TREATMENT OF DIABETIC NEUROPATHY

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[Terapia della neuropatia diabetica]

ABSTRACT

Diabetic neuropathy is the most common variety of neuropathy in the world. It is a disease that recognizes inadequate control or long duration of diabetes as risk factors and one of the features that set it apart from many other neurological diseases is its clinical polymorphism, the most common form of which is distal symmetrical polyneuropathy. It can be asserted that diabetic neuropathy is a constantly growing disease in correlation with incorrect habits typical of modern society. Timeliness of diagnosis is the most important prerequisite to start appropriate treatment, which is the subject of this review.

Key words: Diabetic neuropathy, neuropathy, diabetes, therapy, treatment.

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Introduction

Diabetic neuropathy, a common occurrence in neurology, is the most common variety of neuropathy observed in industrialized countries and perhaps even in the world. It is a disease that recognizes inadequate control or long duration of diabetes as risk factors and one of the features that set it apart from many other neurological diseases is its clinical polymorphism, the most common form of which is distal symmetrical polyneuropathy.

An accurate and especially early diagnosis of diabetes is critical, because the assessment of the prognosis and choice of treatment depend on the degree of metabolic disorder, and this is supported by the fact that in recent years attention has been placed on a possible association between an unmanifest sensory polyneuropathy and impaired glucose tolerance in the absence of overt diabetes, hyperglycemia or increased glycosylated hemoglobin.

It can be asserted that diabetic neuropathy is a constantly growing disease in correlation with incorrect habits typical of modern society.

Timeliness of diagnosis is the most important prerequisite to start appropriate treatment in all possible forms.

Therapy

Several aspects of the treatment of diabetic neuropathies should be taken into consideration.

First you need to consider all patients with peripheral diabetic neuropathy at risk of developing feet ulcers. Therefore, it is important to provide instructions to patients for plantar care possibly with the support of a podiatrist.

A distinction should be made between symptomatic treatment and etiological treatment.

As for symptomatic treatment, pain and autonomic disturbances must be considered.

The treatment of pain is a very frequent problem in both focal neuropathy and distal symmetric polyneuropathy. Unfortunately, however, there is no clear evidence that normalizing blood glucose levels can be useful to reduce the intensity of neuropathic pain but often cruralgia and other truncal

pains end, sometimes due to the start of insulin therapy, which seems to have a certain efficacy in these forms[1]. Because rapid changes from hypoglycemia to hyperglycemia have been shown to induce and worsen neuropathic pain, the stable glycemic control may be as important as the actual level of control in relieving neuropathic pain[2].

The drugs available for the treatment of neuropathic pain are varied. The most commonly used molecules are: gabapentin, pregabalin, duloxetine, lidocaine, capsaicin, and tricyclic antidepressants. The latter give the best results by iv, but it must be borne in mind that they can decompensate an orthostatic hypotension that was asymptomatic because of their anticholinergic effects, among which reflex tachycardia and dizziness should not be forgotten. Among these drugs it must be stressed that for duloxetine and pregabalin there is greater evidential strength based on the results obtained from large experimental case histories[3-5].

Duloxetine is a selective inhibitor of serotonin and noradrenaline re-uptake and hence acts by increasing the central inhibitory tone on pain transmission and, among other things, maintains its efficacy and is well tolerated even for long periods of time. The most common side effects of duloxetine are nausea, sleepiness, constipation, dizziness and excessive sweating. Other drugs that can be used are also traditional tricyclic and dopaminergic antidepressants[6-8].

Pregabalin binds selectively and with a high affinity with a subunit of the calcium channels by reducing penetration in the neurons and thus preventing the release of certain neurotransmitters involved in pain transmission[9]. The most common side effects of pregabalin at doses found to be effective for pain treatment are dizziness, drowsiness, and peripheral edema; there can also be an increase in body weight.

Other drugs that can be used as an alternative to the above are: carbamazepine (keeping in mind that it is a potent enzyme inducer and hence may reduce the plasma concentrations of many other drugs), oxcarbazepine, phenytoin, lamotrigine, and eventually opioids, including tramadol (μ receptor agonist) which has proven to be the most effective[10-11].

It is also possible to use capsaicin or lidocaine-based topical therapies in some patients and especially those with more localized pain or those who cannot take oral medications because of contraindications[12].

Rarely, it is necessary to resort to corticosteroid therapy due to the resistance of pain to the usual therapies and to their general repercussion, the progression of the deficits and possibly in the case of vasculo-nervous inflammatory lesions detected by biopsy.

Finally, in cases of failure to respond to more than one type of drug therapy administered over an appropriate time and at correct dosages, or in cases of onset of serious side effects to the drugs that require suspension or when there are absolute contraindications that prevent use, recourse can be made to non-pharmacological therapies such as acupuncture[13] and various electrical neuromodulation techniques[14-15] whose indications and efficacy are yet to be proven.

The most severe autonomic disorders that typically require treatment are orthostatic hypotension and erectile dysfunction.

In principle, a treatment of orthostatic hypotension is justified only when it is accompanied by functional manifestations. The measure to be taken in the first instance is the use of retentive socks. If this is not enough, you can try to associate high-dose dihydroergotamine, reaching up to 40 mg a day. In case of failure, it is possible to use the midodrine, which is an effective and well-tolerated sympathomimetic and does not cause risks of arterial hypertension due to decubitus. Finally, if the drugs mentioned above do not give satisfactory results, the solution of last resort is fluoroidrocortisone, always bearing in mind the risk of high blood pressure, fluid retention, possible decompensation, the well-known ocular, gastrointestinal, bone metabolism and weight side effects.

For the treatment of erectile dysfunction, as in other cases, recourse is made to a selective inhibitor of phosphodiesterase type 5, the predominant isoenzyme in human corpus cavernosum. Gastric motility can be improved by metoclopramide and levosulpiride (without misusing the dosage to prevent the known central effects on dopaminergic receptors, especially in parenteral administration), by domperidone, and erythromycin per os, while the modifications of the alvus are affected by treatment with common anti-diarrheal or laxative drugs. Frequent urination or, when necessary, intermittent bladder catheterization are useful for treating disorders of bladder voiding.

As for the etiological treatment, the mainstay of treatment of diabetic neuropathy is the optimization of metabolic control, which for the moment is

the only mode of intervention proven to interfere with the natural progression of polyneuropathy.

The achievement of adequate metabolic control makes it possible to prevent the onset or to stop the progression of the neurological damage induced by diabetes in both the somatic and autonomic component of the peripheral nervous system. If, however, in patients with diabetes type 1 it has been shown that good glycemic control has substantial beneficial effects, the same cannot be said for patients with type 2 diabetes for whom there is much less clinical evidence.

In fact, analyzing the data relating to the instrumental parameter used for the evaluation of peripheral neuropathy (vibration perception threshold), there is only a favorable trend in the intensive treatment that does not reach though statistical significance before the fifteenth year of observation[16]; however, other recent observations document the latency of improvement that appears more evident in the demyelinating variants of neuropathies rather than in the axonal varieties[17].

The fact that a good metabolic control also serves to stop the progression of neuropathy, and not only to prevent its development, is demonstrated by a study carried out by Navarro et al. who have unequivocally documented that a long period of euglycemia obtained by pancreas transplantation can stop the worsening of already overt diabetic neuropathy[18]. For 10 years these authors followed a large case history of diabetic patients undergoing pancreas transplantation (isolated or in combination with kidney transplantation) who already at the time of surgery showed peripheral neuropathy and who were compared with another group of non-transplanted diabetics treated with conventional insulin therapy. While in the first group the various clinical and instrumental indices of somatic neuropathy were stable or slightly improving, the control group showed a progressive deterioration of all the parameters examined. This conclusion coincides with another case that I personally observed.

Recently it has also been seen that factors other than hyperglycemia may affect the onset of peripheral neuropathy in humans, such as the presence of hypertension, hyperlipidemia, obesity, smoking and lifestyle[19] as revealed by a Danish study conducted on 80 patients with type 2 diabetes and microproteinuria treated intensively with lifestyle changes and multi-drug therapy aimed to bring blood sugar, blood pressure and plasma lipids within target values indicative of a good control of these vascular risk factors: 8 years later, these patients showed a reduction in the incidence of microvascular complications, including autonomic neuropathy, compared to other patients in whom these measures had not been implemented[20].

In addition to all this, it is also necessary to stress that the difficulty of obtaining and maintaining long-term optimal metabolic control has led to the testing of different compounds belonging to different pharmacological classes that have the ability to interfere with the metabolic processes that are considered pathogenetically important in the onset of neuropathy.

Inhibitors of the aldose reductase enzyme (aldose reductase inhibitor, ARI), which is the first enzyme of the polyol pathway, are the most widely tested, but unfortunately no certainly and significantly positive results have been achieved and the trials of some have been suspended because of significant side effects[21].

Another pharmacological class is that of antioxidants due to their ability to neutralize free radicals of oxygen formed in excess in the peripheral nerves of diabetics. α-lipoic acid (or thioctic acid) is the most widely tested antioxidant drug in controlled clinical trials versus placebo[22].

Furthermore, this compound, at a dose of 600-1800 mg a day for 5 weeks, has shown positive effects on the symptoms of neuropathy even when taken orally[23]. Some studies have also been carried out on ACE-inhibitors, though with a very limited number of cases, and a significant improvement of some electrophysiological parameters has been demonstrated[24].

There is also a report on the results of a recent study of a new therapeutic strategy whose objective is the inhibition of the production of metalloproteinase-2 (MMP-2) and metalloproteinase-9 (MMP-9), which, being overexpressed in diabetics, would cause an extracellular matrix degradation in blood vessels: this has been obtained in male rats thanks to the association of a known metalloproteinase inhibitor, namely minocycline, with a non-selective inhibitor of cyclooxygenase, namely aspirin. After three weeks of treatment, the result was a significant improvement of sensory and motor conduction velocity and of the latency to the response of the stimulus to the tail and exposure to the hot plate[25].

There are also some indications for other compounds (acetyl-carnitine, γ-linolenic acid, C-peptide) for their potential benefit in the treatment of diabetic neuropathy[2,26,28-31].

It is worth noting the significant frequency of a recurring or alternating facial paralysis in patients with diabetes[32].

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