to overcome difficulties in managing patients with neuropathic pain [2]. The assessment of neuropathic pain syndromes, whatever their aetiology, has been facilitated by screening and diagnostic instruments that can
2. Clinical aspects of pain in diabetic sensory polyneuropathy

2.1. General considerations

Neuropathic pain secondary to diabetic sensory polyneuropathy is typically polymorphous. Pain symptoms usually occur with the onset of polyneuropathy and fluctuate for years, independently of the extent of neuropathic lesions. Indeed, there is no correlation between the intensity of pain symptoms and the severity of sensory deficit.

The prevalence of painful neuropathy is estimated to be 10–15% of patients with diabetes [5,6]. In half of these, pain symptoms are initially experienced together with the onset of the neuropathy [7,8]. The symptoms are diverse, but are generally mild in intensity and almost always disabling. During the course of the disease, patients may experience a number of different complaints, resulting in confusion for their physicians [9]. Pain remission tends to be observed when the sensory deficits are nearly complete, and ends in ataxia, or when metabolic balance is reached after a long period of imbalance. In the latter case, the improvement in pain symptoms is always transient. However, in the majority of patients, partial remission of pain symptoms alternates with episodes of deterioration, depending in part on the patients’ psychological and emotional state.

2.2. Pathogenesis

Distal symmetrical sensory polyneuropathy represents the most common presentation of neuropathy in diabetic patients. Diabetic peripheral neuropathy can present as either painful, with or without sensory deficit, or pain-free and mainly characterized by sensory loss. It is not known why some patients experience neuropathic pain and others, with similar nerve lesions, do not. It has been suggested that other concomitant painful conditions (such as osteoarthritis) as well as the patient’s psychological state (for example, anxiety or depression) play a role in the development and severity of pain [9].

In physiological conditions, painful stimuli are transmitted by peripheral nerves along small non myelinated (C-type) and thinly myelinated (A-delta-type) fibres. In diabetic sensory polyneuropathy, these are the fibres typically involved as along with large myelinated fibres (A-alpha and A-beta). The reduction or loss of small fibres leads to loss of pain sensation (heat pain, pin-prick), and temperature perception to cold (A-delta) and warm (C) stimuli. In contrast, the loss of large fibres leads to the reduction/loss of vibration sensation, touch, pressure and tactile discrimination, which finally leads to sensory ataxia.

The progressive loss of small non myelinated epidermal fibres is also known to be painful, leading to a persistent sensation of superficial burning, and the progressive disappearance of temperature and pain sensations. When pain symptoms are present, their pattern follows that of thermal sensory abnormalities. In addition, the concomitant distal loss of epidermal C fibres and large myelinated sensory fibres is frequently related to distal paraesthesias and dysesthesias affecting the toes; in such patients, vibration perception thresholds are also abnormal [10].

The mechanisms of the genesis of pain during different stages of diabetic neuropathy are still not completely understood, and the precise role of small-nerve damage remains to be clarified. Quantitative sensory testing (QST; thermotesting) of thermal and nociceptive thresholds is a useful tool in clinical and experimental conditions for measuring sensory impairment and abnormal function of small nerve fibres. Thermal sensory dysfunction of the feet is associated with an increase in activity thresholds of epidermal C fibres on QST. It was first suggested that thermal sensory dysfunction correlated with the presence of neuropathic pain symptoms in diabetic patients [11]. However, these findings were not confirmed in larger cohorts of patients with diabetic neuropathy, as the reduced perception to thermal stimuli was similar in those with and without painful symptoms due to neuropathy [12–14]. This means that abnormalities of small-fibre function, as determined by cold detection and heat pain thresholds, do not predict either the presence or intensity of pain symptoms.

Another experimental procedure for identifying small-fibre abnormalities is direct examination of intraepidermal nerve fibres via skin biopsy. The density of intraepidermal C fibres is much more reduced in diabetic compared with non diabetic subjects, and is significantly lower in patients with neuropathic pain compared with those without pain [13]. In addition, more severe loss of intraepidermal nerve fibres is associated with neuropathic pain in patients with few or no objective signs of polyneuropathy, as assessed by vibration-perception thresholds. Abnormalities of small fibres are likely to play a key role in the onset of pain in those who exhibit few objective signs of neuropathy, whereas their involvement is less marked in patients with severe signs of neuropathy. High rates of both degeneration and regeneration of small myelinated fibres have been observed more frequently in patients who experienced pain, whereas extremely low levels of epidermal C-fibre density were found in patients who expressed little or no pain [15]. Data suggest that a progressive and ongoing destruction of C fibres may be a key mechanism of pain generation until they are completely destroyed.

Thus, not only the loss of C fibres, but also the regeneration of small non myelinated and myelinated fibres, and subsequent neuroplastic changes, appear to underlie the pathogenesis of neuropathic pain secondary to diabetic polyneuropathy throughout its natural course [16]. Different substrates of pain generation have been identified in such neuropathological conditions, including ectopic and spontaneous firing of C fibres due to
increased sodium channels, transmission of pain signals along large myelinated fibres that do not normally transmit pain, and long-lasting neurochemical changes in the dorsal root ganglia and dorsal horn of the spinal cord after partial loss of sensory afferents [17].

2.3. Symptoms and signs

Pain symptoms are initially distal, affecting the toes and feet bilaterally and more or less symmetrically. They then evolve upwards, beginning in the lower limbs, and progressing to the upper limbs, abdominal median line and scalp.

The pain is usually rated as mild to moderate in intensity, ranging from 3 to 7 on a visual analogue scale (VAS). However, 10–15% of patients have pain symptoms of severe intensity [1,5,9]. The most frequent and long-lasting pain phenomenon is a spontaneous, permanent, superficial sensation of burning in the legs that increases in the late afternoon or at bedtime and is partially relieved by movement. Numbness and tingling are the most frequently associated non pain symptoms, and are not spontaneously reported by patients [7,18]. Numbness as well as paraesthesias are correlated with an abnormal perception of vibration [7].

Several other signs are highly suggestive of neuropathic pain, some of which are spontaneous and others evoked, such as allodynia (pain due to a stimulus that does not normally cause pain) or hyperalgesia (severe pain due to a stimulus that normally causes only slight pain) (Fig. 1). Tactile allodynia (pain induced by gentle brushing of the skin) observed at bedtime on the dorsa of the feet is specifically triggered by skin contact with the sheets. Thermal allodynia is an abnormal sensation—distinct from burning pain—that is induced by contact with an object of a temperature that does not normally induce pain. This infrequent, but extremely disabling, sensation is mainly observed at night (the patient needs to keep the feet clear of the bedding). When coupled to tactile allodynia, thermal allodynia can induce great discomfort in diabetic patients while tending to their foot care. The sensation, described as thousands of slight bites into the calves, is usually experienced while walking, but can also be induced while bathing or showering. Hyperalgesia to light pressure is limited to the calves and ankles, and is often experienced while wearing shoes. When associated with proprioceptive hyperalgesia, symptoms may be mistaken for limping (claudication) of vascular origin. Dysesthesias on the calves are generally variable throughout the day and can be triggered by contact with socks or trousers. In contrast, cramps are not neuropathic pain symptoms as such, but are highly suggestive of motor impairment and are usually reported in the late stages of polyneuropathy (Fig. 2).

Finally, once polyneuropathy has been diagnosed, it has been suggested that patients with type 1 diabetes experience paraesthesias and burning pain more frequently than do patients with type 2 [7]. However, in our experience and to our knowledge, the type of diabetes is not a discriminating factor in the occurrence of pain symptoms in patients with neuropathy.
the neuropathic pain is demonstrated to be diabetes. Soon as the neuropathic source of pain is recognized and before the aetiology of distal sensory polyneuropathy. Note that symptomatic treatment is proposed as Fig. 2. Algorithm for diagnosis of lower-limb pain in a diabetic patient with origins are the most commonly seen. Relevant subjective symp-
toms reported by the patient can guide the physician during the
cal presentations, the physician is likely to repeat the patient’s
development.

However, once a neuropathic origin of the pain syndrome has been clearly identified (see below), the severity of the pain should be assessed using patients’ self-evaluated questionnaires. The Neuropathic Pain Symptom Inventory ([NPSI]; in French) is the first validated questionnaire to specifically address neuropathic pain descriptors with proven sensitivity to changes with treatment [19]. The Neuropathic Pain Scale ([NPS]; in English) is a less-sensitive instrument than the NPSI, and assesses the multidimensional nature of neuropathic pain [20]. A global and rapid evaluation of pain symptoms and associated consequences (affective, emotional and functional) is also provided by the new modified version of the Brief Pain Inventory ([BPI]; in English and French) [21].

2.5. Diagnosing the neuropathic nature of pain

Diabetic patients may experience pain of diverse aetiology in the lower limbs; those of vascular, osteoarthritic and neuropathic origins are the most commonly seen. Relevant subjective symptoms reported by the patient can guide the physician during the diagnostic process. A diagnosis of neuropathic pain secondary to diabetic polyneuropathy can only be made after careful clinical examination. In addition, the neuropathic origin of pain symptoms is easily assessed through a clinician-administered questionnaire called the Douleur Neuropathique en 4 Questions (DN4), which can identify chronic pain with neuropathic features with good specificity and sensitivity [22] (Table 1). DN4 comprises 10 simple items, including pain descriptors and signs related to bedside examination, and is validated in both French and English versions. The questionnaire is a useful tool for the diagnosis of neuropathic pain in clinical research and everyday clinical practice. An algorithm based on DN4 has also been proposed (Fig. 3) for the diagnosis of neuropathic pain in diabetic patients.

QST is another sensitive tool for the assessment of sensory abnormalities associated with pain, and is useful for documenting changes in sensory thresholds in longitudinal evaluations of diabetic patients with neuropathy [23]. However, QST cannot be used in routine clinical practice as it requires a complex setting. Electrophysiological measures (nerve conduction, amplitudes) are limited in detecting diabetic neuropathy as they only apply to the largest myelinated fibres. This means that they can provide only indirect information on symptoms and deficits [5].

According to the grading system for neuropathic pain recently proposed by the International Association for the Study of Pain [24], pain affecting the lower limbs of a diabetic patient is of undoubted neuropathic origin when localized to an area exhibiting sensory loss consistent with a documented neural lesion. If nerve damage is not found (normal electoneuromyography with C-fibre loss as the only abnormality), then neuropathic pain is considered probable—in which case, the pattern of pain symptoms and sensory deficit is crucial. If painful signs are suggestive of neuropathic pain, but no clinical

### Table 1

<table>
<thead>
<tr>
<th>Question 1</th>
<th>Yes or No</th>
<th>Features:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is pain associated in the same area to one or more of the following symptoms:</td>
<td>Yes</td>
<td>Burning</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Burning</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Painful cold</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Painful cold</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Electric shocks</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Electric shocks</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Tingling</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Tingling</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Pins and needles</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Pins and needles</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Numbness</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Numbness</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Itching</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Itching</td>
</tr>
</tbody>
</table>

An item is scored as 1 if present or 0 if absent. Neuropathic pain is considered highly probable if the total score reaches 4/10 (82.9% sensitivity and 89.9% specificity) [22].
examination and exploration of nerve damage are available, then neuropathic pain is considered possible. As some painful signs are highly suggestive of neuropathic pain, the combination of pain symptoms (as described above) with loss of pain, or thermal or vibration sensation, bilaterally and symmetrically in the legs is the most characteristic presentation of neuropathic pain secondary to diabetic polyneuropathy.

3. Treatment of neuropathic pain in diabetic sensory polyneuropathy

3.1. Diabetes therapy

It is now well established that rigorous glycaemic control reduces the risk of peripheral sensory neuropathy and that regular assessment of polyneuropathy, once it is diagnosed, will slow the progression of the complication [2]. However, there are no data demonstrating that preventative or potentially curative measures can reduce the incidence of neuropathic pain in diabetic patients [25]. It is suggested that appropriate control of diabetes and prevention of diabetes complications may well have a positive effect on the occurrence and severity of neuropathic pain symptoms. However, the factors that influence or determine the onset of neuropathic pain in a given patient are, in fact, not known. To date, there is no proven preventative treatment, but only symptomatic treatment, for neuropathic pain secondary to diabetic polyneuropathy.

3.2. Symptomatic treatment outcomes

The efficacy of a given pain treatment is best evaluated using a VAS that measures the intensity of pain experienced by the patient over the course of the past 24 hours. This has been recommended by both clinical practice and controlled clinical trials [26]. The VAS score provides practitioners with a subjective, yet realistic, evaluation of pain that allows incremental follow-up of the patient.

As there are a number of different neuropathic pain symptoms, each can be assessed by a VAS, whereas their improvement with treatment is best followed with the NPSI self-questionnaire. Other major components of chronic pain states—such as anxiety, mood, sleep disturbances, functional impact and quality of life—are especially integrated in diabetic patients. These dimensions can be documented by specific scales, or simply by scoring the rate of change after treatment.

The efficacy of pain treatment is also assessed through the percentage of pain relief (where a visual scale is not appropriate, such as in patients with retinopathy). A 50% drop in pain intensity is considered clinically significant, although achieving 30% is considered a realistic and satisfactory result by most patients [27,28]. Efficacy data should always be weighed against safety data—the adverse events reported by the patient. The acceptable balance between treatment efficacy and safety should ideally be determined by the patient himself, as this can vary widely from one individual to another.

The optimal duration of symptomatic treatment of neuropathic pain is unknown. Recent recommendations by French experts suggest that neuropathic pain treatments should continue for at least 2–3 months, after which the treatment drug doses should be gradually decreased and restarted if necessary [29]. In our experience, the usual duration of treatment at a stable dose is about 6 months.

3.3. Overview of symptomatic treatments

A number of double-blind, randomized, placebo-controlled trials have been carried out on the symptomatic indication of ‘neuropathic pain secondary to diabetic sensory polyneuropathy’—indeed, the most widely used clinical model for demonstrating drug efficacy and safety in peripheral neuropathic pain [3,26]. Systematic reviews and meta-analyses of randomized controlled trials have recently been published [3,30–42], and have provided landmarks for treatment guidelines [4,34,43]. An overview of drug efficacy, based on the most recent meta-analyses [3] and expert guidelines [34], is proposed in Table 2, using the number needed to treat (NNT; number of patients that need to be treated to prevent one patient from having a negative outcome). Although therapeutic options for first- or second-line therapy primarily rely on the efficacy and safety as demonstrated in controlled trials, our proposals also take into account the following considerations:
According to our experience of the management of patients with neuropathic pain referred by endocrinologists, the risks and tolerability issues (such as gastrointestinal impairment, cognitive impairment and sedation) overlap benefits most often with the use of strong opiates, even at low doses. However, this therapeutic option may still be considered for patients who cannot tolerate or do not respond with antidepressants or antiepileptics, despite appropriate dosages and treatment durations [42].

Finally, at present, there is no scientific evidence that spinal cord stimulation is an effective treatment of neuropathic pain due to diabetic polyneuropathy; this procedure is associated with an elevated risk of infections in diabetic patients [47].

### 3.5. Therapeutic options

In our experience of more than 300 diabetic patients, more than 95% were significantly improved with a multifactorial approach that combined specific neuropathic pain treatment, localized care of diabetic feet and global care, including psychological aspects. In addition to the treatment of concomitant nociceptive pain with analgesics and physical therapy, and the management of the subsequent anxiety or depressive mood, the treatment of neuropathic pain is mainly pharmacological and based on specific drugs. In accordance with the above-mentioned considerations, we here offer a treatment strategy that can be followed on a daily basis (Fig. 3). Tricyclics at low doses [37], duloxetine (a serotonin–norepinephrine reuptake inhibitor [SNRI]) [48] or the new antiepileptics (gabapentin, pregabalin) [33] should be given as the first-line treatment, whereas oxycodone (a strong opiate) [49] or venlafaxine (SNRI) [3] should only be prescribed for patients after treatment failure or intolerance with the previous drugs used either alone or in combination. Tramadol, a level-2 analgesic according to the World Health Organization classification system, is an adequate option when combined with specific drugs in patients who also have a nociceptive component (such as osteoarthritis) [3,36]. Table 3 presents the therapeutic preferences and most common side-effects of each drug that should be taken into account before being prescribed.

### Table 3

<table>
<thead>
<tr>
<th>Drug</th>
<th>Preferences</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol</td>
<td>Concomitant nociceptive pain</td>
<td>Elderly patients</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Anxiety signs</td>
<td>Renal impairment</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Sleep disturbances</td>
<td>Renal impairment</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Depressive mood</td>
<td>Same as SSRI and SNRI</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Sleep disturbances</td>
<td>Anticholinergic effects</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Anxiety signs</td>
<td>Sedation</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Sleep disturbances</td>
<td>Cardiac arrhythmia</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Anxiety signs</td>
<td>Patients with cardiac risk</td>
</tr>
</tbody>
</table>

SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin–norepinephrine reuptake inhibitor.
4. Conclusion

In the diabetic patient with sensory polyneuropathy, neuropathic pain is usually independent of the severity of the neuropathic lesion. The intensity of pain is greatly influenced by the patient’s affective (emotional) state. Identification of the neuropathic source of the pain is based on the patient’s clinical examination, although practical tools such as the DN4 questionnaire can help practitioners in their clinical analyses. Once the neuropathic origin of the pain has been diagnosed, symptomatic treatment with specific pain drugs should be started immediately. Antidepressants (tricyclics, duloxetine) or the new antiepileptics (gabapentin, pregabalin) should be given as the first choice, considering their efficacy and safety profiles. Due to the multifactorial nature of chronic pain, however, specific drugs should be used together with localized and global care to ensure significant pain relief, improved functional status and a better quality of life.

5. Conflict of interest

Dr Guastella has participated in clinical trials and been retained as a consultant for Pfizer. Dr Mick has participated in clinical trials and been a consultant for Eli Lilly, Pfizer, Grüenthal, Janssen-Cilag, Glaxo Wellcome, Astra Zeneca, Wyeth and Amirall.

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