

# Should we test for neuropathy in patients with venous leg ulcers – a new hypothesis?

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## WHAT IS THE RATIONALE FOR PROPOSING THE ASSESSMENT OF NEUROPATHY IN VENOUS LEG ULCERS?

In the world of wound healing, neuropathy is commonly associated with diabetic foot ulcers or pressure ulcers. With respect to leg ulcers, peripheral arteriopathies with macroangiopathy or microangiopathy are known to lead to ischemic polyneuropathy, mainly due to hypoxic tissue and nerve damage.<sup>1</sup> However, chronic venous insufficiency (CVI) can also lead to neuropathy, even though it is not commonly discussed.<sup>2</sup> In fact, the most advanced stage of chronic venous disease, which is venous ulceration, also has microangiopathy among its pathogenesis, but little is said about possible involvement of peripheral nerves. In contrast to this lack of evidence in the subject, it is remarkable the frequent symptomatology of patients with CVI that can be considered neuropathic: cramps, dysesthesia, painful sensations and paresthesia.<sup>2</sup> Furthermore, considering the extent of tissue damage in venous leg ulcers (Figure 1), it is intuitive to think that nerve damage is also occurring and that nerve damage may also impair healing. Additionally, nerve involvement may result in muscle dysfunction, alterations in mobility and a decrease in range of motion may lead to gait alterations all affecting calf muscle pump function and, consequently,



Figure 1. Venous leg ulcer

promote CVI.<sup>3</sup> Analogous to neuropathic ulcers in diabetes, the CVI-associated neuropathy may also be a cofactor in the development of venous ulcers.

## WHAT IS THE AVAILABLE EVIDENCE ON THE ASSOCIATION BETWEEN VENOUS LEG ULCERS AND NEUROPATHY?

Few studies have assessed the association between neuropathy and CVI. A research group<sup>1</sup> examined 30 patients with CVI and 20 healthy controls using motor and sensory nerve conduction studies, vibration testing and thermotesting, quantitative sudomotor axon-reflex test, and laser Doppler flowmetry. In this study subjects with possible confounding factors for peripheral neuropathies (diabetes mellitus or peripheral degenerative arteriopathy) were excluded. Their findings were prolongation of distal motor latency of the peroneal nerve, increased limits for warm and cold detection and reduced vibration sense in the CVI group. Consequently, the results demonstrate a disturbance of A-alpha fibers, A-beta fibers, A-delta fibers, and thermos afferent-C fibers, possibly induced by ischemia due to venous microangiopathy and increased endoneural pressure. Their findings are significant and inspiring to think that more importance should be given to the diagnosis and treatment of neuropathy in venous ulcer patients. Few studies have been published since then, in the last 20 years. Moreover, an observational study showed that 65% of patients with stages C3 or C4a Clinical, Etiological, Anatomical and Pathophysiological (CEAP) Classification venous disease and neuropathy noted improvement or resolution of their neuropathic symptoms in patients with CEAP C3 or C4a after successful closure of incompetent great saphenous veins.<sup>4</sup>

Even though specific neurological complementary tests are not always available, questionnaires exist as screening tools for neuropathic pain. A recent study on neuropathy and chronic venous disease has found that patients with worse CVI had significantly worse neuropathy with higher Neuropathy Symptom Score and Neuropathy Disability Score values compared with patients with less severe CVI.<sup>5</sup> The DN4 test has been translated into several languages, including

Spanish, and includes questions to be answered by the patient about the presence of positive symptoms (burning, painful cold, cramps, tingling, pins and needles, numbness, itching) and a physical examination to rule out negative symptoms (hypoesthesia, hypoalgesia and anesthesia) and hyperalgesia.<sup>6</sup> The use of this test is not widespread in leg ulcers, not only because of ignorance of its existence, but also because of a lack of knowledge of the technique for nerve examination of the leg. There is also a general lack of awareness among professionals about considering nerve damage or nerve pathology in making treatment decisions

## WHAT ARE OUR HYPOTHESES BASED ON PUBLISHED LITERATURE AND OUR OBSERVATION IN CLINICAL PRACTICE?

Based on what we observe in our clinical practice and what has been published in the literature, we have generated five hypotheses that need further research:

- Neuropathy may be related to the time to complete epithelialisation of the venous leg ulcer.
- There may be prognostic value in assessing positive and negative symptoms.
- Neuropathy symptoms (positive or negative) may improve after treatment of chronic venous insufficiency with compression therapy/endovenous treatment: If they are reversible, the improvement of neuropathy may correlate with ulcer epithelialisation.
- The real benefit of different therapeutic strategies beyond gabapentinoids, for instance sodium blocker antiepileptics or antidepressants, could be measured.
- The role of neurostimulation in the treatment of leg ulcers with neuropathy could be explored using a diagnostic tool.

## WHAT IS OUR PROPOSAL TO TEST THESE HYPOTHESES?

In order to develop studies that allow us to test these hypotheses, we need a simple and basic neurological examination that can be performed by non-experts and that can be generalisable, and could be inspired by the DN4 test, including a basic exploration of the sensitivity, including or not motor innervation, of the leg and questions related to the presence of typical positive symptoms (burning, painful cold, cramps, tingling, pins and needles, numbness, itching). The aim of this simple exploration, which can be carried out by all professionals (even non experts), is to be a tool similar to the monofilament and tuning fork test on the foot,<sup>7</sup> but on the leg and applicable, not only to people with venous ulcers (which is the most frequent cause of leg ulcers), but to any type of leg ulcer.

Nerve fibres are divided into motor, sensory and vegetative fibres. Sensory and motor fibres are divided into fine, small diameter, myelin and amyelin, which carry thermal and pain sensations, and coarse, medium or large diameter myelin, which carry sensations of touch, pressure and proprioception and motor impulse.

There are tools to measure all these sensitivities, but a simplification that could help us in the consultation are these two examinations on the sensory fibres with the patient's eyes

closed and with the thigh as the control area:

- Hypoaesthesia to touch: patients should indicate whether they feel the touch on the leg
- Hypoaesthesia to blunt needle prick: patients should indicate whether they feel the prick or not

Following the questions and examination we propose, if there is clinical evidence compatible with neuropathy, that compression neuropathy due to oedema must first be ruled out. In this case the priority would be to optimise compression therapy and anti-oedema measures to reverse the damage.

Moreover, we must also assess the patient as a whole, as pruritus may be the symptom of a systemic disease such as renal pathology (uremic pruritus), hepatic pathology (pruritus due to cholestasis), thyrotoxicosis, neoplasms (polycythemia vera, Hodgkin's lymphoma, gastric carcinoid, etc.), side effects of drugs (opioids, cocaine, amphetamine) or even psychogenic causes.

## WHAT THERAPEUTIC IMPACT CAN NEUROPATHY ASSESSMENT HAVE ON PATIENTS WITH VENOUS ULCERS?

If positive symptoms are present, the prescription of gabapentinoids and/or antidepressant drugs may alleviate the neuropathic symptoms.<sup>8</sup> Even if some experts recommend vitamin B complexes or alpha-lipoic acid, the available evidence in peripheral neuropathy, especially in diabetic foot, includes few robust trials and does not allow to determine the real benefit of these treatments.<sup>9,10</sup> Although the finding of negative symptoms has no effective treatment, their exploration can serve to objectify the benefit or otherwise of the aetiological treatment of the venous ulcer (compression therapy and/or intravenous treatment) on the neuropathy.

## WHAT LIMITATIONS DO WE FORESEE WITH THE TOOL WE PROPOSE?

The main limitations of a simplified assessment are that the examination may be not exhaustive, which reduces its sensitivity and, in addition, given that the patients are usually multi-pathological, with other potential causes of neuropathy, it does not allow a causal relationship with chronic venous insufficiency to be established. Moreover, if the test does not include motor fibers examination, which could be one of the causes of muscle impairment in patients with venous leg ulcers, it could be biased. Another important limitation is that the sensitivity exploration is not validated for the intensity required when touching or placing the needle, so, some degree of inter-explorer variability may be expected.

## CONCLUSION

As a conclusion, the scarcity of published studies suggest that neuropathic pain is underdiagnosed and undertreated in patients with venous leg ulcers.<sup>11</sup> This new field of research may not only help to better treat patients' symptomatology, but also increase understanding of the pathophysiology of venous ulcers and enhance and evaluate therapies focused on nerve stimulation.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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