

THE REHABILITATION OF ONCOLOGICAL PATIENTS PRESENTING NEUROPATHIES

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Abstract

The International Association for the Study of Pain (IASP 2011) defines neuropathic pain as “the pain caused by an injury or disease of the somatosensory portion of the nervous system”. The central neuropathic pain is defined as “the pain caused by an injury or disease of the central somatosensory central nervous system”, whereas the peripheral neuropathic pain is defined as “the pain caused by an injury or disease of the peripheral somatosensory nervous system” [1].

The peripheral neuropathy describes any affection of the peripheral nervous system. The etiology is vast, there being a number of over 100 possible causes, which causes the global morbidity rate to reach approximately 2.4%. The chronic nature of the pain superposes the everyday routine and leads to the high intake of medication for pain alleviation. The number of cases of neuroplasia has always increased today. This disturbing diagnosis which can potentiate the signs and symptoms of peripheral neuropathy as well as reduce and limit the treatment options associated with neuropathies. The treatment presupposes a multidisciplinary approach, while the solution to prevent complications involves the control of risk factors and pathophysiological treatment.

Chemotherapy-induced peripheral neuropathy (CPIN) is a significant disabling symptom that is tightly connected to the administration of neurotoxic cytostatic agents used for the treatment of neoplasia. CPIN compromises the quality of life and produces pain or discomfort [2].

I have sought to produce a presentation of the medicated and physical-kinetic treatment options that have proved their effectiveness during clinical studies or random trials and can be applied to cancer patients presenting with symptoms associated with peripheral neuropathy, namely with neuropathic pain, and support it with arguments.

Keywords: neuropathy, neoplasms, rehabilitation

Introduction

Chemotherapy-induced peripheral neuropathy is the final result of lesions at the level of the motor, sensory or autonomous neuron, second to the effect of the neurotoxins which disable the components necessary to the metabolic needs of the axon [2].

Neuropathies can affect the motor neurons, the sensory neurons and the mixed nerves alike, the symptoms varying depending on the type of nerves affected. Consequently, it is difficult to define this condition in only one sentence. Neuropathic pain is the most frequently

encountered and the most disturbing symptom of peripheral neuropathies. Its general characteristics include burning sensations – in some cases paroxysmal and in others perceived as a sensory disorder (allodynia, hyperalgesia, hyperpathia), it may be accompanied by reflex sympathetic dystrophy and its intensity is influenced by fatigue or emotions. Neuropathic pain can affect one nerve (mononeuropathy) or multiple nerves (polyneuropathy) [3].

Neuropathic pain is common in cancer patients and difficult to treat as it requires a wide range of analgesics, from non opioid ones to morphine derivatives. In 10% of cases, interventional techniques are required: nerve blockade or intrathecal administration associated with systemic medication [4].

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In cancer patients, the classification of pain is very important for the treatment of the neuropathy. Thus, the neuropathic symptoms may or may not be related to the neoplasia.

Neuropathic symptoms may occur prior to the onset of neoplasia or as a consequence of it. If connected to the symptoms of neoplasia, we can differentiate between causes determined by the tumor itself, as in the case of malignant plexopathy; mononeuropathy; or through the epidural compression of the spine; and causes determined by the treatment associated with the tumor, as in the case of cytostatic neuropathy – most frequently determined by treatment with vincristine; cranial neuralgia; radiation plexopathy; post-toracotomy pain.

Many chemotherapy agents are associated with neurotoxicity and peripheral polyneuropathy (PNP). The latter occurs in 70-100% of patients treated with chemotherapy agents administered in large doses and in 12% of patients treated with chemotherapy agents administered in minimum doses. The causes of PNP are correlated to the inconsistent repair of the DNA (the interaction between free radicals and proteins, fats and fat acids which causes structural and functional modifications at their level) [5].

Pharmacological agents such as cytoprotective agents, vitamins, electrolytes, infusions, aminoacids, tripeptides, neurotrophic factors, antidepressants, anticonvulsants and some cytokines and carnitines have been the focus of recent research. There is no evidence to support pharmacological interventions on patients presenting with CPIN at present. The effectiveness of pharmacological agents in the prevention or treatment of CPIN has not yet been determined [2].

There are several risk factors associated with neuropathies but unrelated to the presence of neoplasia. The most frequently encountered is diabetes mellitus, which has also made the subject of the most studies on the triggering factors of neuropathies. Vitamin B12 and folic acid deficiencies are also common causes, as shown by a large number of studies. Other causes mentioned in the specialized literature include alcohol consumption, medication – statins, antibiotics (Metrodanizole and Isoniazid) –, autoimmune disease (systemic lupus erythematosus, rheumatoid polyarthritis, Guillan-Barre syndrome), STDs (AIDS, syphilis), renal insufficiency, postherpetic neuralgia, congenital conditions (neurofibromatosis, Fabry disease, Tangier disease, hereditary amyloidosis), hereditary conditions (polyneuropathy, Charcot-Marie-Tooth disease), exposure to toxins (heavy metals, compounds of gold, lead, arsenic, mercury, pesticides).

In the case of diabetic neuropathy, the quality of life of patients is assessed using a so-called Norfolk QoL-DN questionnaire, which is standardized and validated by Eastern Virginia Medical School, USA.

Pathophysiology

The main types of neuron lesions are Wallerian degeneration, demyelinating neuropathy and axonal degeneration. Wallerian degeneration occurs when both the axon and the myelin sheath present simultaneously lesions, which in the case of the peripheral nervous system usually occurs through trauma. Demyelinating neuropathy is characterized by the deterioration of the myelin sheath while the axon either remains intact or is affected subsequently. In the case of axonal degeneration, it is the neuron that deteriorates first and then demyelination follows. Axonal polyneuropathy is potentially reversible when the etiology is eliminated or controlled (e.g. diabetes mellitus).

There are two mechanisms that are most commonly responsible for the occurrence of neuropathies: microangiopathy (a functional or structural lesion at the level of the vasa nervorum) and the direct effect of metabolic factors on nervous components. These two factors act simultaneously. One of the most important connections between them is the nitric oxide (NO) depletion, which may occur as a result of a lesion caused by the blood flow and the exaggerated production of oxygen free radicals (highly reactive molecules, secondary products present in all basal metabolic cells during physical exercise, pathological states, aging). In association with the insufficient antioxidant mechanisms (vitamin C, vitamin E, Glutathione, coenzyme Q, Alpha Lipoic Acid), the latter cause the onset of oxidative stress (which is associated with diabetes mellitus, atherosclerosis, heart disease, neurodegenerative disease, neoplasia). Hyperglycemia stimulates the production of nitric oxide [6].

The inflammation accelerates the production of free radicals, which attack the nervous cells. The mitochondrion plays a central role in cell metabolism, constituting the main location where oxygen free radicals (OFR) form. OFR carry out simple reactions with proteins, fats and nucleic acids, causing structural and functional modifications at their level [6].

Positive diagnosis

In most cases, polyneuropathy sets on as paresthesia in the distal area of the inferior extremities. Sensory examinations reveal hypo-anesthesia (in all sensory aspects), hypo-reflexia, muscular hypotrophy (occasionally even flaccid paralysis) and autonomous involvement. However, polyneuropathy may affect a single limb, a single body area, the symptoms may be predominant at a proximal level or they may involve the cranial nerves. The extension of the demyelination and axonal involvement for a differentiation between myogenic and neurogenic affections and an alteration of the myoneural transmission is possible through electromyography (EMG) or electroneurography (ENoG). Occasionally, nerve or muscle biopsy is required, a histological examination of affected tissues under an optical or an electronic microscope or the

utilization of genetic or enzyme histochemical molecular methods. In addition, a detailed evaluation of the etiology and the selection of treatment require systematic medical, immunological, infection or laboratory evaluations, neuroimaging or other diagnoses methods.

Treatment

Neuropathic pain affects a large number of aspects of a patient's life so that a multidisciplinary approach is essential for its management. The purpose of treatment is to delay, stop or reverse the progression of the consequences of the neuropathy [6].

In the case of neuropathies unrelated to any oncological cause, the first stage consists in the treatment of the underlying disease, which supposes the elimination of risk factors (e.g. the control of the glycemic levels in the case of diabetic neuropathy) and a proper hygienic-dietary regime, followed by symptomatic drug-treatment and an adequate physical-kinetic one.

In the case of neuropathies related to an oncological cause, therapy consists in a "disease modifying treatment" (surgery, radiotherapy or chemotherapy, depending on tumor sensitivity); physical-kinetic therapy and pharmacotherapy are associated to control unpleasant symptoms. Pharmacotherapy is associated with the use of opioid and/or non opioid and adjuvant analgesics, the latter being divided into 3 groups: antidepressants (e.g. amitriptyline, venlafaxine, duloxetine), anticonvulsants (e.g. sodium valproate, phenytoin, carbamazepine) and local anesthetics (e.g. lidocaine) [7]. The guidelines have decided gabapentin (a medicine used in antiepileptic treatments) as the first medicine to be used [8].

Another effective course of treatment includes the intradermal injection of botulinum toxin type A. However, this treatment is not applied because of the elevated costs [9].

No studies have been conducted using alpha lipoic acid (ALA) in patients presenting with neoplasia, but there is evidence of its benefits on diabetic polyneuropathy. A meta-analysis consisting of four trials conducted on 1,258 patients presenting with diabetic polyneuropathy proved that an ALA treatment (600 mg/day I.V.) applied over 4-5 days a week led to a significant improvement in the main symptoms associated with diabetic polyneuropathy [2].

An initial study was performed in 2004, on 161 patients diagnosed with colorectal cancer and treated with oxaliplatin based regimens. 60% of them (96 patients) received IV calcium and magnesium (1 g of each) before and after the oxaliplatin. The results indicated that only 4% of the patients who had been administered calcium/magnesium, rejected the treatment because of the neurotoxic effects of oxaliplatin, while 31% of the patients withdrew from the control group. At the end of the treatment, 20% of the patients in the study group presented neuropathy, while 40% did not.

The weakness of this study was due to the fact that it was retrospective, non-randomized and unblinded. In 2011 the North Central Cancer Treatment Group (NCCTG) started and then published the preliminary results of a double blind, placebo-controlled trial in the adjuvant setting of the colon cancer. The study was closed prematurely because of insufficient patients enrolled in the trial. So the NCCTG has initiated another prospective randomized, double-blinded trial [2,10].

Capsaicin is another method used to treat neuropathic pain, one which has not been studied on oncological patients. Studies on capsaicin have been conducted within the treatment of peripheral neuropathy in diabetic patients. However, the results were inconclusive and therefore this course of treatment is not recommended at present [2].

Other agents with a promising manifestation in preliminary studies but in need of fundamentamentation include Glutamine, Glutathione, N-Acetylcysteine, Oxcarbazepine and Xaliproden [11].

Steroids should be considered in the event of nerve compression. There is evidence that I.V. Lidocaine and its oral correspondent, Mexiletine, constitute a more effective method to reduce neuropathic pain than placebo in adult oncological patients and can alleviate the pain in selected patients [12]. There may be two or more neuropathy etiologies in one oncological patient. In these cases, the treatment method may come with relative or absolute contraindications regarding the oncological etiology (e.g. vitamin supplements).

Vitamins: a risk or a benefit?

B vitamins interfere with cell metabolism (whether healthy or affected by neoplasia). Vitamin B1 (thiamine) is a coenzyme involved in the carbohydrate metabolism and the nervous function; vitamin B2 (riboflavin) and B3 (niacin) are coenzymes integrated in the cycle of citric acid, the metabolism of fat acids and the transportation of electrons. Vitamin B12 is a coenzyme involved in the metabolism of folic acid and the nervous function. Folic acid is a coenzyme involved in the synthesis of DNA and RNA acids.

There are numerous studies proving the effectiveness of vitamin B use for the treatment of neuropathic pain. They alleviate neuropathic symptoms of any etiology both individually and combined. There are few studies on oncological neuropathy!

Vitamin B1 (thiamine) deficiency has proved to be a trigger for peripheral neuropathy post gastrectomy or dietary imbalance [13].

The intake of vitamin B6 lowers the risk of developing colorectal cancer [14].

A study conducted on vitamins B1, B6 and B12 in Finland revealed a significantly lower risk of developing a pulmonary neoplasm in patients with high vitamin B6 levels. Therefore, vitamin B6 plays a protective role against

pulmonary neoplasms as well [15].

The effect of vitamin E on CPIN was assessed within two pilot trials and a minor randomized one which revealed that there are some benefits to the oral administration of vitamin E in association with cisplatin. However, no standard dosage has been established and more randomized controlled trials are required to further assess the neuroprotective effects of vitamin E [2].

Neuropathic pain – treatment. Studies conducted on physical procedures

Objectives:

- Pain management
- Maintaining or improving joint mobility
- Maintaining or improving muscular force
- Gait training
- Easing the performance of activities of daily living (ADL)

- Improving life quality

Transcutaneous electrical stimulation (TENS) is the physical procedure most frequently used in the treatment of peripheral neuropathy regardless of the etiology.

No studies on TENS have been conducted on patients presenting with neoplasia. Studies on the treatment of diabetic neuropathy have proved that TENS is effective and can improve the pain symptoms even after therapy has been interrupted [16,17].

A study revealed an improvement of the numb sensation, stinging pain and allodynia associated with modifications in the perception of vibrations and temperature and a reduction of the pain threshold by means of TENS therapy. Another study revealed that high-frequency muscle stimulation is more effective than TENS as far as the improvement of pain evaluation scores and peripheral neuropathy symptom evaluation are concerned. However, both proved effective in the alleviation of symptoms. No risks regarding the application of TENS therapy in patients presenting with neoplasia have been reported [2].

LASER light radiation therapy is also an option, depending on the case particular features. This treatment is associated with the fewest relative or absolute contraindications. No studies that advise against the use of LASER therapy in oncological patients have been found.

Both therapy methods are applied at a distance from the tumor.

Hydrogymnastics in a pool at a neutral temperature of 35-37° C +/- herbs. This technique causes an improvement in the central and peripheral blood flow and stimulates the cardiorespiratory capacity. Demonstrated effects include the increase of the nerve sensitivity threshold and the stimulation of the metabolism [18].

No studies advising against hydrotherapy in patients presenting with neoplasia are known at present!

Thermal and electrotherapy are avoided on account

of their stimulation of the blood flow and cell metabolism (healthy cells and by analogy, cells possibly affected by neoplasia). Precaution is recommended despite the absence of studies to demonstrate any possible negative effects. The absence of studies explains the fact that these therapeutic methods are associated with relative contraindications rather than with noticed harmful effects.

Occupational therapy guarantees an improvement of fine movements and the reeducation of perception. It uses vibrating platforms and balance systems as support devices.

Neuropathic pain often becomes aggravated or intricate due to the secondary lymphedema of resections or nodal or lymphatic vessel irradiation. It is associated with a wide range of treatment methods from manual compression therapy and tapping to surgical interventions.

Kinetotherapy is applied in parallel with the training in compensatory strategies and the proper use of support devices and orthoses with the purpose of obtaining maximum autonomy during occupational and physical therapy. Motor deficiency is a common complication associated with neuropathy in oncological patients. They can benefit from kinetotherapy (but the intensity and duration must be correlated with the patient's condition). Self care is sought in intermediary/advanced stages.

No studies have been conducted on the effect of physical effort, exercise or kinetotherapy as concerns the prevention or treatment of peripheral neuropathy in patients presenting with neoplasia. However, three minor studies showed a significant improvement (in function, action and nerve conduction velocity of the peroneal and sural nerve) of the progressive endurance and stretching exercises in the case of treatment of peripheral neuropathy and muscle dystrophy [2].

Compensatory strategies are applied as support for orthostatism, transfers or ambulation. Stimulation and energy preservation strategies can also be useful in patients dealing with severe fatigue. The patient is taught to adjust their posture and alter their biomechanics in order to maximize their strength and preserve their muscle groups.

Stretching is used for the antagonists of the muscles affected by neuropathy. Orthoses can also be used to maintain posture. Also within kinetotherapy, physiotherapists must insist on muscle toning exercises with or without the association of bio-feedback techniques, proprioception facilitation or stimulation.

Gait training is conducted using walking devices if the pain or muscular deficiency does not allow orthostatism or ambulation.

Orthoses are useful for the consolidation of stability and security in patients with motor deficiencies (they protect and stabilize the joints controlled by weak muscles, maintain the joints in functional positions and complete the motor function that has been lost).

The supply of proper support devices is critical for

the therapy to be successful. There are no studies related to the utilization of support devices in patients presenting with neoplasia. However, two non-randomized trials have been conducted on the use of canes and orthoses in diabetic patients. These devices proved efficient in the prevention of falls, improvement of balance and proprioception. Although the utilization of support devices does not reduce the effects of peripheral neuropathy directly, some patients enjoy the aforementioned benefits. Consequently, it is recommended that patients presenting with peripheral neuropathy (even oncological patients) be guided towards an occupational therapist that can provide them with a cane, an orthosis or a splint [2].

Acupuncture is another alternative treatment method. Only one minor case study has been conducted on the application of acupuncture in CPIN. This treatment method led to an improvement of the senses and motion as well as a reduction of the dose of analgesics received by the five patients involved in the study. Improvement was also made in terms of gait and no side effects were noticed. The symptom control procedure was conducted over a period of six months in four of the five patients treated. Acupuncture was also studied in patients presenting with diabetes mellitus and infected with the HIV virus. The results were mixed. None of the studies revealed risks or side effects [2].

Conclusions

There are numerous studies that demonstrate the efficiency of B vitamins therapy (vitamins B1, B2, B6, B12 in particular) in the treatment of peripheral neuropathy. The majority of studies focus on the efficiency of this therapy in patients presenting with diabetic polyneuropathy (more common).

There are a number of studies demonstrating the effectiveness of vitamins B in the treatment of chemotherapy-induced neuropathy.

I have found no studies on the relation between the treatment of neuropathy with vitamins B in oncological patients and/or the aggravation of the basal disease.

The majority of conclusions are extrapolations of studies on chronic neuropathy in non-oncological patients [11].

In a summary of the most important 9 Clinical Guidelines related to the treatment of neuropathy in oncological patients, the following conclusions are stated:

The majority of development groups extrapolated their results starting from studies on non-oncological patients in order to formulate recommendations. Therefore, these guides do not provide solutions to important situations, such as altered kinetics and side effects in these patients [11].

Most of the clinical research on the treatment of neuropathic pain targets patients presenting with painful diabetic neuropathy (PDN) or postherpetic neuropathy

(PHN) and rarely in patients manifesting neuropathic pain caused by neoplasia. Patients presenting with neoplasia and neuropathic pain should be treated differently than patients presenting with neuropathy due to other causes, for several reasons. Firstly, approximately 50% of patients with a neoplasm and neuropathic pain also present nociceptive or visceral pain. This is not the case in patients presenting with neuropathy due other causes. Secondly, they are more sensitive as they suffer from a disease that jeopardizes their life. Thirdly, the effect of the antiepileptic or antidepressant agent associated with the opioid drugs is lesser in patients manifesting neuropathic pain caused by neoplasia than in patients manifesting neuropathic pain developed from other causes [12].

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